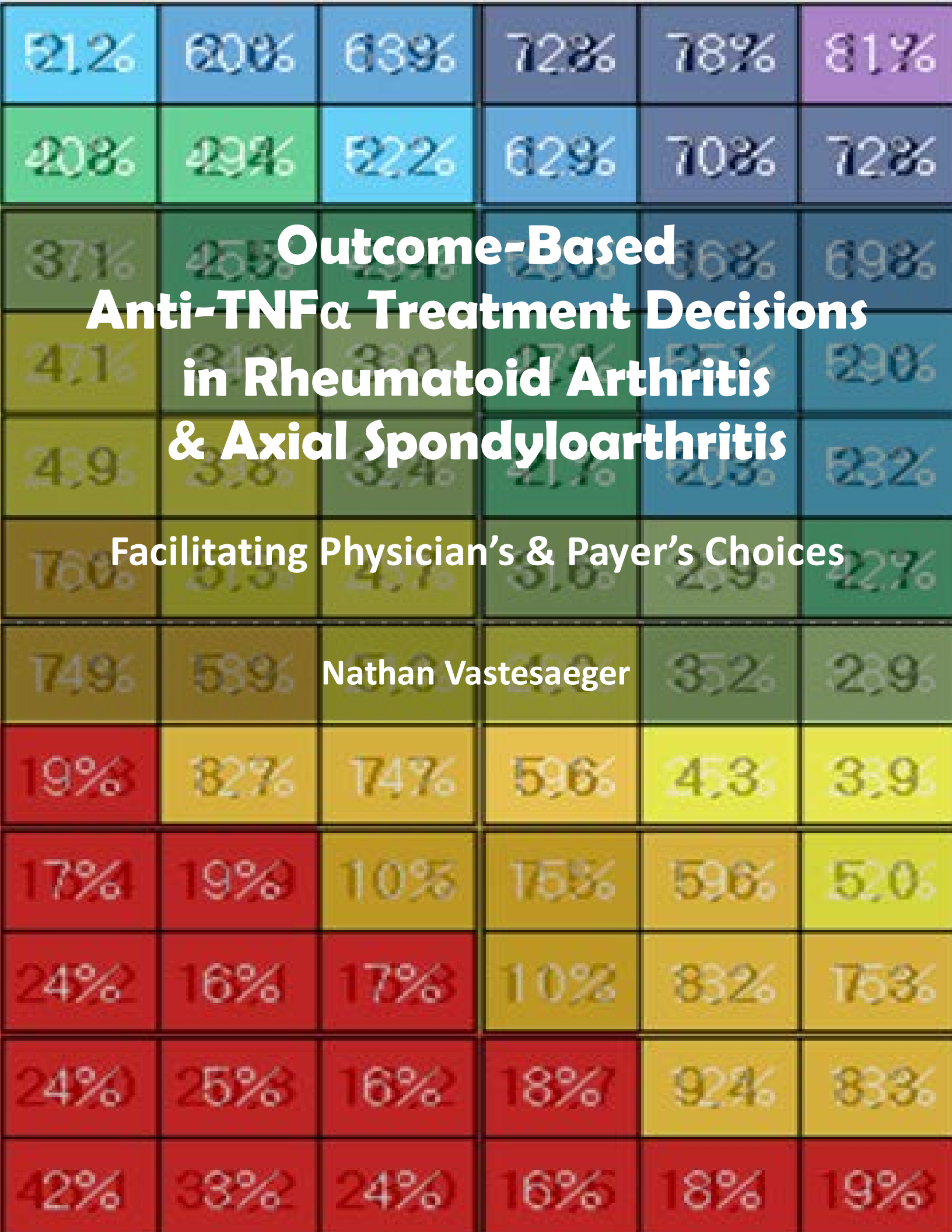

Outcome-Based Anti-TNFα Treatment Decisions in Rheumatoid Arthritis & Axial Spondyloarthritis

Facilitating Physician's & Payer's Choices

Nathan Vastesaeger

"Prediction is very difficult, especially if it's about the future."
Niels Bohr

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Faculty of Medicine and Health Sciences
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This thesis is submitted to fulfill the requirements for achievement of The Grade of

'Doctor in Medical Sciences'

Table of Content

Chapter 1: Introduction p9

1.1. Epidemiology and Diagnosis. p9
1.2. Signs, Symptoms and Clinical Disease Assessment. p12
1.3. Imaging techniques. p15
1.4. Management of patients diagnosed with RA or Axial SpA. p17
1.5. Socio-economic aspects of the management of RA and Axial SpA. p19

Chapter 2: Research aims p27

Chapter 3: Intuitive Anti-TNF alpha Treatment Decisions in Clinical Practice p29

3.1. The epidemiology of ankylosing spondylitis and the commencement of anti-TNFα therapy in daily rheumatology practice. p31
3.2. DAS28 best reflects the physician's clinical judgment of response to infliximab therapy in rheumatoid arthritis patients: validation of the DAS28 score in patients under infliximab treatment. p43

Chapter 4: Prediction Models of Anti-TNF alpha Outcomes in RA and AS p57

4.1. A pilot risk model for the prediction of rapid radiographic progression in Rheumatoid Arthritis. p59
4.2. Validation of the poor prognosis model in Rheumatoid Arthritis. p75
4.3. Prediction of Remission and Low Disease Activity in DMARD-refractory Patients with Rheumatoid Arthritis Treated with Golimumab. p79
4.4. Predicting the outcome of ankylosing spondylitis therapy. p99
4.5. ASDAS high disease activity versus BASDAI elevation in patients with ankylosing spondylitis as selection criterion for anti-TNFα therapy. p121

Chapter 5: Anti-TNF alpha Treatment Discontinuation following Remission p129

5.1. Efficacy and safety of infliximab plus naproxen versus naproxen alone in patients with early, active axial spondyloarthritis: results from the double-blind, placebo-controlled study, INFAST Part 1. p131
5.2. Maintenance of biologic-free remission with naproxen or no treatment in patients with early, active axial spondyloarthritis: results from a 6-month, randomized, open-label follow-up study, INFAST Part 2. p143
5.3. Partial Remission in Ankylosing Spondylitis and Non-Radiographic Axial Spondyloarthritis and Associations between Partial Remission and Baseline Disease Characteristics during Treatment with Infliximab plus Naproxen or Naproxen alone. p155

Chapter 6: Outcome-based Treatment Decisions in RA and Axial SpA Management Recommendations - Discussion p167

6.1. Relevance of value based patient selection in RA. p169
6.2. Relevance of value based patient selection in AS. p185
6.3. Anti-TNFα treatment discontinuation as treatment goal. p191
6.4. Models to select Rheumatoid Arthritis and Axial Spondyloarthritis patients for Anti-TNFα treatment: is it time to introduce personalized medicine into clinical practice p195

Summary p211

Samenvatting p215

Curriculum vitae p219

List of Acronyms p227

Acknowledgements p231

Chapter 1: Introduction

1.1. Epidemiology and Diagnosis

Rheumatoid arthritis (RA) and Axial Spondyloarthritis (SpA) are chronic systemic inflammatory disorders that affect the peripheral joints and the spine respectively.

About 0.5% to 1% of the population has RA [1]. Patients are mostly females and onset is usually between 35 and 50 years old [1]. It is typically a poly-articular disease (i.e. 5 or more joints affected) and primarily involves the smaller peripheral joints (e.g. wrists, inter-phalangeal joints and the metacarpo- & metatarso-phalangeal joints) which are inflamed due to proliferation of the synovium. Persistent synovitis leads to progressive destruction of articular structures due to cartilage destruction and erosions of the sub-chondral bone resulting in irreversible function loss and disability; **Figure 1** [2-4].

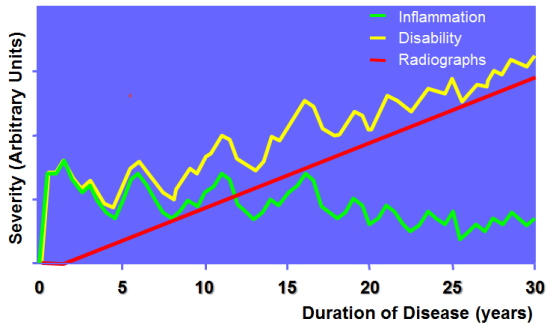

FIG. 1: *Association of joint damage & inflammation with disability. Adapted from Kirwan JR. J Rheumatol. 2001;28:881-886.*

Axial SpA is primarily seen in men and usually starts in the second or third decade. It has a reported prevalence ranging from 0.6% to 1.2% of the population and primarily affects the joints of the axial skeleton but may also affect some peripheral, large joints such as hips and knees (usually less than 5 joints affected) and the entheses of the Achilles tendon and plantar fascia [5-7]. The hallmark characteristic of AS is sacroiliitis and ankylosis of the spine which can be visualized on conventional X-rays. This leads to irreversible reduction in the range of motion of the axial skeleton which results in loss of function; **Figure 2** [8].

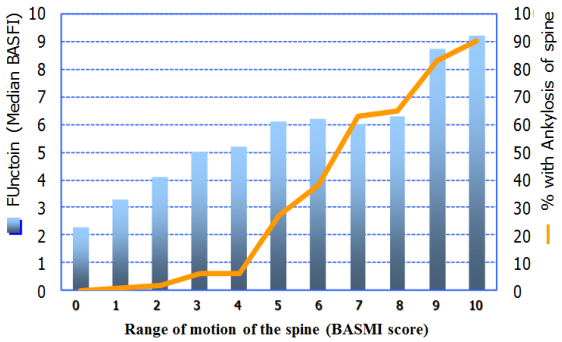

FIG. 2: *Relationship between imaging findings, range of motion of the axial spine and function. From the ASPECT study, unpublished data.*

For both diseases there have recently been important efforts towards improvement of the criteria for diagnosis. The purpose of these revised criteria is to increase sensitivity and specificity to diagnose and treat RA and Axial SpA in an early phase of disease. In RA emerging evidence has highlighted a window of opportunity during which effective therapy can lead to long-term benefits in outcomes including limiting or preventing occurrence of radiographic progression which can no longer be achieved once the disease is more established [9]. As such, where the 1987 ACR classification criteria for RA helped to correctly identify patients with RA and to minimize misclassification in clinical or epidemiological studies, the 2010 diagnostic criteria allow doctors to diagnose an RA patient in the clinic at a time when early DMARD therapy is prompted to modify the disease course on the long run; **Table 1** [10, 11].

TABLE 1	**1987 American College of Rheumatology (ACR) Classification criteria for rheumatoid arthritis (10)**	**2010 ACR/European League Against Rheumatism (EULAR) classification criteria for early rheumatoid arthritis (11)**
Criteria	1. Morning stiffness (at least 1 hour) 2. Arthritis in 3 or more joint areas 3. arthritis of hand joints (>=1 swollen joints) 4. Symmetric arthritis 5. Rheumatoid nodules 6. Serum Rheumatoid Factor positive 7. Radiographic Changes (erosions) on X-rays of hands	1. Joint involvement (score 0 to 5) • 1 medium large joint (0) • 2 to 10 large joints (1) • 1 to 3 small joints (with or without involvement of large joints) (2) • 4 to10 small joints (with or without involvement of large joints) (3) • >10 joints (at least 1 small joint) (5) 2. Serology (score 0-3) • Negative Rheumatoid Factor (RF) and negative Anti-Citrillunated Protein Antigen (ACPA) (0) • Low-positive RF or low-positive ACPA (2) • High-positive RF or high-positive ACPA (3) 3. Acute-phase reactants (sore 0-1) • Normal C-Reactive Protein (CRP) and normal Erythrocyte Sedimentation Rate (ESR) (0) • Abnormal CRP or abnormal ESR (1) 4. Duration of symptoms (score 0-1) • <6 weeks (0) • >=6 weeks (1)
Target	All arthritis patients	Undifferentiated Arthritis patients
Results in	Classification of RA (yes/no)	Classification of early RA (yes/no)
Positive in case	Four of 7 criteria must be present. Criteria 1 through 4 must have been present for at least 6 weeks.	Scoring >=6 points. In the presence of erosiveness seen in light of inflammatory disorder, no other points need to be obtained for the classification of RA.
Test Characte-ristics	Sensitivity: 79%-80%, specificity: 90%-93% for established RA. Sensitivity: 77%-80%, specificity 33%-77% for early RA.	Sensitivity and specificity for established RA and early RA unknown.

Similarly, according to the 1984 modified New York criteria for Ankylosing Spondylitis (AS), definite disease can only be diagnosed when sacroiliitis is observed on conventional X-rays [12]. Patients without X-ray damage but with clinical features have probable AS [12]. X-ray signals only become visible at an advanced stage of the disease and usually manifest several years after symptom onset. This frequently leads to a long delay in diagnosis and appropriate treatment which prompted the development of new classification criteria for Axial SpA allowing earlier recognition and treatment it in clinical practice [13, 14]. Unlike RA where the need for imaging techniques has been abandoned, imaging with either X-rays or Magnetic Resonance remains a diagnostic criterion in Axial SpA, albeit not a mandatory one. See **Table 2** below.

TABLE 2	**1984 Modified New York Criteria for Ankylosing Spondylitis (12)**	**2009 ASAS Criteria for Axial Spondyloarthritis (13, 14)**
Criteria	Clinical criteria: • Low back pain and stiffness for more than 3 months which improves with exercise, but is not relieved by rest. • Limitation of motion of the lumbar spine in the sagittal and frontal planes. • Limitation of chest expansion relative to normal values corrected for age and sex. Radiological criterion: • Sacroiliitis grade >2 bilaterally or grade 3–4 unilaterally.	Spondylo-Arthritis features: • Inflammatory back pain • Arthritis • Enthesitis of the heel • Uveitis • Dactylitis • Psoriasis • Crohn's disease or Ulcerative Colitis • Good response to Non-Steroidal Anti-Inflammatory Drugs • Family history of SpA • Human Leucocyte Antigen-B27 genotype • Elevated CRP (in context of back pain) Sacroiliitis on imaging: • Active inflammation on MRI highly suggestive of sacroiliitis associated with SpA - OR • Definite radiographic sacroiliitis according to the modified New York Criteria
Target	General population	Patients with back pain >=3 months and age at onset <45 years old.
Results in	Classification of Definite AS (yes/no) or Probable AS (yes/no)	Classification of Axial SpA (yes/no)
Positive in case	Definite AS if the radiological criterion is associated with at least one clinical criterion. Probable AS if 3 clinical criteria are present or the radiological criterion is present without any signs or symptoms satisfying the clinical criteria.	Sacroiliitis on imaging plus at least one of the above SpA features OR HLA-B27 genotype positive and at least 2 of the SpA features.
Test Characteristics	Specificity 83% in healthy controls.	Sensitivity of 82.9%, specificity 84.4%. Imaging alone: sensitivity 66.2%, specificity 97.3%.

In the most recent ASAS classification setting, Axial SpA encompasses both patients with chronic back pain in whom radiological signs of sacroiliitis can be measured with conventional X-rays (radiographic Axial SpA or AS) and those in whom damage on radiographs cannot be observed (non-radiographic Axial SpA). Patients who do not have sacroiliitis nor signs of inflammation of the spine on MRI can still be diagnosed with Axial SpA if Human Leucocyte Antigen B27 is present [13, 14].

1.2. Signs, Symptoms and Clinical Disease Assessment

For both diseases, onset tends to be insidious and the articular (RA) and axial skeletal (Axial SpA) symptoms are usually accompanied by systemic symptoms such as fatigue and malaise [15].

Rheumatoid arthritis

In RA the hallmark disease feature is synovitis of the peripheral joints and symptoms include early morning stiffness of the joints which are tender or painful, red, warm, swollen, and stiff. Stiffness frequently lasts more than 60 min after rising in the morning and may also occur after prolonged inactivity, resulting in typical nocturnal pain. The pattern of peripheral joint affection is symmetric and virtually any joint can be involved but especially the small joints of the hands and feet, wrist, elbows, shoulders, knees and ankles tend to be affected. Synovitis of the distal inter-phalangeal (DIP) joints and the axial skeleton are rarely seen with exception of the upper cervical spine [16]. In different validated assessments of disease activity up to 66 joints are measured for swelling and up to 68 for tenderness. The 44 joint count in which the joints of the feet are also assessed is frequently used in studies but as with the 66 / 68 joint counts this is more time consuming and cumbersome to perform. The 28 joint count is the most frequently used joint count in clinical practice and the below figure highlights which joints are then assessed for swelling and tenderness [17]. This is shown in **Figure 3**.

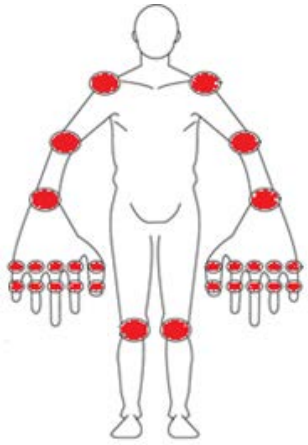

FIG. 3: *Joints that are assessed for swelling and tenderness in the 28 joint counts (modified from hindawi.com).*

The number of tender and swollen joints combined with the patient's global assessment of disease activity (PG) measured on a Visual Analogue Scale (VAS) of 100 mm, and the erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) are combined in a composite disease activity assessment instrument called the Disease Activity Score (DAS or DAS28, in which the 44 and 28 joint counts are used respectively). Patients who have a DAS28 more than 5.1 have high disease activity, those with DAS28 between 3.2 and 5.1 have moderate disease activity, those with DAS28 between 2.6 and 3.2 have low disease activity and those with a score less than 2.6 are in remission (17-20).

In the EULAR response criteria both the change in the DAS28 score and the disease state in which a patient is brought with therapy are needed to determine whether a patient has good or moderate response or no response [19]. See **Table 3** below.

DAS28 Improvement / Present DAS28	>1.2	0.6 - 1.2	<0.6
<3.2	good response	moderate response	no response
3.2 - 5.1	moderate response	moderate response	no response
>5.1	moderate response	no response	no response

TABLE 3: European League against Rheumatism response criteria.

Joints are often held in flexion to minimize pain and this may lead to fixed deformities like flexion contractures resulting in the very typical swan-neck and boutonniere deformities. Tendon rupture due to inflammation also occurs. Joint instability due to stretching of the joint capsule can also occur [8, 16]. These changes and the tenderness and swelling of the joints and surrounding tendons itself lead to disability which is measured with patient reported outcomes (PRO) questionnaires that assess quality of life (QoL) and function. The most frequently used PRO questions used for the assessment of function in RA are the disability scales of the Health Assessment Questionnaire (HAQ). In the HAQ score, disability is assessed by eight categories (dressing, arising, eating, walking, hygiene, reach, grip, and common activities). The score for the disability index ranges from 0 to 3 and is the mean of the eight category scores which are individually scored from 0 (without any difficulty) to 3 (unable to do). As such patients with a high score have severe disability and those with a low score have limited disability [21, 22].

Extra-articular manifestations are not so common anymore in RA. Subcutaneous rheumatoid nodules are the most known and develop in up to 30% of patients, usually at sites of pressure and chronic irritation. Pulmonary nodules may occur in severe RA and are usually asymptomatic. Other extra-articular signs include symptoms of vasculitis such as leg ulcers, mononeuritis multiplex, pleural or pericardial effusions, pulmonary infiltrates or fibrosis, pericarditis, myocarditis, lymphadenopathy, Felty syndrome, Sjögren syndrome, scleromalacia, and episcleritis [8, 16].

Axial Spondyloarthritis

Axial SpA affects the axial skeleton and inflammatory back pain is the main symptom of this disease. Patients may wake up in the second half of the night because of pain and usually have morning stiffness of the back that lasts more than 30 minutes and improves with exercise. Morning pain and improvement with exercise and not with rest are important characteristics which allow to distinct the pain pattern of inflammatory back pain from that of mechanical back pain. The latter tends to improve with rest and usually appears after exercise (e.g. in the evening). The involvement of the sacroiliac joints in Axial SpA may result in alternating buttock pain. Patients are relieved of the pain in the lower back and the associated muscle spasms when they bend forward and this is a posture that is very typical for the disease. If the joints of the ribs are inflamed, the pain may limit the ability to expand the chest to take a deep breath. Stiffness (fusion) of the spine can restrict the ability to expand the chest wall as well and may lead to an irreversibly bent over posture [16, 23].

When peripheral joints are affected in Axial SpA, symptoms are similar to those in RA (i.e. swelling, tenderness, redness, stiffness) but the pattern differs as usually only few and large joints (hip or knee)

are affected in a non-symmetric fashion. Dactylitis or 'sausage finger or toe' is often seen and consists of diffuse swelling and redness of the entire digit.

Enthesitis is also a frequent disease characteristic and leads to tenderness and swelling, redness and stiffness of the affected site [24]. The most frequent sites where enthesitis presents itself in Axial SpA patients are at the insertion of the Achilles tendon and the tendon of the fascia plantaris of the heel. Yet also other sites such as the costo-chondral sites, the iliac crest and the processsus spinosus L5 can be assessed for tenderness suggesting enthesitis. The Maastricht Enthesitis Ankylosing Spondylitis Enthesitis Score, the Berlin and the San Francisco scores for enthesitis have all been validated and have different counts for enthesitis based on different enthesial sites and differences in the total number of points where pressure needs to be applied to evaluate tenderness [25, 26]. Pressure points are also used to diagnose fibromyalgia and the differential diagnosis between enthesitis and fibromyalgia may be difficult in the absence of more objective signs of inflammation at the affected sites (e.g. redness or swelling). Echography may also be useful to determine whether inflammatory processes are at the origin of the tenderness if swelling or other clinical symptoms are not obvious [27].

The back is not as accessible as joints are and, assessment of disease activity in AS is therefore mostly based on patient reported outcomes. The Bath ankylosing spondylitis disease activity index (BASDAI) score measures disease activity based on six questions on fatigue, spinal pain, joint pain/swelling, areas of localized tenderness and morning stiffness. The BASDAI score ranges from 0 to 10 with a higher score corresponding to higher disease activity [28]. Function is also assessed through PRO in AS and one of the most frequently used assessment instruments for function in AS is the Bath ankylosing spondylitis functional index (BASFI). The BASFI has ten questions of which 8 evaluate activities related to functional anatomical limitations due to the course of this inflammatory disease and 2 evaluate the patients' ability to cope with everyday life [29]. As with BASDAI it rates function with a score from 0 to 10 and patients with a higher score are more functionally impaired.

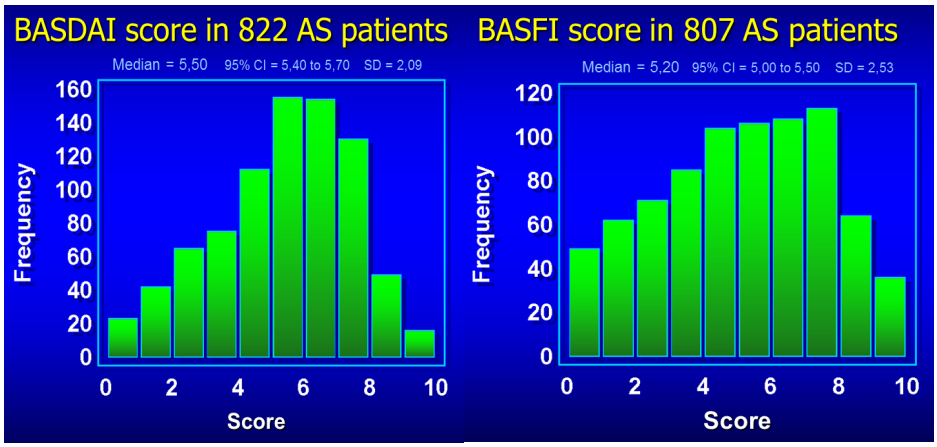

FIG. 4: *BASDAI and BASFI score across the ASPECT study population for patients with AS. From the ASPECT study, unpublished data.*

The range of motion of the axial skeleton is most frequently assessed through measurement of chest expansion, cervical rotation, lateral and frontal spinal flexion of the spine, the occiput to wall distance and abduction of the hips. The 5 latter measurements can be combined into the Bath AS metrology index which ranges from 0 to 10 with a higher score meaning less range of motion [30-32].

Extra-articular manifestations are more common in Axial SpA than in RA and are important to establish the diagnosis early in this disease. More than 50% of patients with ankylosing spondylitis will have uveitis, psoriasis or inflammatory bowel disease at one time of their disease [33, 34]. One third of the people have recurring attacks of mild eye inflammation (uveitis), which usually does not impair vision if treated promptly [35].

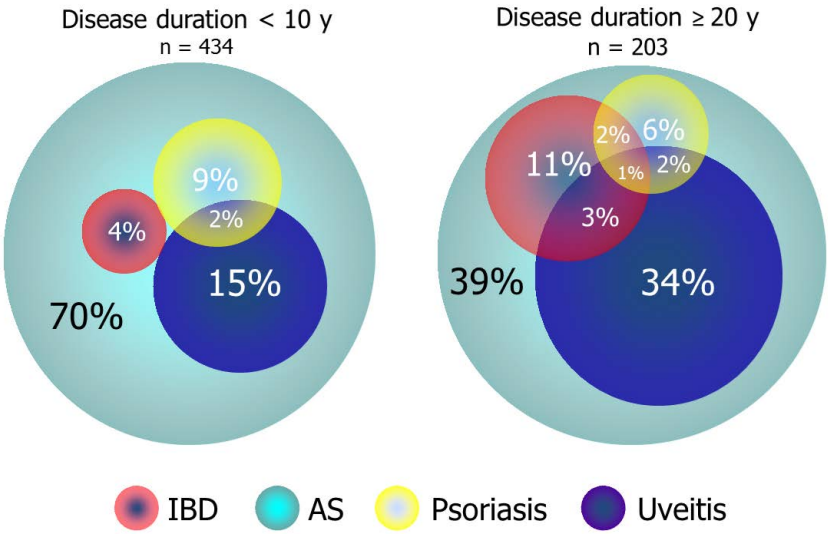

FIG. 5: *Proportion of AS patients with a history of extra-articular manifestations over time in the ASPECT study population. From the ASPECT study, unpublished data.*

1.3. Imaging techniques

Imaging techniques such as conventional X-rays and, more recently frequently magnetic resonance imaging (MRI) have been used in clinical practice and in clinical studies as tools to assess progression and prognosis of both diseases.

Rheumatoid arthritis

In RA, aside from soft-tissue swelling, X-rays show periarticular osteoporosis, joint space narrowing (caused by destruction of the articular cartilage) and erosions (caused by synovial invasion of the bone, typically occurring at the osteo-chondral junction). Erosions often develop within the first year but may occur at any time. Driven by persistent, severe and long-standing inflammation of the synovia of the joints, severely disabled rheumatoid arthritis (RA) patients with completely destructed wrists and hands were seen in every rheumatology practice until not so long ago [37-41]. The most frequently used method to measure joint damage is through the modified Sharp van der Heijde (SvH) method for which 16 areas for erosions and 15 areas for joint space narrowing in each hand are combined with 6 areas for erosions and 6 areas for joint space narrowing in the feet. The maximum score for erosion and joint-space narrowing in a single joint of the hand is 5 and 4 for the foot and the total SvH score ranges from 0 to 448 [42, 43].

MRI is more sensitive than X-rays to detect inflammatory signals (e.g., bone marrow lesions, bone marrow edema) and erosive changes in the bone which cannot be visualized with X-rays. It can also identify and quantify articular inflammation in a way that is not possible with clinical joint assessment. In

spite of these advantages of MRI there are also disadvantages like availability and cost which place this imaging technique in the research setting much more than in clinical practice [44].

Axial Spondyloarthritis

In Axial SpA, conventional X-rays are still used to stage the disease and allow to distinct non-radiographic disease from ankylosing spondylitis through measurement of the sacroiliac joints (see classification of AS) [13, 14]. In the Modified Stoke Ankylosing Spondylitis Spine Score (mSASSS), lateral cervical and lumbar spine X-rays allow to score 24 vertebral corners from 0 to 3 resulting in a range from 0 to 72 for the total score [45]. The typical lesions that can be visualized on X-rays are syndesmophytes (i.e. bone growth at the anterior corner of a vertebra, corresponding with an mSASSS score of 2) and bony bridges between 2 vertebras which are also called ankylosis (score 3) and are more frequently seen in men than in women [45]. Progression of ankylosis is slow and it usually takes several years for syndesmophytes and bridging to occur.

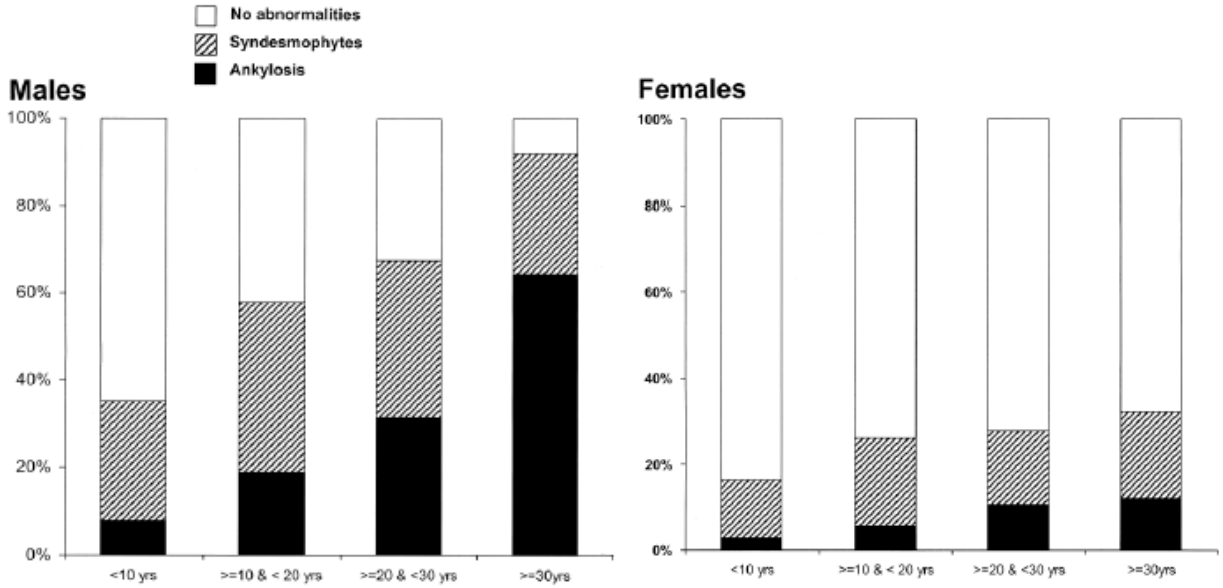

FIG. 6: *Radiographic signals according to gender and disease duration in the AS population of the ASPECT study. From Boonen et al. J Rheumatol. 2009;36(6):1249-55.*

In contrast to X-rays, MRI can also detect inflammation which is thought to be the underlying mechanism of ankylosis. This method is therefore more useful in the early stages of the disease at which time changes on X-rays may not be visible yet. Both imaging techniques are still used to determine whether there is sacroiliitis on imaging in the ASAS classification for Axial SpA. Active inflammatory lesions of the SI joints and located in the typical anatomical areas (subchondral or peri-articular bone marrow (reflecting active sacroiliitis) are required for the definition of ''sacroiliitis on MRI'' (46-49).

Several scoring methods for assessing inflammatory activity in the spine and sacroiliac joints are used and further explored and established. This is still a rapidly evolving field and is not further described.

1.4. Management of patients diagnosed with RA or Axial SpA

Both the EULAR recommendations for management of RA and the ASAS/EULAR recommendations for management and treatment of Axial SpA introduce the importance of non-pharmacological measures,

such as physical, occupational and psychological therapeutic approaches which may help lead to therapeutic success [49, 50]. Even though the management of these diseases thus rests on more than only the principle of pharmacological treatment, application of drugs is arguably the most important aspect of therapy. Medicinal treatment in patients with RA and SpA is mostly situated in the secondary prevention (diagnose and treat existing disease early before it causes significant morbidity), tertiary prevention (reduce negative impact of existing disease by restoring function and reducing disease related complications) and palliative care setting (relieving and preventing the suffering of patients) [16]. Cure has not been shown to be achievable with the currently available therapeutic armamentarium and occasional prolonged drug-free disease control that has been reported in selected patients with these diseases is arguably the closest achievable proxy to cure.

Rheumatoid arthritis

Disease-modifying anti-rheumatic drugs (DMARDs), with as anchor drug methotrexate (MTX) are used to reduce and control RA symptoms and modify the disease course (i.e. preserve normal architecture and function of the joints) [37-41]. As soon as the diagnosis of RA is made, MTX can be used alone or in combination with other DMARD (when there are no contraindications). The goal for every patient should be to establish remission or low disease activity and if no improvement is measured within 3 months or the target is not achieved at 6 months, therapy should be adjusted. If the treatment target is not achieved with the first DMARD strategy, in the absence of poor prognostic factors, change to another DMARD strategy should be considered. When poor prognostic factors are present, addition of a biological agent should be considered and biologicals should also be considered when MTX and DMARD strategies fail. Upon failure of a first biological subsequent biologicals with the same or a different mechanism of action can be tried and new oral treatments like tofacitinib are reserved for patients failing multiple biologics [49].

If an RA patient is in persistent remission after having tapered glucocorticoids, physicians are recommended to consider tapering biological agents, especially if this treatment is combined with a DMARD. In cases of sustained long-term remission, cautious reduction of the DMARD dose could also be considered, as a shared decision between patient and physician [49].

Axial Spondyloarthritis

In Axial SpA non-steroidal anti-inflammatory drugs (NSAIDs) are recommended as first line drug treatment for patients with pain and stiffness. Analgesics, such as paracetamol and opioids, might be considered for pain control in patients in whom NSAIDs are insufficient, contraindicated and/or poorly tolerated. Sulfasalazine (SSZ) may be considered in patients with peripheral arthritis but there is no evidence for the efficacy of DMARDs (including SSZ and MTX) for the treatment of axial disease [51]. All patients should have tried a minimum of two NSAIDs (at the maximally tolerated dose) for a minimum of 4 weeks in total before Anti-TNFα treatment is recommended for patients with persistently high disease activity (BASDAI score >= 4/10) despite conventional treatments. Treatment with an anti-TNFα agent should be installed by a doctor, usually a rheumatologist, with expertise in Axial SpA and the use of biological agents. The expert should consider clinical features (history and examination), serum acute phase reactant levels and/or imaging results, such as radiographs demonstrating rapid progression or MRI indicating ongoing inflammation. Treatment effect should be assessed after at least 12 weeks of continued treatment with an anti-TNFα agent at which time the BASDAI should have had a 50% relative improvement or an absolute improvement of 2 which should allow the expert to decide upon the desirability to continue treatment or not [51].

TABLE 4	EULAR recommendations for the treatment of RA (49)	ASAS/EULAR recommendations for the treatment of Axial SpA (51)
Indication	As soon as diagnosis of RA is made	In Axial SpA patients with pain & stiffness
Treatment Goal	Remission or Low Disease Activity in every RA patient	Not specified for NSAID treatment. 50% or 2 units improvement in the BASDAI score for anti-TNFα treatment and expert in favor of continuing.
Monitoring frequency & treatment adjustment	Every 1 to 3 months; therapy should be adjusted if there is no improvement by at most 3 months after the start of treatment or the target has not been reached by 6 months.	Assessment of effectiveness 2 weeks after initiation of an NSAID. Assessment at least 12 weeks after initiation of an anti-TNFα agent.
1st Line	First DMARD strategy including MTX with or without other DMARD(s). In case MTX is not tolerated or contraindicated start with another DMARD.	First NSAID (Cox-specific NSAID as indicated)
2nd Line	Second DMARD strategy if poor prognostic factors are not present. [1] Addition of a biological agent when poor prognostic factors are present.	Second NSAID
3rd Line	Biological agent if patients respond insufficiently to MTX and/or other DMARD strategies	Anti-TNFα agent for patients with high disease activity (BASDAI score >= 4/10) for more than 4 weeks despite conventional treatment and as indicated by an expert. [2]
In case of biologic failure	New biological agent. This may be a second anti-TNFα agent or an agent with a different mode of action.	Limited information available for switch from a first to a second anti-TNFα agent.
Biologic failures	Tofacitinib	Not specified.
Treatment titration	Taper biologic in case of persistent remission. Cautious reduction of DMARD therapy in case of sustained long-term remission.	Not specified.
Cortico-steroids	Low to moderately high GCs doses added doses to DMARD(s) provide benefit and should be tapered rapidly.	Local injections for enthesitis or arthritis. Systemic CS not active.

[1] These risks have been well defined over the years and include a high disease activity state, autoantibody positivity (rheumatoid factor and/or antibodies to citrullinated proteins) and the early presence of joint damage [49].

[2] In the 2003 recommendations which was the basis for the 2010 revisions, expert opinion should include clinical features, acute phase reactants, and imaging modalities. To make an informed decision, the expert should have available clinical features (history and examination), as well as either serum acute phase reactant levels or imaging results and should assess the likelihood of response to treatment. At the time it was concluded that most patients will benefit from anti-TNFα therapy and it was recognized that there are no good predictors for treatment response [52].

Treatment of RA and Axial SpA must be based on a shared decision between patient and rheumatologist. This includes the need to inform the patient on the risks of the disease and the benefits & risks of its therapies. As the presence of comorbidity or of disease manifestations may have an important impact on the choice of the management strategy, multidisciplinary treatment may be required. The perturbation of the immune-system causing RA & Axial SpA may also lead to other immune-mediated disorders (e.g. uveitis, vasculitis, Crohn's disease) and high disease activity on itself is associated with some typical comorbidities such as cardiovascular disease, osteoporosis and even lymphoma which activity control with effective therapeutic intervention may prevent [49, 51].

Adequate anti-conceptive measures should be taken before initiating agents like MTX and alternatives like SSZ or anti-malarials may be chosen in case there is a pregnancy wish. Contraindications to any therapeutic option should be considered before initiation of any therapy. Screening measures before start and during use of a specific therapy may be required. For anti-TNF, preventive screening and treatment of latent tuberculosis has led to a sharp decrease of the incidence of tuberculosis in treated patients. Since reactivation of Hepatitis B virus may occur, latent carriers should be identified. Throughout the treatment patients should be carefully monitored for (serious) adverse events. Due to the elevated risk of infections with anti-TNF agents (including opportunistic infections for which symptoms may be a-specific) this includes careful evaluation of any signs and symptoms that signal infection. The association of anti-TNF agents with no signals have been of concern this far. Occurrence of adverse events and/or intolerance to an agent may require change of therapy.

1.5. Socio-economic aspects of the management of RA and Axial SpA

Since they have been introduced in markets around the world in the beginning of the millennium, anti-Tumor Necrosis Factor alpha (anti-TNFα) agents and subsequently other biologics have had a large impact on the management of rheumatologic conditions. The suppressive effects on inflammation of these agents in RA leads to better control of disease activity and thus also halted further deterioration of joint destruction which allows stabilizing functional capacity of patients [37-41, 53-56]. The availability of anti-TNFα agents has also led to a significant improvement in the use of the available therapeutic DMARD armamentarium in RA, especially MTX [57]. Earlier diagnosis and referral, earlier and more aggressive DMARD treatment strategies before biologics and availability of better treatments – anti-TNFα agents initially but subsequently also other biologics - have thus changed the RA population characteristics to the extent where researchers are evaluating whether management of RA patients has improved or whether RA as a disease has become milder instead [58]. Coinciding with the increase in use of MTX and TNF inhibitors, elective musculoskeletal surgical procedures for RA patients have almost halved and RA inpatient bed days have halved over the past 15 years [59]. For Axial SpA patients the impact of anti-TNFα agents has been as dramatic as for RA patients, yet the success of bringing pharmacological treatment innovation to this disease population has been more limited than in RA as this far biological agents with another mechanism of action than anti-TNFα are not yet available outside the experimental setting.

Health care systems and society has recognized the considerable costs associated with the care of RA and AS. Several economic evaluations have been published and differ substantially in their objectives, methods, study populations, health care setting which is very different from one country to another [60-66]. It is not really possible to compare the studies but they all seem to agree in their general findings: the inflammatory activity and gradual physical impairment associated with RA and AS leads to substantially increased health care costs, severe limitations in the ability to work and reduced quality of

life. Functional disability has been identified as by far the strongest predictor of costs, while disease activity appears to play a minor role as well [67-74].

The association of disease activity as measured with the BASDAI score and functionality measured with BASFI is shown in **Figure 7** [73]. **Figure 8** shows that the increase in cost does not only relate to treatment but that also indirect costs such as that of early retirement and hospital services increase in patients with higher BASDAI combined with BASFI.

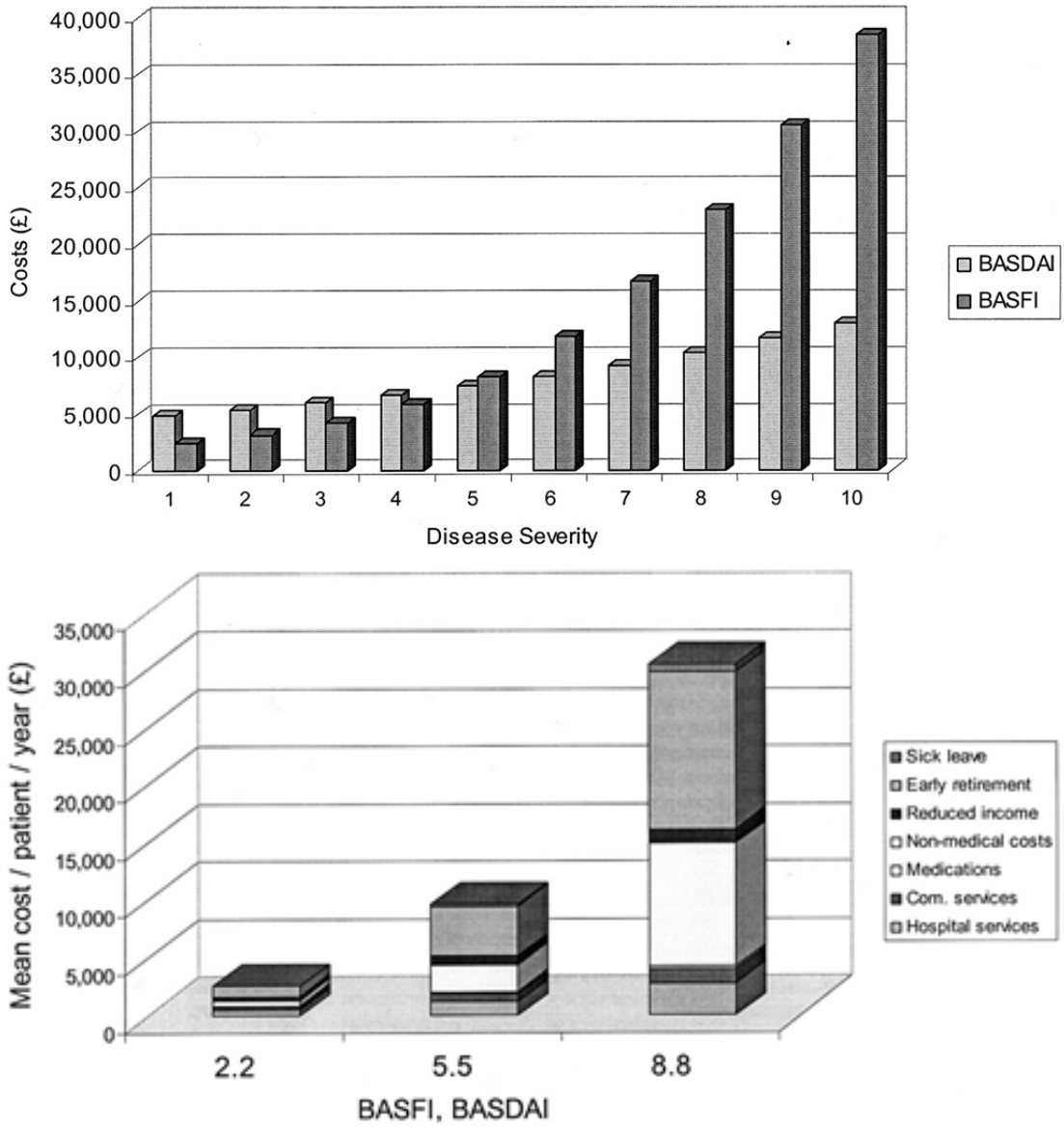

FIG. 7 and 8: *Influence of disease severity as measured by BASDAI and BASFI scores on cost of care in ankylosing spondylitis patients. From Kobelt G et al. Rheumatology. 2004; 45:1158-1166.*

The annual cost of RA management according to health state and disease activity state are summarized in **Table 5** [68-72, 74, 75]. This highlights how also indirect costs, which do not include medicine, have a tremendous impact especially in patients who are not in a controlled disease state.

Mean annual cost of RA according to disease severity levels (HAQ)

HAQ score	Sweden n=183 None on biologic (68)			United Kingdom n=916 None on biologic (68)			Canada n=1086 On biologic (74)	HAQ score	Germany (69)	Sweden (70)	Netherlands (71,72)
	Direct	Indirect	Total	Direct	Indirect	Total	Total		Sick leave	Disability (HCA)	Disability (FCA)
<0.6	$723	$0	$723	$1,228	$148	$1,376	$4,157	≤1.2	€ 856	€ 4,731	€ 752
0.6 < 1.1	$1,293	$5,997	$7,290	$3,152	$2,524	$5,676	$5,073				
1.1 < 1.6	$1,924	$8,524	$10,448	$2,091	$3,474	$5,565	$5,645	1.2 - 1.7	€ 3,212	€ 12,707	€ 2,019
1.6 < 2.1	$3,672	$15,588	$19,260	$3,087	$5,300	$8,387	$9,861				
2.1 < 2.6	$3,363	$24,838	$28,201	$3,401	$8,070	$11,471	$14,225	> 1.7	€ 7,619	€ 18,894	€ 3,002
≥2.6	$1,782	$27,067	$28,849	$2,697	$8,407	$11,104					

Annual Cost Per RA Patient per disease activity level measured with DAS28 or SDAI

Disease State	87% on biologic (total n=1086) Mean (95% CI) Total Healthcare service utilization costs in Canadian Dollar (75)		36.2% on biologic (total n=356) Mean Costs (SD) in Euros within different levels disease state (76)			
			Resource use	Sick leave	Work disability (HCA)	Work disability (FCA)
	DAS28	SDAI	SDAI	SDAI	SDAI	SDAI
In Remission	n = 175, $3130 (2644–3617)	n = 46, $2945 (1771–4120)	€828.28 (2,491.24)	€1,285.2 (1,502.1)	€5,772.8 (3,388.7)	€917.5 (538.3)
In Low Disease Activity	n = 911, $5992 (5333–6652)	n = 1040, $5670 (5075–6266)	€1,039.02 (2,561.41)	€1,874.2 (2,185.9)	€7,186.6 (4,864.9)	€1,142.1 (772.8)
In Median or High Disease Activity			€1,702.39 (3,500.74)	€3,291.9 (2,871.3)	€10,525.7 (6,129.2)	€1,672.5 (973.7)

TABLE 5: *Mean annual cost of RA according to disease severity as measured by DAS28 and HAQ scores. From Vastesaeger et al., submitted manuscript.*

Use of medicine and combination of drugs – NSAIDs, DMARDs and biologics – requires physicians to balance the anticipated benefits with the risks and cost. More intensive treatment strategies in which combination of immune-modulator agents is used tends to be more effective and induces remission more frequently than treatment strategies that do not include immune-modulators or use only one DMARD agent in RA [53-56]. Since NSAIDs may have effects on progression of ankylosis In Axial SpA whereas solid proof of such effect from anti-TNFα agents currently does not exist, there is a scientific and clinical basis to use combination of these 2 therapies also in this disease. If peripheral arthritis is present, also sulphasalzine is frequently combined with an anti-TNFα agent with or without an NSAID [77-80]. RA and AS are chronic diseases and in the absence of a possibility to cure, biologic agents are frequently continued for many years and even life-long after they are started. This results in a large increase of costs to manage these disorders.

In the EULAR recommendations for the management of RA, the individual, societal and medical costs of RA patient management should be considered by the treating rheumatologist when selecting a treatment strategy. The high cost of modern therapies including anti-TNFα should be considered specifically [49] and are a reason why DMARDs are recommended before biologics are used. Biologic use in immune-modulator naïve RA patients with inflammatory pathology is however approved per label (approved labels for various biologics are available on http://www.ema.europa.eu/ema/). Reimbursement and consequently use of biologic agents in clinical practice is usually also restricted to the more severely ill patients and those in whom one or more previous DMARDs have failed. As such, disease control at a population level is achieved through 'trial and error strategy' of a predefined sequence of medicine (i.e. step up therapy) in which more effective and expensive agents are reserved to patients with longer disease duration and in those who are refractory to several previous agents. However, also the likelihood of these agents to achieve profound disease control or remission goes down in patients with longstanding and refractory disease [81, 82]. In addition, a prolonged state of non-controlled synovitis leads to continued progression of radiographic damage and irreversible disability.

In 2013 the therapeutic area of rheumatology was the 2nd largest worldwide drug market (after oncology) with sales of anti-rheumatic agents being worth $ 44.9 billon. Analysts predict it will continue to grow over the next 6 years towards 57.1 billion USD market in 2020, only surpassed by oncology and anti-diabetic agents [83]. These numbers reflect the widespread use of the biological drugs which is a testimony to the benefits they bring to individual patients and explains the willingness of society to pay or reimburse. At the same time, in an era of financial crisis physicians, hospital management and governments need to keep the increasing health care costs under control. Beyond the already described treatment recommendations and reimbursement conditions, price reductions mandated by regulators and payers and price competition with other biological agents and biosimilar agents are ways to control cost as the number of patients treated with these agents continues to increase.

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Chapter 2: Research aims

Persistence of elevated disease activity and subsequent destruction of peripheral joints for Rheumatoid Arthritis (RA) and ankylosis of the axial joints & spine for Axial Spondyloarthritis (SpA) lead to functional impairment and disability, which may be irreversible.

The 2 outcomes that RA treatment recommendations focus on are avoidance of poor prognosis and achievement of a controlled disease activity state. The therapeutic goal for treatment of RA is to achieve remission or low disease activity and when that is not achieved with non-biologic Disease Modifying Anti-Rheumatic Drugs (DMARDs); rheumatologists should use presence of poor prognostic factors to decide whether or not to add a more expensive biological agent. Once persistent disease activity control is then installed, tapering and/or discontinuation of that biologic can be considered.
A treatment goal has not been adopted in the management guidelines of Axial SpA and use of outcome-predictors to guide treatment choice is not recommended at this time either. Biological agents should be used as second-line agents in this disease when elevated disease activity persists in spite of repeated trial with Non-Steroidal Anti-Inflammatory drugs (NSAIDs).
There is limited understanding of what really drives clinical decision for these diseases in daily practice. In addition, even if there has been a lot of research to identify outcome-predictors, it is not well understood how they should be used in treatment recommendations and in the clinic to ensure that the appropriate anti-TNF treatment candidates are selected for treatment. Both aspects have been investigated as part of this thesis.

In light of this, the research questions in this thesis were:

- What are the characteristics of RA and Axial SpA patients that rheumatologists select for treatment with an anti-TNF agent?
- How can disease characteristics that predict treatment outcome be used to decide when to start anti-TNF in clinical practice?
- Can anti-TNF treatment be stopped for early Axial Spondyloarthritis patients who are in remission?

In **Chapter 3**, two studies that coincided with the introduction of biological therapy in RA and Axial SpA in Belgium, and that help understand what characteristics are relevant to clinicians who are making anti-TNF treatment decisions, are reported.
According to the protocol of the *Expanded Access Program (EAP)* in RA, physicians could decide whether there was a need to increase the dose of infliximab 22 weeks after treatment initiation.
In the AS project, for each patient included in the *Ankylosing Spondylitis Patients Epidemiological Cross-sectional Trial (ASPECT)*, rheumatologists were asked whether or not an anti-TNF agent had been initiated.
There were no requirements per protocol to adjust or initiate anti-TNF therapy in either study; this decision was at the discretion of the treating physician. The associations of a large number of demographic, disease specific, laboratory and imaging characteristics with the clinical decision to start (ASPECT) or adjust (EAP) anti-TNF therapy were used to discriminate the discretionary/intuitive treatment decision of a rheumatologist in clinical practice.

In **Chapter 4**, four studies that had as aim to investigate for which patients anti-TNF treatment would be most valuable as determined by the likelihood of achieving a desired outcome are reported.
Inspired by a model of poor prognosis of cardiovascular disease (SCORE), a post-hoc analysis of the *Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset (ASPIRE)* and the *Anti–Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT)* studies was initiated with the goal to create a model that can assist rheumatologists to make an informed treatment choice based on the risk of poor prognosis associated with a potential treatment choice. A number of research groups were approached to further explore the value and validity of our preliminary model in other RA databases. These data are briefly described in this chapter as well.
Since disease activity control is the goal of treatment in RA, prediction of this outcome and creating a similar model allowing to identify patients in whom anti-TNF treatment can install remission or low disease activity was included as secondary objective of the GO-MORE study. The report of this analysis is a second key paper on RA outcome prediction included in this thesis. Comparison of the analyses resulting from ASPIRE / ATTRACT with that of GO-MORE gives insight on what the consequences are of aiming for remission while selecting based on prognosis in RA.
The treatment objectives for Axial SpA are less clear and a lot of work is ongoing to refine the outcome instruments and to define treatment goals in this disease. Rather than focusing on one specific outcome at one specific time-point, a post-hoc analysis aimed at identifying baseline predictors of response 3 months after AND good disease activity state 6 months after initiation of anti-TNF therapy was done in the *Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy (ASSERT)* and *GO-RAISE* studies. This approach was chosen in order to obtain one model allowing the prediction of multiple outcomes of this disease. This is reported shown in the 3rd publication included in this chapter.
C-Reactive Protein (CRP) was retained as predictor in the work described above and it is a component of the Ankylosing Spondylitis Disease Activity Score (ASDAS) but not of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI; this is the most frequently used tool to select patients in clinical trials and for treatment with anti-TNF in clinical practice). The objective for the last paper presented in this chapter was to investigate the population profile (including CRP) of patients selected with ASDAS versus that of those selected with BASDAI. The hypothesis is that a better profile of selected population in terms of outcome predictors will lead to better outcomes in that population when treated with an anti-TNF agent.

Chapter 5 includes 3 publications from the *Infliximab as First Line Therapy in Patients with Early Active Axial Spondyloarthritis Trial (INFAST).* Part 1 of this study was a randomized comparison to understand whether patients with Axial SpA treated with infliximab plus naproxen have a higher likelihood to achieve remission than similar patients treated with placebo plus naproxen. In part 2, for patients achieving remission, a randomized withdrawal design to understand if disease control could be maintained without continued use of the anti-TF agent was chosen, and the role of NSAIDs (naproxen) in maintenance of biologic free-remission was explored. Hypothesizing that treatment discontinuation would be possible in case of a controlled disease state in early Axial SpA, prediction of which patients would achieve remission was an objective of this study and this is the 3rd manuscript in this chapter.

In **Chapter 6** a critical review of the RA and Axial SpA management recommendations is done. Specific proposals on how the clinical tools and data presented in **Chapter 4** and **Chapter 5** may help refine guidelines are formulated.

Chapter 3: Intuitive Anti-TNF alpha Treatment Decisions in Clinical Practice

Two studies that coincided with the introduction of biological therapy in RA and Axial SpA in Belgium, and that help understand what characteristics are relevant to clinicians who are making anti-TNF treatment decisions, are reported.

The epidemiology of ankylosing spondylitis and the commencement of anti-TNF therapy in daily rheumatology practice.

Vander Cruyssen B, Ribbens C, Boonen A, Mielants H, de Vlam K, Lenaerts J, Steinfeld S, Van den Bosch F, Dewulf L, Vastesaeger N.
Ann Rheum Dis. 2007 Aug; 66(8):1072-7. Epub 2007 Jan 29.

DAS28 best reflects the physician's clinical judgment of response to infliximab therapy in rheumatoid arthritis patients: validation of the DAS28 score in patients under infliximab treatment.

Vander Cruyssen B, Van Looy S, Wyns B, Westhovens R, Durez P, Van den Bosch F, Veys EM, Mielants H, De Clerck L, Peretz A, Malaise M, Verbruggen L, Vastesaeger N, Geldhof A, Boullart L, De Keyser F.
Arthritis Res Ther. 2005; 7(5):1063-71. Epub 2005 Jul 8.

3.1. The epidemiology of ankylosing spondylitis and the commencement of anti-TNF therapy in daily rheumatology practice

3.1.1. Abstract

Objectives

This study aimed to describe the epidemiology of ankylosing spondylitis (AS) in rheumatology practice at the beginning of the anti-TNF (tumor necrosis factor) era, and to evaluate the initiation of anti-TNF therapy in a clinical setting where prescription is regulated by the authority's imposed reimbursement criteria.

Methods

Between February 2004 and February 2005, all Belgian rheumatologists in academic and non-academic outpatient settings were invited to register all AS patients who visited their practice. A random sample of these patients was further examined by an in-depth clinical profile. In a follow-up investigation, we recorded whether patients initiated anti-TNF therapy and compared this to their eligibility at baseline evaluation.

Results

89 rheumatologists participated and registered 2141 patients; 1023 patients were clinically evaluated. These 847 fulfilled the New York modified criteria for definite AS and 176 for probable AS. The profile of AS in rheumatology practice is characterized by longstanding and active disease with a high frequency of extra-articular manifestations and metrological and functional impairment. At a median of 2 months after the clinical evaluation, anti-TNF therapy was initiated in 263 of 603 (44%) evaluable patients with definite AS and in 22 of 138 (16%) evaluable patients with probable AS (total 38%). More than 85% of the patients who started anti-TNF therapy had an increased Bath Ankylosing Spondylitis Disease Activity Index despite previous NSAID (non-steroidal anti-inflammatory drug) use.

Conclusions

Of a representative cohort of 1023 Belgian AS patients seen in daily rheumatology practice, about 40% commenced anti-TNF therapy. Decision factors to start anti-TNF therapy may include disease activity and severity.

3.1.2.Introduction

Ankylosing spondylitis (AS) is the prototype of spondyloarthropathy (SpA) characterized by sacroiliitis and may lead to a completely ankylosed spine in a substantial number of patients. In addition, peripheral arthritis and different extra-articular manifestations, such as gut inflammation and eye involvement, are common features that add to the burden of the disease.

Until recently, the therapeutic options for AS have been limited to non-steroidal anti-inflammatory drugs (NSAIDs), alongside education and physiotherapy (which remain the cornerstone of the treatment) [1, 2]. Disease modifying anti-rheumatic drugs (DMARDs) such as sulphasalazine and methotrexate (MTX), demonstrated little or no effect on axial disease and are recommended only in patients with peripheral arthritis [2–5]. However, tumor necrosis factor (TNF) inhibitors have recently been introduced in AS and have been shown to be effective drugs, improving the signs and symptoms of AS with a good benefit-risk profile [6–9]. With the aim of treating a population most likely to benefit (thus limiting widespread use of these expensive agents), recommendations on TNF agent use have been formulated by national [10] and international experts (for example, ASAS) [2, 11, 12] and served for prescription/reimbursement laws and guidelines in different countries. The aims of the present study were (1) to elucidate a profile of the Belgian AS population followed in daily clinical practice by rheumatologists in secondary and tertiary care centers at the time anti-TNF therapy was introduced for treating AS, and (2) to evaluate the proportion of AS patients starting anti-TNF therapy during the first year that these agents became available and determine the clinical characteristics of the patients who received them.

3.1.3.Methods

3.1.3.1. Rheumatologist selection

All Belgian rheumatology centers were contacted and asked to participate in this study.

In order to assure a representative sample, demographic data of the participants were collected and were compared with demographic data of the total Belgian rheumatologist population provided by the Royal Belgian Society of Rheumatology (KBVR-SRBR).

3.1.3.2. Patient selection

Rheumatologists registered, in a confidential logbook, the birth dates and initials of all AS patients visiting their outpatient clinic during the study period. The number of registered patients in the logbook served as a denominator for a random selection of AS patients in whom the disease was documented further. For the in-depth clinical evaluation, every week's first and fourth registered patient was evaluated using the study's case report form. If a patient was already included or refused to participate, the next consecutive patient of the same week was evaluated. This selection method was preferred over inclusion of consecutive patients as it allowed for time distribution of the amount of study related work, especially in academic centers. The maximum number of patients included per rheumatologist was limited to 20, thereby ensuring the study population was distributed between the participating rheumatologists' sites. All patients were informed about the study before inclusion and gave written informed consent with regard to data privacy.

3.1.3.3. Study parameters

The following data were collected in all patients who were randomly selected for epidemiological profiling: demographic data, previous and current pain patterns, peripheral disease, previous and current clinical extra-articular disease (psoriasis, inflammatory bowel disease, uveitis), surgery, and

comorbidities (arthroplasty, osteoporosis, spinal fracture). The following composite indices were evaluated: Bath Ankylosing Spondylitis Functionality Index (BASFI: 0–10 rated on a numerical rating scale), [13] Bath Ankylosing Spondylitis Disease Activity Index (BASDAI: 0–10 rated on a numerical rating scale) [14] numerical scale and the components of the Bath Ankylosing Spondylitis Metrology Index (BASMI) [15] Laboratory testing included available HLA-B27 status and latest available C reactive protein (CRP) value. Available radiographic data assessed were as follows: grading of the individual sacroiliac joints, presence of syndesmophytes, or presence of an ankylosis on latest available x rays. Patient history was also documented, including first degree family history of inflammatory diseases collected for AS, inflammatory bowel disease (IBD), uveitis, psoriasis, psoriatic arthritis, as well as current and previous treatment included physiotherapy, NSAIDS (including duration and types of NSAIDs), corticosteroids, sulphasalazine, methotrexate, azathioprine, TNF blockers. For further analyses, patients who fulfilled the New York modified criteria for AS were categorized as having definite AS or probable AS [16] (**Table 16**). Also, for each patient, fulfilment of ASAS recommendations to start anti-TNF therapy was computed. For this study, this implied that AS patients should have tried at least two NSAIDs and have a BASDAI ⩾4 before starting anti-TNF therapy [2, 11, 12, 17].

(1) Low back pain with inflammatory characteristics
(2) Limitation of lumbar spine motion in sagittal and frontal planes
(3) Decreased chest expansion
(4) Bilateral sacroiliitis grade 2 or higher
(5) Unilateral sacroiliitis grade 3 or higher
*Definite AS when the fourth or fifth criterion mentioned presents with any clinical criteria

TABLE 16: *New York modified criteria (1984) for ankylosing spondylitis**

During an inquiry, approximately one year after the collection of all the above information, rheumatologists were asked to indicate whether anti-TNF therapy was initiated in their patients. Rheumatologists were not informed beforehand that that this query would take place.

3.1.3.4. Quality assurance

The protocol and file were developed by collaboration of a board of academic and non-academic rheumatologists and the study sponsor (Schering Plough). The protocol was designed to allow the maximum amount of data to be captured in a minimum amount of time during daily clinical practice. The CRF was tested in a peripheral Centre (JL) on five patients and adapted according to the suggestions before its use in the protocol. The protocol was approved by the Belgian national license bureau for non-interventional research (Pharma.be) for good clinical practice and ethical approval.

In order to ensure data quality, two independent data nurses were assigned to the project and checked informed consents of all patients, logbooks, and CRF completeness.

3.1.3.5. Time frame

In-depth profiling of patients occurred at one visit between February 2004 and February 2005. Between December 2005 and January 2006, rheumatologists were retrospectively asked whether anti-TNF therapy was initiated since that in-depth profile.

3.1.3.6. Study era and background

At that time infliximab (March 2003) and etanercept (November 2003) were registered but are reimbursed from March 2004 and September 2004, respectively. Between December 2005 and January 2006, rheumatologists were asked whether patients had started anti-TNF therapy since that clinical evaluation. The reimbursement of anti-TNF therapy in Belgium is similar for both drugs. To satisfy conditions set by the authorities. patients must fulfil the modified New York criteria for AS, insufficiently respond to conventional therapy, and present with the following: (1) severe axial symptoms reflected by a BASDAI $\geqslant$4; (2) a CRP value higher than the upper limit of normal for the applicable laboratory (without specification about the time point that CRP must be elevated); (3) unless contraindicated, an insufficient response to previous optimal use of at least two NSAIDs at anti-inflammatory doses for at least three months; and (4) an absence of active or latent tuberculosis. Furthermore, anti-TNF treatment can only be prescribed by a board certified rheumatologist.

3.1.3.7. Statistical analyses

Consistent with the epidemiological objective of the study, descriptive statistics were used for the data. Differences between subgroups were compared by means of a Mann-Whitney test for continuous variables and $\chi 2$ statistics for dichotomous data. Logistic regression models were fitted using the significant variables of a univariate analysis and after backward elimination using p values of 0.05 for removal. Different interaction terms were initially added to the models (but none remained in the final models). Analyses were performed by the commercially available statistical package SPSS 12.0 (Chicago, IL, USA).

3.1.4.Results

3.1.4.1. Enrolment of rheumatologists

Eighty-nine of all 204 (44%) board certified Belgian rheumatologists from 57 centers agreed to participate in the study. The majority of those rheumatologists (75%) worked in non-academic centers; 45 of them worked in the French speaking part and 44 in the Dutch speaking part of Belgium; 40/49 rheumatologists were female/male. When comparing these rheumatologist demographics with the data provided by the Belgian rheumatologists' society, KBVR-SRBR, there were no significant differences with regard to sex, type of practice, and geographical distribution. The mean study participation of the rheumatologists was 15 weeks (SD 7.4). Each week, the rheumatologists saw a mean of 2.2 AS patients (range 1–7, interquartile range 1.4).

3.1.4.2. Evaluation of the patients' sampling

In the logbooks, 2141 AS patients were registered. The planned in-depth profiling was further conducted in 1023 patients. All patients fulfilled modified New York classification criteria [16] 647 (83%) patients were classified as definite AS and 176 remained as probable AS (**Figure 9**). The lag time between CRP measurement and the clinical evaluation was median 0 months (interquartile range 0.6 months). The lag time between radiology and the clinical evaluation was median 0.5 year (interquartile range 1.8).

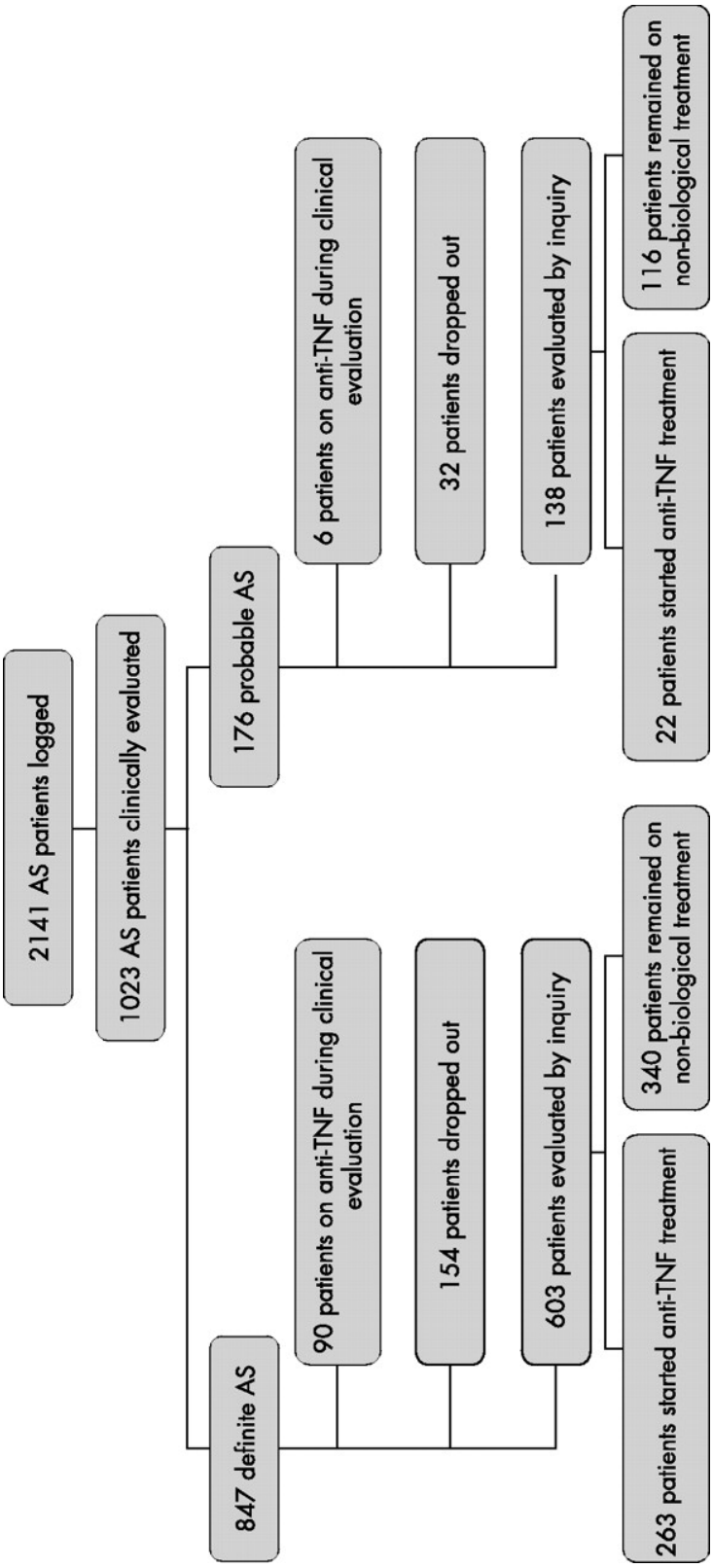

FIG. 9: *Patient flow chart. AS, ankylosing spondylitis; TNF, tumor necrosis factor.*

3.1.4.3. Comparison of patients with definite and probable AS

Table 7 describes the baseline characteristics of the AS patients. An important difference between patients with definite AS and patients with probable AS is the difference of symptom duration, which is significantly higher in patients with definite AS ($p<0.001$). Patients with definite AS also had a higher disease activity (higher BASDAI, BASFI, and elevated CRP) and disease severity (higher BASMI, more syndesmophytes, bamboo spine, and hip involvement).

Baseline evaluation	Definite AS (n = 847)	Probable AS (n = 176)	p Value
Male sex	68%	49%	<0.001
HLA-B27 (n = 816)	83%	77%	0.074
Ever arthritis	58%	56%	0.576
Ever enthesitis	50%	52%	0.573
Elevated CRP	37%	18%	<0.001
Syndesmophytes	49%	15%	<0.001
Bamboo spine	21%	0%	<0.001
Hip involvement	27%	15%	<0.001
BASDAI*	5.3 (2.1)	4.7 (2.0)	<0.001
BASDAI ⩾4	75%	66%	0.014
BASFI*	5.1 (2.5)	3.6 (2.4)	<0.001
BASMI*	3.6 (2.4)	2.4 (1.7)	<0.001
Symptom duration*	18.0 (12)	9.3 (9)	<0.001
Disease duration*	12.0 (66)	5.8 (40)	<0.001
Disease duration <1 month	6%	12%	0.003
Age*	45 (11)	40 (12)	<0.001
Psoriasis	11%	11%	0.846
Uveitis (ever)	27%	17%	0.002
Crohn's disease	8%	7%	0.854
Ulcerative colitis	3%	2%	0.678
Ever MTX	19%	18%	0.616
Ever SSZ	61%	53%	0.056
Ever azathioprine	4%	7%	0.102
At least 2 NSAIDs used	92%	82%	0.001
Current NSAIDs	72%	63%	0.020

TABLE 7: *Description of patients at baseline.* Definite AS and probable AS are defined according to the *New York modified criteria [16]. Percentages are given, except for continuous data: *mean (SD).*

3.1.4.4. Anti-TNF therapy in AS patients

At the time of the clinical evaluation (between February 2004 and February 2005), 90 (11%) patients with definite AS and six (3%) patients with probable AS were already being treated with anti-TNF therapy. Most of these patients received anti-TNF therapy in the context of studies or medical need programs. These patients were further excluded from the analysis.

Of the remaining patients, 603 were evaluable for the inquiry into anti-TNF treatment (between December 2005 and January 2006); 263 of those patients with definite AS started anti-TNF therapy. The lag time between the clinical evaluation of the patient and the start of anti-TNF therapy was estimated as median 2 months (range 0–23 months, interquartile range 5 months). In 121 patients, this lag time was less than 1 month. Table 8 describes the differences in baseline characteristics in function of the initiation of anti-TNF treatment.

	Definite AS				Probable AS		
Baseline evaluation	Without anti-TNF at query (n = 340)	With anti-TNF at query (lag time <1 month) (n = 121)	With anti-TNF at query (all patients) (n = 263)	p Value	Without anti-TNF at query (n = 116)	With anti-TNF at query (n = 22)	p Value
MALE	60%	73%	73%	0.001	46%	64%	0.123
HLA-B27	77%	92%	88%	0.001	76%	68%	0.451
Arthritis	22%	27%	29%	0.029	28%	46%	0.114
Enthesitis	17%	17%	21%	0.206	24%	27%	0.754
Elevated CRP	26%	56%	48%	<0.001	16%	18%	0.840
Syndesmophytes	38%	57%	45%	<0.001	16%	15%	0.920
Bamboo spine	16%	25%	24%	0.023	0%	0%	NA
Hip involvement	22%	37%	36%	<0.001	14%	32%	0.038
BASDAI*	4.7 (2.2)	6.4 (1.6)	6.1 (1.7)	<0.001	4.4 (2.0)	6.0 (1.6)	0.001
BASFI*	4.4 (2.6)	6.1 (2.0)	5.9 (2.3)	<0.001	3.2 (2.2)	5.6 (2.0)	0.000
BASMI*	3.0 (2.3)	4.1 (2.2)	4.0 (2.4)	<0.001	2.3 (1.6)	2.9 (1.8)	0.179
Age*	45 (11)	44 (11)	44 (11)	0.094	40 (12)	38 (12)	0.607
Symptom duration	18 (12)	19 (13)	19 (13)	0.163	10 (8)	11 (9)	0.286
Psoriasis	10%	12%	12%	0.560	9%	23%	0.051
Uveitis	25%	26%	31%	0.096	12%	32%	0.018
IBD	9%	9%	10%	0.901	5%	14%	0.116
Any extra-articular manifestation	39%	42%	44%	0.342	23%	55%	0.003
BASDAI ⩾4	63%	95%	90%	<0.001	60%	91%	0.006
BASDAI ⩾4 and failing NSAID	55%	90%	85%	<0.001	51%	84%	0.008
BASDAI ⩾4 and failing NSAID + elevated CRP at evaluation	17%	55%	45%	<0.001	22%	8%	0.085

TABLE 8: *Description of patients with AS as a function of the presence of anti-TNF treatment at inquiry. Definite AS and probable AS are defined according to the New York modified criteria [16] Percentages are given, except for continuous data: * mean (SD). P Values are calculated for the contrast without anti-TNF at inquiry vs with anti-TNF at inquiry for all patients.*

Table 9 shows that patients who started anti-TNF therapy, stratified for whether or not they fulfilled the ASAS recommendations [2], tended to have a higher disease activity, more functional impairment, and a worse metrology.

	No fulfilment of ASAS criteria[2] BASDAI <4 or no NSAID failing			Fulfilment of ASAS criteria[2] BASDAI ⩾4 and failing NSAID		
	Without anti-TNF at query (n = 131)	With anti-TNF at query (n = 34)	p Value	Without anti-TNF at query (n = 160)	With anti-TNF at query (n = 187)	p Value
BASDAI						
- Mean	3	3.7	0.041	6.2	6.5	0.028
- SEM	0.13	0.34		0.11	0.09	
BASFI						
- Mean	3.1	3.6	0.3	5.6	6.2	0.005
- SEM	0.18	0.41		0.18	0.14	
BASMI						
- Mean	3	3.3	0.5	3.3	4.3	0.002
- SEM	0.25	0.38		0.22	0.26	

TABLE 9: *BASDAI, BASMI, and BASFI as a function of the fulfilment of the ASAS criteria and the decision to start anti-TNF treatment.*

Different logistic regression models (Table 10) to predict the start of anti-TNF therapy were fitted after backward elimination of the significant variables of Table 8. Model 1 was fitted in a subgroup of 121 patients with definite AS who started anti-TNF treatment within 1 month after the in-depth profiling. This model revealed that BASDAI, CRP, and HLA-B27 significantly contributed to the model, with the highest contribution for BASDAI and the lowest contribution for CRP. Model 2 was fitted in the subgroup of patients with probable AS and highlighted the potential added value of the presence of extra-articular manifestations in this subgroup of patients. Finally, model 3 was fitted in the total population and highlighted the added value of hip involvement, BASFI, male sex, and a definite diagnosis of AS.

Model 1 Inclusion: patients with definite AS and a lag time to start anti-TNF therapy <1 month			
	Beta	p Value	OR (95% CI of OR)
Elevated CRP	1.089	0.005	2.972 (1.385 to 6.377)
Carriage of HLA-B27	1.473	0.022	4.361 (1.242 to 15.316)
BASDAI >4	2.051	0.001	7.774 (2.266 to 26.668)
Intercept	−4.800	0.000	.008

Model 2 Inclusion: patients with probable AS			
	Beta	**p Value**	**OR (95% CI of OR)**
Presence of any extra-articular manifestation	0.778	0.027	2.177 (1.093 to 4.338)
BASDAI >4	1.806	0.019	6.084 (1.338 to 27.656)
Intercept	−3.388	0.000	.034
Model 3 Inclusion: all probable and definite AS patients			
	Beta	**p Value**	**OR (95% CI of OR)**
NYm_Def	1.056	0.001	2.876 (1.533 to 5.394)
Elevated CRP	0.736	0.000	2.087 (1.383 to 3.150)
Hip involvement	0.635	0.005	1.887 (1.214 to 2.932)
HLAB27	0.619	0.019	1.858 (1.106 to 3.121)
Male sex	0.504	0.016	1.655 (1.098 to 2.493)
BASDAI*	0.228	0.001	1.256 (1.102 to 1.431)
BASFI*	0.114	0.041	1.121 (1.005 to 1.251)
Intercept	−3.862	0.000	.021

TABLE 10: *Result of a logistic regression model to predict the start of anti-TNF therapy in AS patients. OR, odds ratio; 95% CI, 95% confidence interval; CRP, C reactive protein; BASDAI, Bath ankylosing spondylitis disease activity index; BASFI, Bath ankylosing spondylitis functional index. *BASDAI and BASFI were considered as continuous variables in model 3.*

3.1.5.Discussion

This study describes a representative, nationwide sample of Belgian AS patients, followed at different academic and non-academic centers. Patients were included based on clinical expert diagnosis for AS: 83% of them fulfilled the New York modified criteria for definite AS and 17% of patients were considered as probable AS [16]. This clearly shows that, in daily clinical practice, rheumatologists care for a substantial number of AS patients not fulfilling the definite criteria, and this group should receive the attention they merit [16]. Not surprisingly, patients with probable AS showed a lower radiological grading of sacroiliac joints on conventional radiographs (Table 7). Also, they had a shorter disease duration and it thus might be hypothesized that at least a subgroup of those patients would fulfil the criteria for definite diagnosis if followed up for a longer time (Table 7) [18] A longer disease duration may account for the more severe disease (higher BASMI [15], more syndesmophytes, bamboo spine, and hip involvement) in patients with definite AS [19–21].

The profile of definite AS patients was characterized by longstanding, severe, and active disease with a high frequency of comorbidities and important metrological restriction and functional impairment. Also, most patients followed up in rheumatology practice have active disease, which was reflected by a mean BASDAI of 5.3 (SD 2.1) and a mean BASFI of 5.1 (SD 2.5) (Table 7).

The high frequency of comorbidities, functional impairment, and active disease despite optimal use of NSAID therapy explains why anti-TNF therapy was initiated in a large proportion of AS patients. After one year, anti-TNF therapy was initiated in 44% of the patients with definite AS and in 16% of patients with probable AS. The need for anti-TNF therapy was previously estimated as 30% [10] to 49% (38%–78%) [17]. While these studies asked the treating rheumatologist whether they thought the patient

would need to be treated by a TNF blocker, the present study evaluated the effective start of anti-TNF therapy under the regulation of reimbursement criteria.

In accordance with ASAS guidelines and Belgian reimbursement criteria, an elevated BASDAI is the main characteristic of patients with probable and definite AS, who start anti-TNF therapy. More than 90% of patients who started anti-TNF therapy had a BASDAI ⩾4 [17, 22] However, other recommendations given by the Belgian reimbursement criteria appeared to add little value to the BASDAI. Although a significant contributor in two of the logistic regression models (Table94, model 1, model 3), the value of an increased CRP seems to be moderate since less than half of the patients who started anti-TNF therapy had an elevated CRP at the time of the clinical evaluation. The finding that a number of patients who started on anti-TNF therapy had a normal CRP may be explained by the fact that the reimbursement criteria do not require an elevated CRP when the decision is made to start anti-TNF therapy (that is, the criteria can be interpreted as requiring an elevated CRP at any time in disease course).

At least two NSAIDs were used in more than 90% of patients with definite AS involved in this cohort. This suggests that trying different NSAIDs is commonly used in the Belgian daily clinical rheumatologists' practice and thus should be recommended before starting anti-TNF therapy.

A high BASDAI is not the sole criterion on which the physician decides to start anti-TNF therapy. In both probable and definite AS patients, functional impairment and hip arthritis (Table 10) also seemed to be contributing in the decision to start anti-TNF therapy. Although the presented logistic models require further validation, it is an interesting finding that HLA-B27 positivity came up in two models (Table 10, model 1 and 3). It can be hypothesized that physicians do not decide on HLA-B27 itself but rather on associated variables, such as earlier onset, comorbidities, or severity of AS [23–26].

One additional important finding in this study was that anti-TNF therapy was started in a small proportion of patients who did not have a definite diagnosis of AS. Our data suggest that the decision to start anti-TNF therapy in this subgroup of patients might be justified by the extra-articular manifestations in half of these patients with probable AS (Table 8). This has also been suggested in the logistic regression model (model 2 in Table 10) and may suggest that comorbidities contributing to the burden of disease can be independent reasons to start anti-TNF therapy [27].

A few limitations of the study should also be noted. Firstly, the clinical evaluations were performed at a distance from the initiation of the therapy. This time lag was important to avoid the suggestion that patients were encouraged to overestimate their BASDAI in order to fulfil the reimbursement criteria. Although this time lag was limited (with a median of 2 months) changes in disease activity and treatment during this time lag might explain why some patients not fulfilling the reimbursement criteria started anti-TNF therapy and, inversely, why some patients with a high BASDAI at the clinical evaluation did not receive anti-TNF therapy. Secondly, a selection towards a more active and severe disease course may have occurred as patients who visited the rheumatologist more frequently may have had a higher probability of being included in this study. Finally, it is important to stress that some AS patients may be treated by generalists or orthopedic surgeons who have no access to anti-TNF therapy. These patients were not sampled in this study.

In conclusion, we described a large cross sectional cohort of Belgian AS patients. These data provide important information on clinical and radiological features of the disease. Some patients started anti-TNF therapy despite not fulfilling the reimbursement criteria and, inversely, other patients did not start anti-TNF therapy despite fulfilling the recommendations. Recommendations play a major part when

starting TNF inhibitors. However, in daily clinical practice other factors, dealing with the expert's opinion and patients' needs and expectations, also contribute to the decision to start TNF blocking therapy.

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3.2. DAS28 best reflects the physician's clinical judgment of response to infliximab therapy in rheumatoid arthritis patients: validation of the DAS28 score in patients under infliximab treatment.

3.2.1. Abstract

This study is based on an expanded access program in which 511 patients suffering from active refractory rheumatoid arthritis (RA) were treated with intravenous infusions of infliximab (3 mg/kg + methotrexate (MTX)) at weeks 0, 2, 6 and every 8 weeks thereafter. At week 22, 474 patients were still in follow-up, of whom 102 (21.5%), who were not optimally responding to treatment, received a dose increase from week 30 onward. We aimed to build a model to discriminate the decision to give a dose increase. This decision was based on the treating rheumatologist's clinical judgment and therefore can be considered as a clinical measure of insufficient response. Different single and composite measures at weeks 0, 6, 14 and 22, and their differences over time were taken into account for the model building. Ranking of the continuous variables based on areas under the curve of receiver-operating characteristic (ROC) curve analysis, displayed the momentary DAS28 (Disease Activity Score including a 28-joint count) as the most important discriminating variable. Subsequently, we proved that the response scores and the changes over time were less important than the momentary evaluations to discriminate the physician's decision. The final model we thus obtained was a model with only slightly better discriminative characteristics than the DAS28. Finally, we fitted a discriminant function using the single variables of the DAS28. This displayed similar scores and coefficients as the DAS28. In conclusion, we evaluated different variables and models to discriminate the treating rheumatologist's decision to increase the dose of infliximab (+MTX), which indicates an insufficient response to infliximab at 3 mg/kg in patients with RA. We proved that the momentary DAS28 score correlates best with this decision and demonstrated the robustness of the score and the coefficients of the DAS28 in a cohort of RA patients under infliximab therapy.

3.2.2.Introduction

Rheumatoid arthritis (RA) is a complex disease with a broad spectrum of manifestations that requires an early intensive therapy in order to avoid joint destruction and physical disability. In order to measure the effect of therapy in daily practice and in clinical trials, many variables are recorded and different composite indices have been proposed to measure the remaining disease activity or the response to treatment. Those variables may cover items such as patient self-reported questionnaires, physician's scores including different joint scores, and serum markers of systemic inflammation.

Infliximab, in combination with methotrexate (MTX), is a highly effective therapy for a majority of RA patients. After an induction scheme at weeks 0, 2 and 6, the indicated dose of this therapy is 3 mg/kg every 8 weeks, although the ATTRACT trial suggested that a higher dose of 10 mg/kg every 8 weeks or a shorter perfusion interval may add benefit [1-3].

The present study is based on an expanded-access program in which patients suffering from active refractory RA were treated with intravenous infusions of infliximab (3 mg/kg + MTX) at weeks 0, 2, 6 and every 8 weeks thereafter. At week 22, patients not optimally responding to treatment could receive a dose increase of 100 mg (1 vial) per infusion from week 30 onwards [4]. The effect of dose escalation for the patients of this cohort has been discussed previously [4]. The decision to increase the dose was based on the treating rheumatologist's clinical judgment and can be considered as a measure of insufficient response to infliximab. It might be questioned which variables can be measured to best evaluate the effect of therapy and remaining disease activity in daily practice (and in clinical trials). The aim of the present analyses was to evaluate whether the decision to increase the dose could be reflected by using single variables or composite indices, alone or together in a model. We also wanted to evaluate whether this decision was mainly based on differences over time or on momentary disease activity.

3.2.3.Methods

3.2.3.1. Study population

A total of 511 patients, suffering from active refractory RA [5], were treated with intravenous infusions of infliximab (3 mg/kg) at weeks 0, 2, 6 and every 8 weeks thereafter in combination with MTX (a minimal dose of 15 mg/kg was recommended). Between week 0 and week 22, 37 patients dropped out for the following reasons: 16 patients stopped due to side effects (four infusion reactions, five infections, one malignancy, one pancytopenia, five disease-related complications), 12 patients stopped for withdrawal of consent and 9 patients stopped for protocol violation. Of the remaining 474 patients, 102 (22%) patients, who were not optimally responding to treatment according to the treating rheumatologist's opinion, received a dose increase of 100 mg (1 vial) per infusion from week 30 on. Throughout the first 22 weeks, dosage of MTX, steroids and non-steroidal anti-inflammatory drugs remained unchanged.

3.2.3.2. Evaluated variables

When designing the model, we took the following single variables into account at weeks 0, 6, 14 and 22: 28 and 66/68 swollen/tender joint counts, erythrocyte sedimentation rate (ESR; mm/h), C-reactive protein (CRP; mg/l), Health Assessment Questionnaire (HAQ; 0–3), physician's global assessment of disease activity (visual analogue scale (VAS); 0–100 mm), patient's global assessment of disease activity (VAS 0–100 mm), patient's assessment of pain (VAS 0–100 mm), patient's assessment of fatigue (VAS 0–100 mm) and all subscales of the SF-36 questionnaire (0–100 points) [6]. DAS28 (Disease Activity Score

including a 28-joint count) [7] and other composite scores such as simplified disease activity index (SDAI), clinical disease activity index (CDAI) [8, 9] and the alternative DAS28 scores [10, 11] (**Table 11**) were calculated after data collection so that the treating rheumatologist was unaware of the exact values of those composite scores. Also, differences over time and the DAS28 response (no, moderate or good) and the ACR (American College of Rheumatology) response (no/20/50) were computed [12, 13].

Score	Formula	AUC (95% CI)	Sens at 95% spec, % (95% CI)
DAS28	0.56*sqrt(28TJC) + 0.28*sqrt(28SJC) + 0.70*ln(ESR) + 0.014*pt global VAS	0.840 (0.791–0.889)	42.5 (36.9–48.1)
DAS28-3	[0.56*sqrt(28TJC) + 0.28*sqrt(28SJC) + 0.70*ln(ESR)]*1.08 + 0.16	0.815 (0.763–0.868)	37.8 (32.3–43.3)
DAS28-CRP	0.56*sqrt(28TJC) + 0.28*sqrt(28SJC) + 0.36*ln(CRP+1) + 0.014* pt global VAS + 0.96	0.829 (0.782–0.876)	35.8 (30.4–41.2)
DAS28-CRP-3	[0.56*sqrt(28TJC) + 0.28*sqrt(28SJC) + 0.36*ln(CRP+1)] * 1.10 + 1.15	0.806 (0.755–0.858)	28.9 (23.8–33.9)
SDAI	28TJC + 28SJC + CRP/10 + pt global VAS/10 + phys global VAS/10	0.824 (0.776–0.873)	40.7 (35.1–46.2)
CDAI	28TJC + 28SJC + pt global VAS/10 + phys global VAS/10	0.821 (0.772–0.870)	37.8 (32.3–43.2)
DAS28-3 and DAS28-CRP-3 are the DAS28 and DAS28-CRP scores calculated without the patient's global disease activity VAS.			

TABLE 11: *Formulas to calculate the different DAS and SDAI score.*

3.2.3.3. Statistics

We opted to use only statistical methods that are available in a classical statistical package (SPSS 12.0; SPSS, Inc., Chicago, IL, USA) or could be computed manually. When needed, the continuous variables were normalized (by taking the square root of the joint counts and the natural logarithm of CRP and ESR). Robustness of the discriminant analyses and logistic regressions was confirmed by the use of a random train and test set. Missing values were handled by pairwise complete case analysis. This means that a case with no missing values for a group of variables is included in the analysis of that group of variables. The case may have missing values for variables used in other analyses. Confidence intervals (95% CI) for sensitivity or specificity were calculated based on the method proposed by Harper [14]. The areas under the curves (AUCs) of receiver operating characteristic (ROC) curves were calculated. A higher AUC indicates that a single variable has better discriminative characteristics. A statistical test to compare AUCs of two variables tested on the same population has been described by Hanley [15]. Continuous and categorical variables were compared by adapting the cut-off of the continuous variables to the same specificity level as the categorical variable so that sensitivities could be evaluated and compared [16]. The selection and comparison of variables by curve analysis was performed since this method gives a valid ranking of variables and does not (in contrast to ranking methods based on *p* values) depend on the number of subjects available for that specific variable [17]. In order to find the true maximal model and to avoid sticking at a local maximal model, we used different strategies for the construction of the final model: binary logistic regressions and discriminant analyses were performed

with the default options of SPSS 12.0 and stepwise construction of models was performed by conditional forward and backward elimination for logistic regression and by Wilk's lambda for discriminant analysis using the strategy described by Hosmer and Lemeshow [18].

3.2.3.4. Ethics

All patients signed informed consent. This study was approved by the local ethics committees.

3.2.4.Results

3.2.4.1. Ranking of continuous variables

In order to select the most important variables that correlate with the decision to give a dose increase at week 22, we calculated the AUC of ROC curve analysis for all continuous variables and ranked them based on this AUC [17]. Since crossing over of ROC curves may affect the diagnostic properties of a variable without changing the AUC, we also ranked the variables based on sensitivity levels by adapting the cut-off to a given pre-set specificity level of 95% [16].

Both ranking methods displayed that the DAS28 score at week 22 had the highest ability to discriminate the physician's decision to give a dose increase. **Table 12** displays the 10 most important variables ranked by AUC of ROC curve analysis and by the sensitivity at the 95% specificity level. Using the method described by Hanley [15], we found that there was a significant difference in AUC between the two first ranked parameters: DAS28 at week 22 and the 28 tender joint count at week 22 (AUC = 0.840 versus 0.797, p = 0.02). Additionally, most variables were ranked in such a way that each variable was represented first by its measure at week 22 before it was represented by a measure at another week.

	AUC	95% CI of AUC
DAS28 w22	0.840	0.791–0.889
28 TJC w22	0.797	0.744–0.850
Physician global VAS w22	0.786	0.736–0.836
Patient pain VAS w22	0.764	0.71–0.814
DAS28 w14	0.750	0.685–0.815
Patient disease activity VAS w22	0.750	0.689–0.802
66TJC w22	0.740	0.689–0.791
28TJC w14	0.721	0.662–0.780
66SJC w22	0.717	0.660–0.774
ESR w22	0.716	0.654–0.779

	Sensitivity (%) at 95% specificity level	95% CI of sensitivity
DAS28 w22	42.5	36.9–48.1
Physician global VAS w22	32.7	28.4–37.0
28SJC w22	29.8	24.7–34.9
Patient pain VAS w22	26.8	22.7–30.9
66SJC w22	24.5	20.6–28.4
ESR w22	24.1	19.7–28.5
66SJC w14	23.0	18.6–27.4
CRP w22	21.3	17.3–25.3
Patient disease activity VAS w22	20.4	16.6-4.2
DAS28 w14	20.3	15.3–25.3

TABLE 12: *Validation of the DAS28 score and coefficients (see text).*

3.2.4.2. Evaluation of the response scores

To evaluate categorical scores, we adapted the cut-off of the variable with the highest ranking (DAS28 at week 22) to the specificity of the categorical score and compared the sensitivities [16]. For the decision to give a dose increase, ACR response not reaching the ACR20 criterion ('no ACR response') had a sensitivity of 69.6% (95% CI: 65.2–74.0) and a specificity of 64.2% (95% CI: 59.6–68.8). When we adapted the cut-off of the DAS28 at week 22 to a specificity of 64.2% (DAS28 = 4.01), we obtained a sensitivity of 80.0% (95% CI: 75.2–84.7). 'No DAS28 response' had a sensitivity of 46.7% (95% CI: 40.8–52.6) and a specificity of 83.3% (95% CI: 78.9–87.7). When we adapted the cut-off of the DAS28 to a specificity of 83.3% (DAS28 = 4.77), we obtained a sensitivity of 67.5% (95% CI: 61.9–73.1). Similar results were obtained when looking at the ACR50 and the good DAS28 response criterion (Table 13).

	Sensitivity and specificity of the different response scores		Sensitivity of DAS28 at the same specificity level	
	Specificity (%)	Sensitivity (%)	Sensitivity (%)	According DAS28 score
No moderate DAS response	83.3	46.7	67.5	4.8
No good DAS response	42.4	96.3	97.3	3.1
No ACR20 response	64.2	69.6	80.0	4.0
No ACR50 response	33.6	85.9	97.5	2.9

TABLE 13: *Sensitivity and specificity of the response scores compared with DAS28 set at equal specificity.*

Additionally, we fitted a logistic regression model with the decision to give a dose increase as a dependent variable and DAS28 at week 22, DAS28 response and ACR response as categorical covariates. These analyses retained DAS28 at week 22 as the only significant covariate in the model (data not shown).

3.2.4.3. Effects of change of scores over time on the physician's decision

To evaluate the effect of differences over time, we plotted the means of the most important normalized continuous variables over time (Figure 10).

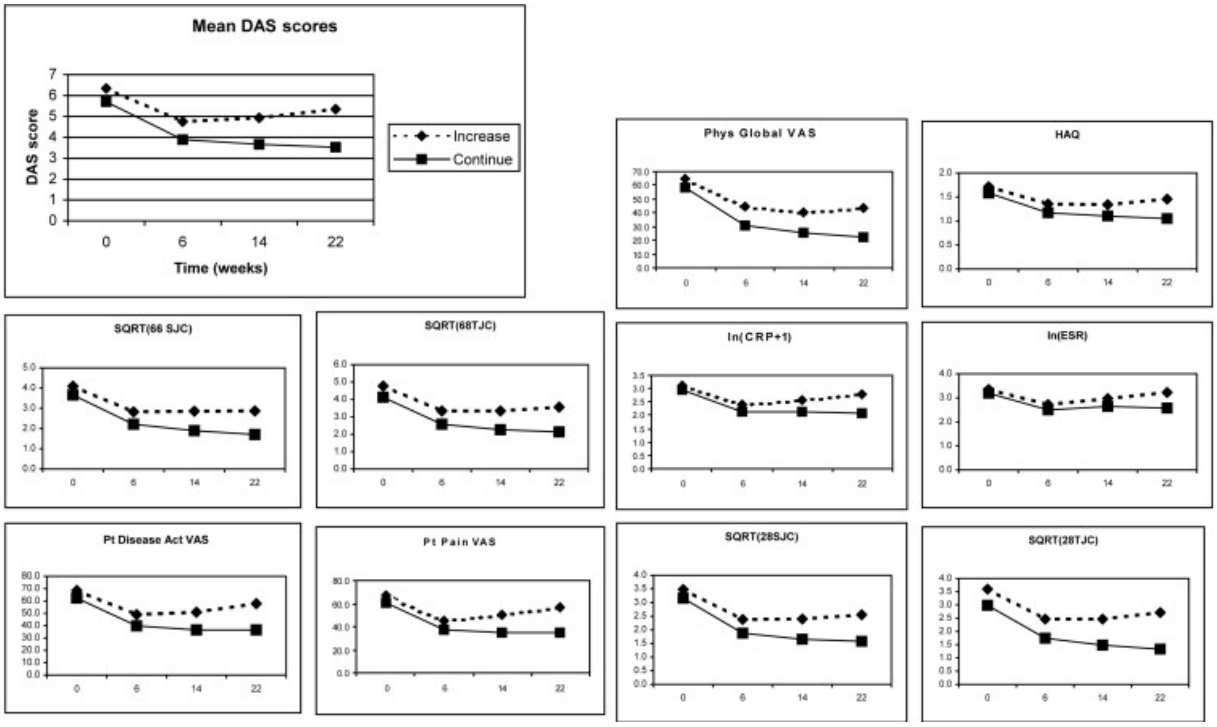

FIG.10. *Plot of the mean scores over time.*

The plot of the variable with the highest ranking (DAS28) shows that patients who get a dose increase have a (significantly) higher disease activity at baseline and, after an initial decrease of disease activity, regain disease activity from week 6 on. To evaluate this, we calculated differences in DAS28 scores between baseline and week 22 (delta DAS28 0–22), and between week 6 and week 22 (delta DAS28 6–22). Indeed, patients who get a dose increase regain some disease activity between week 6 and week 22 (mean delta DAS28 6–22: -0.4 versus +0.4, $p < 0.001$), which is reflected in a smaller decrease of disease activity between baseline, and week 22 (mean delta DAS28 0-22: -2 versus -1, $p < 0.001$). However, the AUC of the ROC curve of delta DAS28 0–22 was 0.725 (95% CI: 0.659–0.790) and the AUC for delta DAS28 6–22 was 0.672 (95% CI: 0.590–0.754), which is much lower than the AUC of the momentary DAS28 (0.840) at week 22. Additionally, when we fitted a logistic regression model with the decision to give a dose increase as a dependent variable and DAS28 at week 22, delta DAS28 0–22 and delta DAS28 6–22 as covariates, only DAS28 at week 22 was a significant variable in the model.

Similar analyses were performed for the other variables. The AUC of the differences between weeks 0–22, weeks 6–22 and weeks 14–22 of the other variables were all less than 0.700 (data not shown). These analyses indicate that, although the differences in disease activity over time are statistically significant,

those differences over time are not important enough to incorporate in a model to discriminate the physician's decision.

3.2.4.4. Building a model to discriminate the physician's decision to give a dose increase

The first three analyses (ranking of continuous variables, evaluation of the response scores and effects of change of scores over time on the physician's decision) allowed us to narrow the selection of variables for the model by eliminating variables that are already incorporated into the DAS28 (or are highly related to them such as CRP and 68 tender joint and 66 swollen joint count) and taking into account only those variables at week 22. This resulted in the following list: DAS28, HAQ, physician global VAS, patient pain VAS, patient fatigue VAS and the scores of the SF36 questionnaire at week 22. We screened those variables using forward and backward elimination in a logistic regression model and by the stepwise Wilk's lambda method. The probability scores of the logistic regression and discriminant scores we thus obtained were compared using ROC curve analysis. The model with the highest AUC was a model from discriminant analysis with the following variables (and standardized canonical discriminant function coefficients): DAS28 week 22 (0.863), physician global VAS (0.796), patient pain VAS (0.735), and physical functioning (-0.227). The discriminant score of this model had an AUC of 0.870 (95% CI: 0.828–0.912) with a sensitivity at the 95% specificity level of 45.5% (95% CI: 38.7–50.3).

3.2.4.5. Evaluation of the discriminant score of the variables of DAS28

To validate the score and coefficients of the DAS28, we calculated a discriminant function using the (normalized) variables of the DAS28 score: 28 tender and swollen joint count, ESR and patient global VAS. After rescaling, we obtained the following discriminant coefficients: 0.52 for 28 tender joint count (28TJC), 0.28 for 28 swollen joint count (28SJC), 0.56 for ESR and 0.025 for patient disease activity. This discriminant score had an AUC of 0.844 (0.797–0.891) and a sensitivity at the 95% specificity level of 43.8% (95% CI: 38.1–49.2), which is equal to the DAS28 at week 22. The Pearson's correlation coefficient between this discriminant score and the DAS28 was 0.986 (**Figure 11**). We also performed logistic regression with similar results (data not shown).

3.2.4.6. Comparison with the other DAS scores and SDAI/CDAI

Since different alternative methods are available to calculate the DAS scores (**Table 11**), we additionally evaluated the properties of those alternative scores. We also evaluated the SDAI and CDAI [8, 9], after normalization, by taking the squared root. The Pearson's correlation coefficient of those alternative scores with the DAS28 at week 22 was 0.982 for the DAS28-3, 0.952 for the DAS28-CRP, 0.928 for the DAS28-CRP-3, 0.914 for the SDAI and 0.893 for the CDAI. The AUC and sensitivity at the 95% specificity level are shown in **Table 11** and indicate that all those alternative scores perform similarly or slightly worse than the original DAS28.

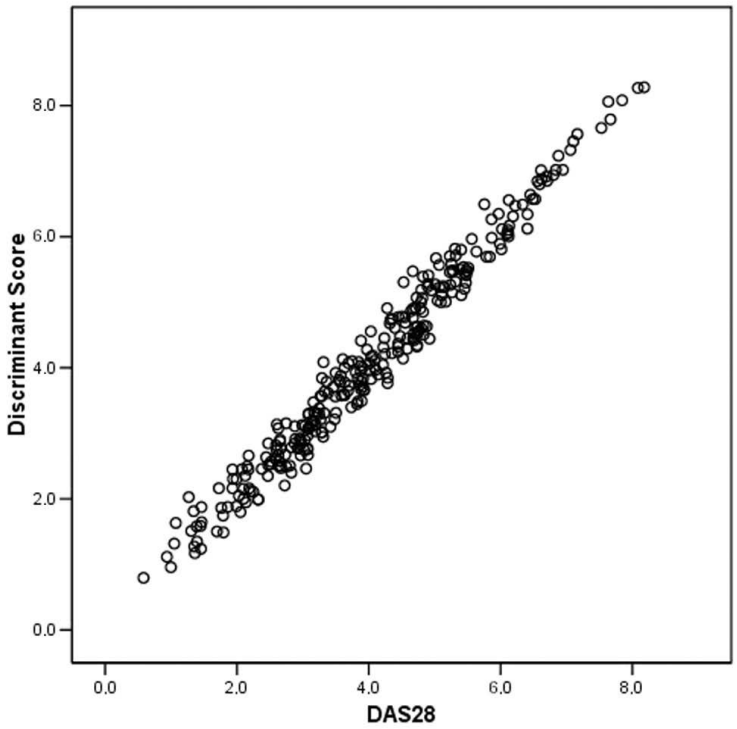

FIG.11. *Validation of the DAS28 score and coefficients (see text).*

3.2.4.7. Detailed ROC curve analysis of the DAS28

We plotted the ROC curve of the DAS28 in Figure 12 and listed sensitivities and specificities in Table 14. Also, predictive values and the accuracies of classification in function of the different DAS28 cut-offs are shown in Table 14. Beneath a cut-off of 3.2, we found a high predictive value for continuing the current dose as a measure of good response. The maximal accuracy of 84% could be found at a cut-off of 5.5.

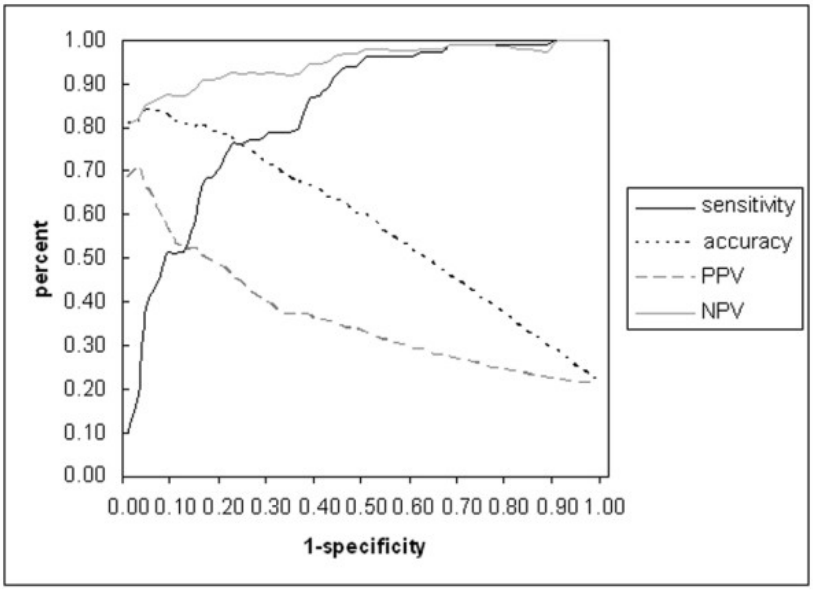

FIG. 12: *ROC curve analysis of the DAS28 at week 22 (plotting the 1-specificity versus the sensitivity). Also the accuracy, PPV and NPV are plotted.*

DAS cut-off	Sensitivity	Specificity	PPV	NPV	Accuracy
2.0	0.99	0.13	0.23	0.98	0.31
2.5	0.99	0.22	0.25	0.99	0.38
2.6	0.99	0.26	0.26	0.99	0.41
3.0	0.98	0.38	0.29	0.98	0.50
3.2	0.96	0.46	0.32	0.98	0.57
4.0	0.79	0.66	0.38	0.92	0.68
4.5	0.76	0.77	0.47	0.92	0.77
5.0	0.58	0.87	0.55	0.89	0.81
5.1	0.53	0.88	0.55	0.88	0.81
5.5	0.43	0.95	0.69	0.86	0.84
6.0	0.34	0.97	0.73	0.85	0.83
6.5	0.19	0.98	0.72	0.82	0.81

DAS, disease activity score; PPV, positive predictive value (predictive value to give a dose increase as a measure of insufficient response); NPV, negative predictive value (predictive value to continue on the current dose as a measure of good response); PPV, NPV and accuracy were calculated using the following formulae:

a) $$PPV = \frac{sensitivity * a\_priori\_chance}{sensitivity * a\_priori\_chance + (1 - specificity) * (1 - a\_priori\_chance)}$$

b) $$NPV = \frac{specificity * (1 - a\_priori\_chance)}{specificity * (1 - a\_priori\_chance) + (1 - sensitivity) * a\_priori\_chance)}$$

c) $Accuracy = sensitivity * a\_priori\_chance + specificity * (1 - a\_priori\_chance)$

The *a priori* chance is given by the percentage of patients that need a dose increase as a measure of insufficient response.

TABLE 14: *Performance at different cut-offs of DAS28 at week 22 for dose increase.*

3.2.5.Discussion

The aim of the present analyses was to evaluate which single or composite variables, combined in a model, could discriminate the treating rheumatologist's decision to give a dose increase of infliximab to RA patients not optimally responding to an indicated dose of 3 mg infliximab every 8 weeks. Since different variables on different time points were available, we started to rank the continuous variables based on the AUC of ROC curves and sensitivities at the 95% specificity level. This strategy has previously been proposed for microarray data [17]. The calculation of sensitivities at the 95% specificity level is important in order not to overlook some variables with a relative small AUC but with a high specificity [16]. So, both methods ranked the DAS28 at week 22 as the variable which best discriminates the decision to give a dose increase. In a second and third analysis, we looked at whether response scores and differences in disease activity over time could give additional information to discriminate the rheumatologist's decision. Those analyses indicated that variables, including differences over time, seem

to be less important than the momentary remaining disease activity at week 22, to discriminate the rheumatologist's decision.

After the prior selection of variables, based on the findings of the previous steps, we built the final model to discriminate the rheumatologist's decision, which was only slightly better than the DAS28. We think that the small gain in discriminative properties in comparison with the DAS28 is not enough to accept the increased complexity of this model. Moreover, in contrast to the DAS28, this model included the physician's global assessment of disease activity (VAS), which is investigator-dependent and has the draw-back that it cannot be calculated by a study nurse. All four analyses together indicated that the DAS28 is an important variable for evaluating insufficient response to infliximab therapy (especially in daily practice) and that this variable can only slightly be improved by adding supplemental variables.

DAS was developed in the early 1990s [19, 20] and later on, it was transformed into the DAS28 [7] in an era when therapy with biologicals was not yet available. In those initial studies, patients were scored by the same two independent nurses and the decision to change disease-modifying anti-rheumatic drug (DMARD) therapy during a follow-up period of up to 3 years was considered as a measure of insufficient response [20]. The present study is a multi-centre study where patients were scored by the treating physician and the decision to give a dose increase of infliximab could happen only at one time point. This difference in study design and therapy may explain why in the present study the AUC of DAS28 is smaller than in other studies (AUC = 0.840 versus 0.933) [21]. Therefore, it is remarkable that despite those differences in study design, we could calculate a discriminant function (in the fifth analysis) that correlated so well with the DAS28 by using the 28SJC, 28TJC, ESR and patient disease activity VAS as independent variables and the physician's decision as a grouping variable. Not only the discriminant scores, but also the coefficients of this discriminant function were quite similar to the coefficients of the DAS28, indicating the robustness of the scores and coefficients of the DAS28 score.

In another, final analysis, we evaluated the alternative DAS scores and the squared root transformed SDAI and CDAI. All those alternative scores have a slightly worse AUC than the original DAS28, but seem good enough to be useful when some other variables are not available. We think the use of the DAS28 is feasible and time-effective using a preprogramed calculator, spreadsheet or web-based calculator [11]. The unique characteristics of the DAS score make it a useful measure in a lot of applications. DAS28 as a continuous variable is a sensitive tool for measuring response to treatment in randomized controlled trials and facilitates the use of more complex statistical methods that can handle repeated measures over different time points [22-24].

Other studies demonstrated that a low DAS is an important prognostic factor of persistent remission and that DAS correlates with radiological progression [25, 26]. DAS may also be a useful parameter in daily clinical practice as a treatment goal and to evaluate the actual disease activity (which cannot be assessed by the categorical response scores) [27-31]. Our findings that the physician's decision to give a dose increase can best be modelled by a combination of measurements of remaining/momentary disease activity, represented by the DAS28 does not reduce the value of the response scores such as ACR response or DAS response scores. Indeed, those scores are important for measuring differences over time as a measure of global treatment effects in clinical trials [12, 13] but, as demonstrated by the present study, are not useful for evaluating the momentary disease activity in a single patient, which is important in daily practice. The continuous properties of the DAS28 score provide the additional opportunity for a cut-off, which can be chosen as a function of the purpose. Interestingly, we found a high predictive value for continuing the current dose as a measure of good response below a cut-off of 3.2. It is noteworthy that a DAS score of 3.2 is an important threshold for a good DAS response according to the EULAR criteria [12]. In contrast, for classification purpose, a higher cut-off (5.5) is more

appropriate since this level displayed the highest accuracy. One should be aware that the displayed predictive values and accuracies may be highly influenced by the prevalence of insufficient response, reflected by the need for a dose increase, which was 21.5% in the present study. A lower *a priori* chance of the need for a dose increase may increase the accuracy of DAS (given the fixed cut-off of 5.5) and vice versa. Indeed, at a cut-off with a high specificity, the accuracy will increase when the *a priori* chance decreases (applying formula c given in the legend to **Table 14**).

Conclusion The results of the present analyses indicate that the momentary DAS28 as a continuous composite index correlates best with the decision to give a dose increase of infliximab, which is a measure of insufficient response. The discriminative characteristics of the DAS could be slightly improved by the use of supplemental variables, although this results in the disadvantage of a more complex model and calculations. This study also demonstrates the robustness of the scores and coefficients of the DAS28 in a cohort of RA patients under infliximab therapy and therefore validates the DAS28 as a measure of disease activity in patients under treatment with biologicals.

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Chapter 4: Prediction Models of Anti-TNF alpha Outcomes in RA and AS

Four studies that had as aim to investigate for which patients anti-TNF treatment would be most valuable as determined by the likelihood of achieving a desired outcome are reported.

A pilot risk model for the prediction of rapid radiographic progression in rheumatoid arthritis.

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Predicting the outcome of ankylosing spondylitis therapy.

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ASDAS high disease activity versus BASDAI elevation in patients with ankylosing spondylitis as selection criterion for anti-TNF therapy.

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Reumatol Clin. 2014 Jul-Aug; 10(4):204-9. Epub 2014 Mar 2.

4.1. A pilot risk model for the prediction of rapid radiographic progression in rheumatoid arthritis

4.1.1. Abstract

Objectives

Identifying patients with RA at high risk of rapid radiographic progression (RRP) is critical for making appropriate treatment decisions. We developed an exploratory prediction model for the risk of RRP using an RA study population undergoing either conservative or aggressive disease management.

Methods

Using data from the active-controlled study of patients receiving infliximab for the treatment of rheumatoid arthritis of early onset (ASPIRE) early RA study, RRP was defined as a threshold change in modified Sharp/van der Heijde score (SHS) of $\geqslant$5 U/year. Spearman's rank analysis was used to identify baseline risk factors for RRP. Logistic regression was used to calculate the probability of RRP in 1 year. The results were combined into a matrix model that consisted of risk factors and initiated treatment arranged in increasing risk of RRP. Data from the anti-TNF trial in rheumatoid arthritis with concomitant therapy (ATTRACT) established RA study were applied to the model to test its generalizability in another population.

Results

The 28 swollen joint count, RF, CRP and ESR are included as trichotomous variables and initiated treatment (monotherapy or combination therapy) as a dichotomous variable. Two models, one incorporating all risk factors except CRP and another incorporating all risk factors except ESR, were developed to adjust for collinearity. These models identify subpopulations of RA patients at higher predicted risk for RRP.

Conclusions

These preliminary matrix models predict the risk of RRP using initiated treatment and easily accessible clinical and laboratory variables. Further testing in other populations and with other therapies is needed to obtain a definitive risk model that will guide rheumatologists in making treatment decisions for individual RA patients.

4.1.2. Introduction

RA is a chronic systemic inflammatory disease predominantly characterized by joint inflammation and frequent progression of joint destruction resulting in decreased functional capacity, work disability and reduced quality of life [1-4]. Rapid radiographic progression (RRP) in RA usually occurs in a minority of treated patients. In these patients, effective therapy can reduce the odds of progression by as much as 78% [5], and both early and intensive treatment can alter the course of the disease by slowing the rate of radiographic progression [6-8]. The identification of individual RA patients at high risk of RRP is therefore critical to making appropriate treatment choices. Various clinical and biological markers have been identified as baseline risk factors for the progression of joint damage in patients with RA [8-12]. Although the use of any single baseline variable has limited value [13], combining multiple markers has been shown to improve predictive power [12-16].

One of the most widely used risk models in medicine is the Systematic Coronary Risk Evaluation (SCORE) Risk Chart [17]. This model predicts the 10-year probability of cardiovascular mortality based on a number of widely accepted risk factors (e.g. sex, blood pressure, lipid levels and tobacco use) that have been organized into a simple, visual, color-coded matrix relative to an individual's specific risk profile. However, a limitation of the SCORE chart is that it does not account for the associated adverse effects of the therapies that may influence the risk of adverse outcomes.

We aimed to create a similar visual matrix model that would predict the 1-year risk of RRP for individual RA patients based on associated risk factors and the type of initiated therapy (conservative *vs* aggressive management). We describe the first stage of development of this exploratory model using data from the active-controlled study of patients receiving infliximab for the treatment of rheumatoid arthritis of early onset (ASPIRE) from an early RA study population [18] and test whether the proposed method for outcome prediction could also be used in the anti-TNF trial in rheumatoid arthritis with concomitant therapy (ATTRACT) from an established RA study population [19]; both these groups were receiving either DMARD monotherapy or intensive anti-TNF plus DMARD combination therapy.

4.1.3. Methods

4.1.3.1. The ASPIRE and ATTRACT studies

In ASPIRE, 1049 MTX-naïve, early RA patients (disease duration 3 months–3 years) were double-blinded to randomly receive MTX monotherapy or MTX in combination with 3 or 6 mg/kg infliximab through 46 weeks [18]. In ATTRACT, 428 established RA patients with active disease despite treatment with stable-dose MTX (⩾12.5 mg/week) were continued on MTX and additionally double-blinded to randomly receive placebo or 3 or 10 mg/kg infliximab through 54 weeks [19]. For this analysis, the infliximab plus MTX groups were combined in each respective study, since all dose groups within each study were well balanced for demographics and baseline disease characteristics and showed similar rates of radiographic progression through Week 54. This study is a subanalysis of the ASPIRE and the ATTRACT studies, both of which had ethical approval and informed patient consent. The authors had full access to the data of these studies. Relevant baseline demographics and disease characteristics are summarized in **Table 15**.

	ASPIRE	ATTRACT
n	1049	428
Age, years	51 (41, 60)	53.5 (45, 60)
Sex, female	742 (71.1)	332 (77.6)
Disease duration, years	0.6 (0.4, 1.1)	8.4 (4.3, 14.7)
HAQ score (scale 0–3)	1.5 (1.0, 1.9)	1.8 (1.3, 2.1)
TJC	31 (22, 44)	31 (19, 44)
SJC	19 (14, 26)	20 (13, 29)
CRP, mg/dl	1.4 (0.4, 4.1)	2.6 (1.1, 5.1)
ESR, mm/h	40 (23, 61)	42 (32, 65)
RF, U/ml	175 (30, 357)	178 (48, 425)
Total modified SHS	5.0 (1.5, 14.0)	51.5 (20.6, 113.0)
Patients with joint erosion	854 (82.0)	415 (99.1)
Patients with joint space narrowing	687 (65.9)	402 (95.9)
Patients with prior joint surgery	3 (0.3)	90 (21.0)

TABLE 15: *Baseline demographics and disease characteristics across treatment groups. Data are presented as median (interquartile range) or* n *(%).*

In both studies, patients were assessed at baseline for the 68 tender joint count (TJC), the 66 swollen joint count (SJC), ESR, CRP, RF and radiographs of the hands and feet. The Westergren method was used to determine ESR at the local laboratory. CRP was measured by nephelometry. IgM-RF was evaluated at the central laboratory. Two readers blinded to treatment and timepoint scored the radiographs independently. The average of the two readers' scores at each timepoint was used to calculate joint damage progression as defined by the change in the van der Heijde modification of the Sharp score (SHS) [20] from baseline to Week 54. In ASPIRE, the intraclass correlation coefficients were 0.87 at baseline and 0.88 at Week 54. The smallest detectable difference in SHS was defined at 9.0 and 8.6 U from baseline, respectively, in the ASPIRE and the ATTRACT studies.

4.1.3.2. Determination of RRP

To define RRP for the model, the proportions of patients in ASPIRE who rapidly progressed according to a range of thresholds of annual change in SHS (>0 to ⩾9) were compared with the mean/median progression rate and to the proportion of patients who had any progression. Sensitivity analyses using other thresholds of annual change in SHS were done to determine whether using an equally higher or lower definition of RRP would significantly affect the multivariate model.

4.1.3.3. Selection of baseline risk factors

Baseline risk factors to be included in the model were identified from the ASPIRE data set. The ASPIRE study design, which allowed for the inclusion of a range of RA patients (e.g. those with normal CRP, negative RF or no erosive disease) [18], provides an apt data set for examining 1-year radiographic progression in relation to various clinical and biological variables as well as administered therapy.

Without making any assumptions on the distribution of the variables, Spearman's correlation coefficients were used to evaluate the relationship between all available baseline variables and radiographic progression. Any two risk factors having a correlation coefficient >0.3 were investigated for collinearity to minimize the inclusion of duplicative factors. A comparison of the maximum rescaled R^2 was used to evaluate whether including only one of any pair of collinear factors would improve the face validity of the model without significantly reducing the predictive power.

Logistic regression analyses were performed to predict the risk of RRP from the selected baseline risk factors after adjustment for treatment group. These baseline risk factors include SJC, RF, and ESR or CRP, treated as ordinal variables. No adjustments were made for multiple testing. Predicted probability of RRP was calculated using a logistic regression analysis. For selected risk factors that are continuous variables, treatment group differences in the change in SHS from baseline to Week 54 were further explored using analysis of variance on van der Waerden normal scores to test for interaction among baseline characteristics. Statistical analyses were done using the SAS system (SAS Institute, Cary, NC, USA). All statistical tests were two-sided and tested at $\alpha = 0.05$.

4.1.3.4. Development of the matrix risk model

The selected baseline risk factors and initiated treatments were combined and arranged so that the risk of RRP increases from left to right and from bottom to top in the matrix model. Each continuous risk factor was presented in approximate tertiles based on clinical utility and the ability to identify subgroups of relevant size. A colour scheme ranging from blue (low risk) to red (high risk) was used to enhance visual readability. Patient baseline and radiographic data from ASPIRE were then used to generate the probabilities of RRP to populate the exploratory matrix risk model. Absolute and relative risk ratios and numbers needed to treat (NNT) were calculated using this generated model to evaluate the relative benefit of MTX monotherapy *vs* MTX plus infliximab in ASPIRE.

4.1.3.5. Application of the matrix risk model

To assess whether our matrix risk model—i.e. the method we used to arrange the combination of selected risk factors for risk prediction in an early RA data set—would be similarly predictive of the same definition of RRP in more advanced RA populations undergoing similar treatment, patient baseline and radiographic data from the ATTRACT study were used to generate the probabilities of RRP in a second, exploratory matrix risk model.

Finally, to highlight the impact of the choice of conservative *vs* aggressive management on actual radiographic progression early in the disease course, we show the cumulative probability plots as described by van der Heijde *et al*. [21] of two ASPIRE patient subgroups selected based on their baseline risk factor profiles.

4.1.4. Results

4.1.4.1. Determination of RRP

The observed proportion of patients with radiographic progression in ASPIRE was inversely related to the threshold values tested, i.e. higher proportions for lower thresholds and vice versa (**Table 16**).

	MTX monotherapy	Infliximab plus MTX
Progression in the modified SHS, U/year		
Mean ± s.d.	3.7 ± 9.6	0.5 ± 5.6
Median (interquartile range)	0.3 (0.0, 4.4)	0.0 (−1.0, 1.3)
Range	(−22.3, 67.9)	(−34.7, 48.0)
Patients with progression in SHS, U/year, %		
>0	52.0	39.2
>=1	42.3	30.4
>=2	32.9	20.1
>=3	29.5	13.6
>=4	26.5	10.7
>=5	22.8	8.3
>=6	19.1	6.5
>=7	17.8	5.2
>=8	15.4	4.8
>=9	14.1	3.9

TABLE 16. *Radiographic progression through Week 54 according to various thresholds in the ASPIRE early RA population. The bold values were calculated from the sensitivity analysis. Higher SHS U/year indicates more severe radiographic progression of joint damage.*

Based on our clinical experience and the fact that the complete destruction of one joint during 1 year is equal to an increase of 5 SHS units [22, 23], we arbitrarily selected this increase in SHS of ⩾5 U/year as the definition of RRP for conceptual simplicity. Among patients who showed any radiographic progression, a threshold of ⩾5 U/year in the SHS identified ~23% of those on MTX monotherapy and 8% of those on infliximab plus MTX. Sensitivity analysis with the threshold changes in SHS of ⩾2 and ⩾8 U/year demonstrated the same inversely proportional relationship for the logistic regression modelling of the selected baseline risk factors and the identified subgroups of patients with radiographic progression, i.e. the higher the threshold change, the smaller the identified subgroup. As an example, the sensitivity analysis for CRP is shown in **Figures 13A and B**.

4.1.4.2. Selection of baseline risk factors

In ASPIRE, the following continuous baseline risk factors were selected for inclusion in the model as trichotomous variables: CRP (<0.6, 0.6–3 or >3 mg/dl), ESR (<21, 21–50 or >50 mm/h), SJC (<10, 10–17 or >17) and RF (<80, 80–200 or >200 U/ml) (**Figures 13C–F**).

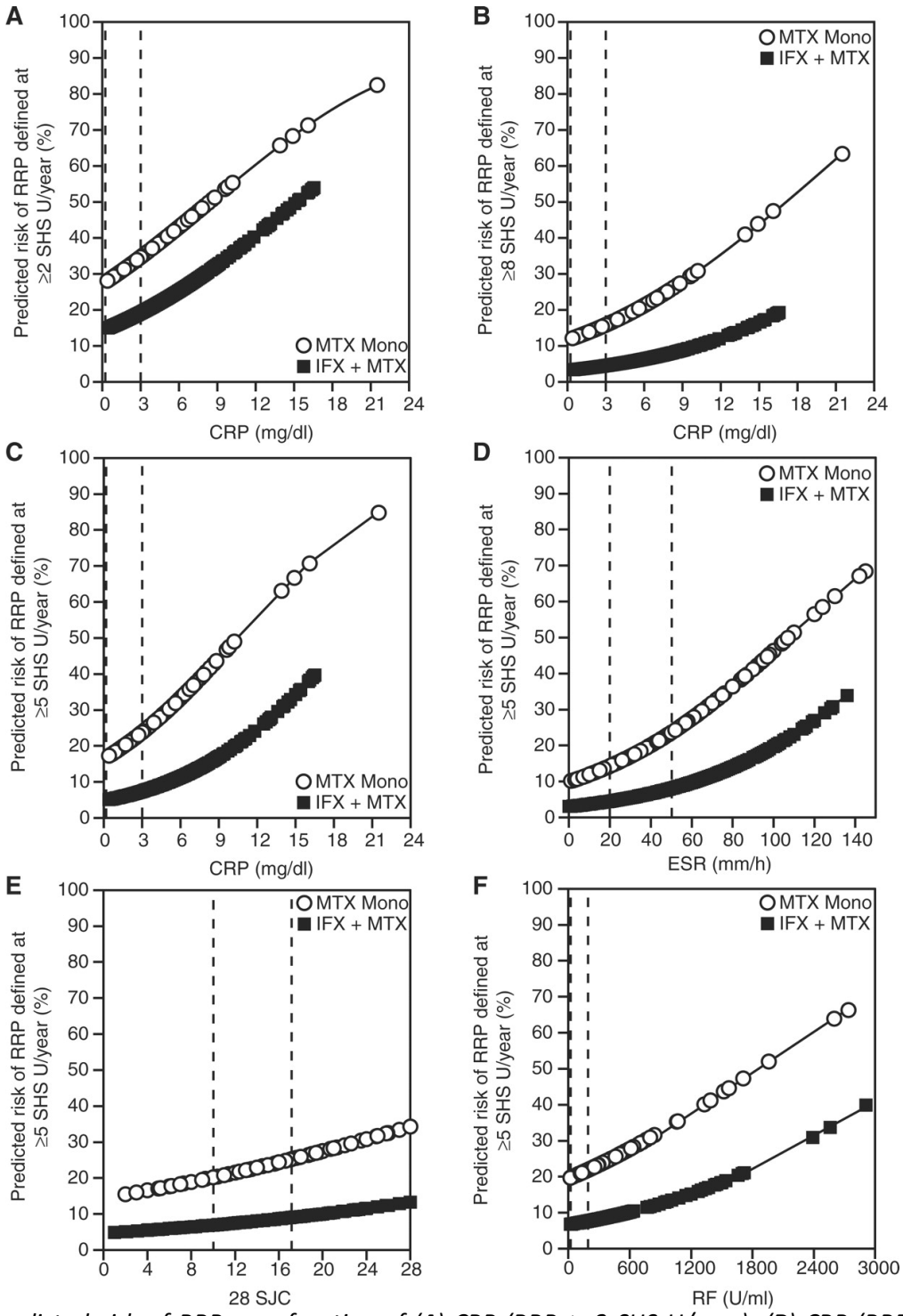

FIG.13. *Predicted risk of RRP as a function of (**A**) CRP (RRP ⩾ 2 SHS U/year); (**B**) CRP (RRP ⩾ 8 SHS U/year); (**C**) CRP (RRP ⩾ 5 SHS U/year); (**D**) ESR (RRP ⩾ 5 SHS U/year); (**E**) 28 SJC (RRP ⩾ 5 SHS U/year); (**F**) RF (RRP ⩾ 5 SHS U/year) at baseline in the ASPIRE population. Dotted vertical lines represent the selected ranges. Higher percentage indicates more severe radiographic progression of joint damage.*

CRP and ESR were highly correlated (coefficient = 0.61) and showed limited collinearity. When ESR was excluded from the model, the maximum rescaled R^2 decreased only slightly, from 0.1616 to 0.1428.

From this decrease, we concluded that the model could be simplified by using just one of the two risk factors without compromising its predictive power. Although both the 66 (data not shown) and the 28 joint counts for SJC correlated similarly with radiographic progression, the 28 joint count was selected for its greater practicality in the clinical setting [24]. RF titer was included as a trichotomous variable, because it contributed significantly to the model as a continuous variable but not as a categorical variable (i.e. RF-positive or -negative). Initiated treatment (MTX monotherapy or infliximab plus MTX) was included in the model as a dichotomous variable. Treatment through 46 weeks with infliximab plus MTX resulted in significantly better radiographic outcome compared with MTX monotherapy for the total sample patient population and for all high-range subgroups defined by risk profile (Figure 14).

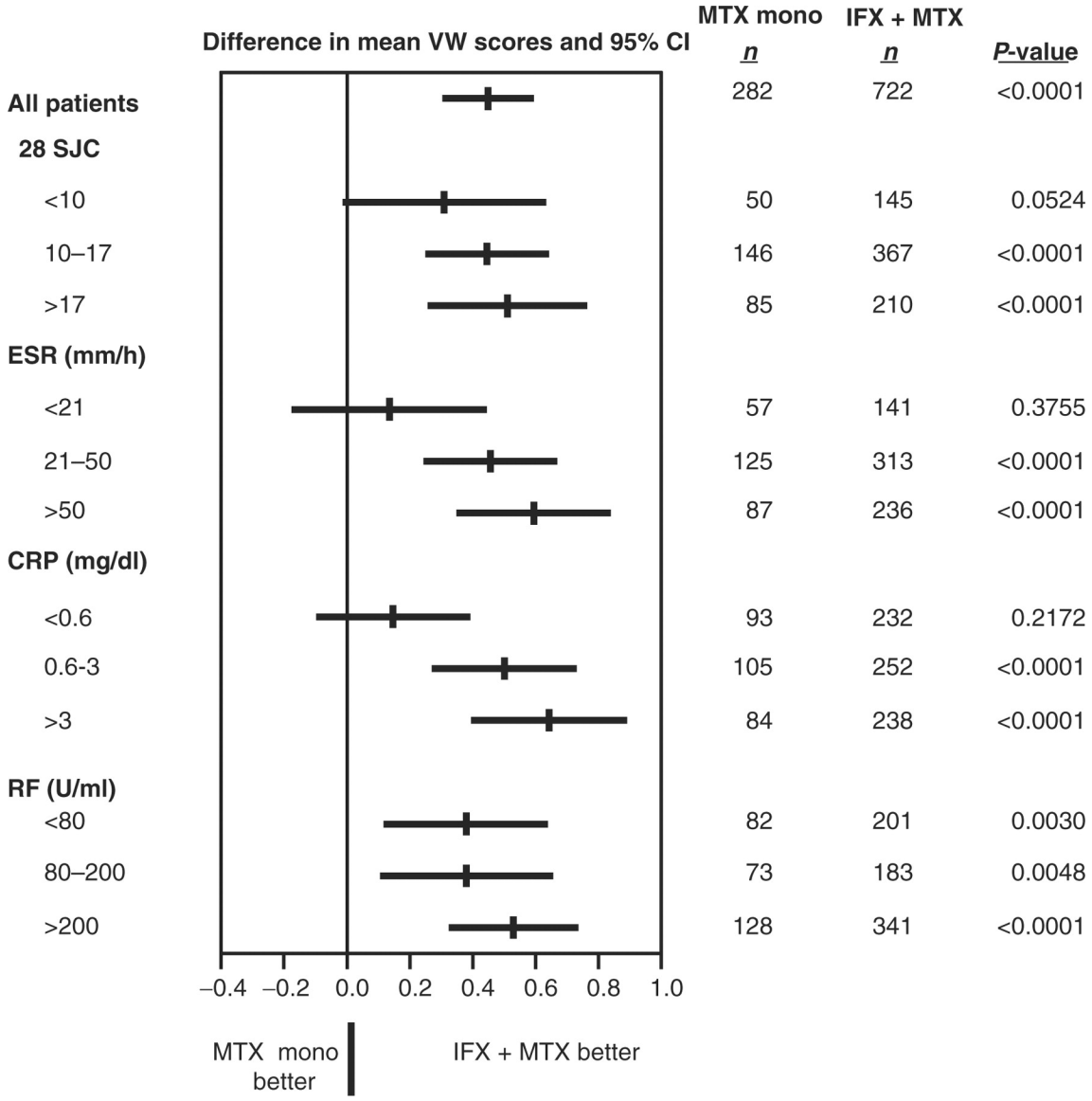

FIG. 14. *Differences between treatment groups in mean van der Waerden (VW) normal scores of the change of ⩾ 5 U/year in total modified SHS for subgroups defined by selected baseline risk factors in the ASPIRE population.*

Notably, radiographic damage or radiographic score at baseline was not a prognostic variable. Eighty-two percent and 66% of the patients had erosions and joint space narrowing, respectively, at baseline,

which did not allow us to take into account the presence of damage at baseline as a prognostic factor in our model. Radiographic score at baseline was inversely associated with the radiographic progression in patients treated with infliximab plus MTX and was, therefore, not retained as a negative prognostic factor in the model.

4.1.4.3. Development of the matrix risk model

Using clinical, serological and radiographic data from the ASPIRE early RA population, two alternate models—one incorporating all risk factors except ESR (Figure 15A) and another incorporating all risk factors except CRP (Figure 15B)—were generated to enable the interchangeable use of these two acute-phase measures depending on clinical availability.

A

28 SJC	CRP (mg/dl)	IFX + MTX RF (U/ml) <80	IFX + MTX RF (U/ml) 80–200	IFX + MTX RF (U/ml) >200	MTX mono RF (U/ml) <80	MTX mono RF (U/ml) 80–200	MTX mono RF (U/ml) >200
>17	>3	8 (5,14)	11 (7,16)	14 (9,20)	33 (22,47)	40 (30,51)	47 (36,59)
10–17	>3	8 (5,12)	10 (7,14)	13 (9,18)	31 (21,44)	38 (28,48)	45 (34,56)
<10	>3	7 (4,12)	9 (6,15)	12 (7,19)	29 (18,44)	35 (24,49)	42 (29,57)
>17	0.6–3	6 (4,10)	8 (6,11)	10 (7,15)	17 (11,26)	22 (16,30)	27 (19,37)
10–17	0.6–3	6 (4,8)	7 (6,10)	10 (7,13)	16 (11,23)	20 (16,26)	25 (19,33)
<10	0.6–3	5 (3,8)	7 (4,10)	9 (6,13)	15 (9,23)	19 (13,27)	23 (16,33)
>17	<0.6	4 (2,8)	6 (3,10)	8 (4,13)	8 (4,15)	11 (6,19)	14 (7,24)
10–17	<0.6	4 (4,7)	5 (3,8)	7 (4,11)	7 (4,13)	10 (6,16)	12 (7,21)
<10	<0.6	4 (2,7)	5 (3,8)	6 (4,11)	7 (4,13)	9 (5,15)	11 (6,20)

B

28 SJC	ESR (mm/h)	IFX + MTX RF (U/ml) <80	IFX + MTX RF (U/ml) 80–200	IFX + MTX RF (U/ml) >200	MTX mono RF (U/ml) <80	MTX mono RF (U/ml) 80–200	MTX mono RF (U/ml) >200
>17	>50	11 (7,17)	14 (9,19)	17 (12,23)	30 (20,42)	35 (26,46)	41 (31,52)
10–17	>50	9 (6,14)	12 (8,16)	15 (11,20)	26 (18,37)	32 (24,40)	37 (29,47)
<10	>50	8 (4,14)	10 (6,16)	13 (8,19)	23 (14,36)	28 (19,40)	33 (23,46)
>17	21–50	6 (4,9)	7 (5,11)	9 (6,14)	18 (12,27)	22 (16,30)	27 (19,36)
10–17	21–50	5 (3,8)	6 (5,8)	8 (6,11)	15 (11,22)	19 (15,25)	23 (17,31)
<10	21–50	4 (2,7)	5 (3,8)	7 (4,11)	13 (8,21)	17 (11,24)	20 (14,30)
>17	<21	3 (2,6)	4 (2,7)	5 (3,9)	10 (6,17)	13 (8,20)	16 (9,26)
10–17	<21	3 (1,5)	3 (2,5)	4 (3,7)	9 (5,14)	11 (7,17)	14 (8,21)
<10	<21	2 (1,4)	3 (2,5)	4 (2,7)	7 (4,13)	9 (5,15)	12 (7,20)

FIG.15. *Matrix risk model for the probability of RRP in 1 year including all selected baseline risk factors except (**A**) ESR or (**B**) CRP, generated from the ASPIRE early RA data set. The numbers in each cell represent the percentage (95% CI) of patients who had RRP out of all patients who have the baseline characteristics and receive the initiated treatment as indicated. Colour scheme: blue: 0–9%; green: 10–19%; yellow: 20–29%; orange: 30–39%; red: 40–100% predicted probability of RRP. Higher percentage indicates more severe radiographic progression of joint damage.*

The numbers in each cell of the matrix represent the percentage (95% CI) of patients who had RRP out of all patients who have the baseline characteristics and receive the initiated treatment as indicated by the location of the cell within the matrix. For example, a patient with RA who has 18 swollen joints and 7 mg/dl CRP and 380 U/ml RF serum concentrations would have a 47% (95% CI 36%, 59%) probability of RRP if treated with MTX monotherapy or a 14% (95% CI 9%, 20%) probability if treated with infliximab plus MTX combination therapy. Due to the even distribution of the ASPIRE patient population over each of the selected risk factors (also see patient numbers in **Figure 14**), approximate tertiles were used to identify subgroups of relevant size in these matrix models. For example, the subgroup at the highest risk (SJC >17, RF >200 U/ml, CRP >3 mg/dl) comprised 65 patients in the CRP-based model shown in **Figure 15A**.

The relative risk reduction of RRP with infliximab plus MTX *vs* MTX monotherapy was 43 and 71% for those within the low ranges and 70 and 59% for those within the high ranges of all baseline risk factors, respectively, in the CRP- and ESR-based models. The absolute risk reduction of RRP with infliximab plus MTX as compared with MTX monotherapy was 3 and 5% for those within the low ranges and 33 and 24% for those within the high ranges of all baseline risk factors, respectively, in the CRP- and ESR-based models. The NNT with aggressive management to prevent one patient from rapidly progressing with conservative management was 3 for those within the high ranges for CRP, SJC and RF and 33 for those within the low ranges.

The cumulative probability plots of a subpopulation with a high risk of radiographic progression (CRP >3 mg/dl, RF >200 U/ml, SJC >17; *n* = 65) and a subpopulation with a low risk of radiographic progression (CRP <0.6 mg/dl, RF <80 U/ml, SJC <10; *n* = 68) from ASPIRE are presented in **Figure 16A and B**.

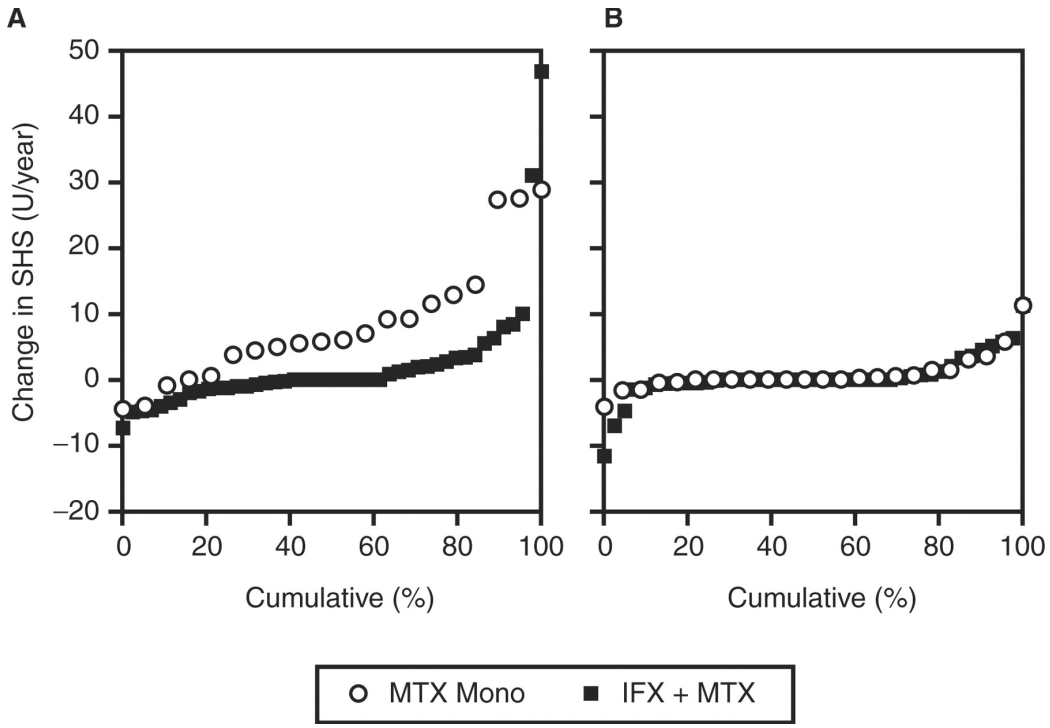

FIG.16. *Cumulative probability plots of actual radiographic progression in modified SHS (U/year) in (**A**) an ASPIRE subpopulation with a high risk of radiographic progression (CRP > 3 mg/dl, RF > 200 U/ml, SJC > 17;* n *= 65) and in (**B**) an ASPIRE subpopulation with a low risk of radiographic progression (CRP < 0.6 mg/dl, RF < 80 U/ml, SJC 10–17;* n *= 68). Higher SHS U/year indicates more severe radiographic progression of joint damage.*

4.1.4.4. Application of the matrix risk model

As expected, all patients who received conservative management in the ATTRACT study tended to be at high risk of RRP, irrespective of baseline risk factor values (Figures 17A and B). To a greater extent than observed in the ASPIRE data set, combination therapy with infliximab considerably reduced the proportion of ATTRACT patients with RRP, since these patients were not initiating MTX but rather continuing their pre-study MTX despite having active disease. By contrast, patients receiving aggressive therapy within the low or intermediate ranges of all baseline risk factors tended to be at low risk of RRP; and only those within the highest ranges of baseline risk factors tended to be at high risk, albeit to a lesser degree than patients receiving conservative management.

A

28 SJC	CRP (mg/dl)	IFX + MTX RF (U/ml) <80	IFX + MTX RF (U/ml) 80–200	IFX + MTX RF (U/ml) >200	MTX Mono RF (U/ml) <80	MTX Mono RF (U/ml) 80–200	MTX Mono RF (U/ml) >200
>17	>3	19 (10,32)	20 (13,30)	22 (13,33)	54 (32,75)	56 (37,74)	58 (38,76)
10–17	>3	14 (8,23)	15 (9,22)	16 (10,25)	45 (27,64)	47 (31,63)	49 (31,67)
<10	>3	10 (4,20)	10 (5,20)	11 (5,23)	35 (18,57)	37 (21,58)	39 (21,62)
>17	0.6–3	9 (5,19)	10 (6,18)	11 (6,19)	51 (31,70)	53 (36,69)	55 (37,72)
10–17	0.6–3	7 (3,12)	7 (4,12)	8 (4,13)	41 (26,58)	43 (31,57)	46 (31,61)
<10	0.6–3	5 (2,10)	5 (2,10)	5 (2,12)	33 (18,51)	34 (21,51)	36 (21,56)
>17	<0.6	4 (1,14)	5 (2,14)	5 (2,15)	48 (22,75)	50 (25,75)	52 (26,77)
10–17	<0.6	3 (1,9)	3 (1,9)	4 (1,10)	38 (17,65)	40 (20,65)	42 (20,68)
<10	<0.6	2 (1,7)	2 (1,7)	2 (1,8)	30 (12,57)	31 (13,58)	33 (14,61)

B

28 SJC	ESR (mm/h)	IFX + MTX RF (U/ml) <80	IFX + MTX RF (U/ml) 80–200	IFX + MTX RF (U/ml) >200	MTX Mono RF (U/ml) <80	MTX Mono RF (U/ml) 80–200	MTX Mono RF (U/ml) >200
>17	>50	18 (9,31)	19 (12,29)	20 (12,31)	62 (41,79)	63 (46,78)	65 (47,80)
10–17	>50	13 (7,22)	13 (8,21)	14 (9,23)	52 (33,70)	54 (38,68)	55 (38,71)
<10	>50	9 (4,18)	9 (5,18)	10 (5,20)	42 (23,63)	43 (26,63)	45 (26,66)
>17	21–50	11 (6,20)	12 (7,19)	13 (7,21)	48 (29,68)	50 (33,67)	52 (34,69)
10–17	21–50	8 (4,13)	8 (5,12)	9 (5,14)	38 (24,55)	40 (28,54)	42 (28,57)
<10	21–50	5 (2,11)	6 (3,11)	6 (3,12)	29 (6,47)	31 (18,47)	32 (18,51)
>17	<21	7 (2,17)	7 (3,17)	8 (3,18)	35 (15,62)	37 (17,61)	38 (18,64)
10–17	<21	5 (2,11)	5 (2,11)	5 (2,12)	26 (12,48)	28 (14,48)	29 (14,52)
<10	<21	3 (1,8)	3 (1,8)	4 (1,10)	19 (8,39)	20 (9,40)	22 (9,44)

FIG17. *Matrix risk models for the probability of RRP in 1 year including all selected baseline risk factors except (**A**) ESR or (**B**) CRP, generated from the ATTRACT established RA data set. The numbers in each cell represent the percentage (95% CI) of patients who had RRP out of all patients having the baseline characteristics and receiving the initiated treatment as indicated. Colour scheme: blue: 0–9%; green: 10–19%; yellow: 20–29%; orange: 30–39%; red: 40–100% predicted probability of RRP. Higher percentage indicates more severe radiographic progression of joint damage. Mono: monotherapy; IFX: infliximab.*

4.1.5. Discussion

We developed two preliminary, exploratory matrix risk models for the prediction of radiographic outcome in RA based on multiple risk factors associated with joint damage and related to treatment type. The uniqueness of our preliminary models lies not in the included baseline risk factors whose prognostic capabilities are well recognized [13, 25-30], but in the way the combination of these markers are arranged into a visual matrix that is able to predict the 1-year risk of RRP based on where a patient's baseline risk factors fall within the matrix. This preliminary matrix risk model, once refined to a finalized model through further development—using a greater variety of RA populations, such as those seen in daily practice, and treatment options reflective of the daily clinical setting (e.g. treatment adjustment upon non-response), and perhaps in the future the inclusion of genetic markers—may be used in clinical practice to predict the risk of RRP in the individual RA patient. Further, the inclusion of conservative *vs* aggressive management in our models can guide rheumatologists in making appropriate treatment choices for patients, particularly for early RA patients naïve to DMARDs. The data sets available to perform this exploratory analysis limited our comparison of the drug regimen (MTX *vs* infliximab plus MTX). The management choices that can be made in light of the predicted prognosis need not be limited to the choice of drug regimen but can be an adjustment of the frequency and the method for measuring disease activity, the rapidity of including a biological agent in the regimen after an initial course with DMARDs, and the choice of imaging method for detecting joint damage. Rather than defining risk in terms of means, medians, ranges and S.D., we predicted risk in terms of 'probability', as the more practical method to refer to risk (prognosis) in a patient–doctor conversation.

For our matrix model, we chose an annual progression rate of ⩾5 SHS U/year as our definition of RRP. Whereas harder endpoints, such as surgery and death, may be interesting to pursue in the future, both are usually very distant outcomes and becoming less prevalent in recent years [31-33]. Prevention of death is not thought to be a primary goal for treatment in RA. With better use of the therapeutic armamentarium that rheumatologists currently have access to, it can also be argued that joint surgery still has a place in the therapy for RA [33]. Although HAQ is an important outcome for clinicians and especially for patients, whether it can be considered an objective hard outcome is debatable. HAQ is primarily determined by disease activity [34], and much of the functional impairment is therefore reversible, especially early in the disease course [35]. However, it is well established that radiographic damage has an important effect on long-term functionality [1, 4, 34]. Therefore, choosing joint damage over a 1-year time-frame as our predicted outcome is a good surrogate of the consequences of disease activity as the driver of destruction and long-term disability resulting from this damage.

Of course, we do not consider progression <5 SHS U/year insignificant, given the increase in irreversible disability with the accrual of joint damage [1, 35]. Applying a lower threshold of ⩾2 SHS U/year in the sensitivity analysis resulted in models showing the same inversely proportional relationship between threshold value and subgroup size, but with higher probabilities of RRP overall. Conversely, although the smallest detectable difference in SHS U/year was 9 U in ASPIRE, we did not choose a higher threshold value because a threshold of 9 SHS U/year was deemed too high by the advisory board and, as seen in **Table 16**, using a definition of ⩾9 SHS U/year identified much smaller subsets of patients meeting this rigorous definition of extensive RRP. Although ⩾5 SHS U/year was also deemed too high a threshold by the advisory board, our chosen definition identified subsets of relevant size.

The 1-year endpoint was chosen because it is the most commonly reported radiographic endpoint and yearly progression rate is therefore likely to be the easiest for clinicians to interpret. Radiographic progression from baseline to Week 52 was the co-primary endpoint in the ASPIRE study [18] and it was the primary radiographic outcome parameter in the ATTRACT study [19]. Epidemiological studies have

shown that progression of radiographic damage on the group level is more or less linear [36]. Radiographic data at Week 30 were available for both ASPIRE and ATTRACT studies and confirmed the linearity of progression within the first year at the group level (data not shown). In light of this, as we are reporting on a yearly progression rate rather than the overall SHS, progression times <1 year (e.g. 3 and 6 months) or >1 year can be extrapolated from the yearly progression rate. Thus, because our aim was to focus on extensive radiographic progression rather than any progression, our definition was chosen based on practicality, clinical experience, and conceptual simplicity to reflect only a subgroup of patients with extensive progression [22, 23].

Interestingly, two types of risk factors were identified from the early RA population in ASPIRE as well as the established RA population in ATTRACT: 'disease activity-related factors' such as CRP, ESR and SJC, and 'serological factors' such as RF. Indeed, serum markers reflecting acute inflammation have been described to be the most important predictors of radiographic progression [37] and in our models, the probabilities of rapid progression increase mainly with increasing CRP and ESR (i.e. higher slopes in **Figure 15**). Similarly, SJCs but not TJCs were associated with RRP [30]. Finally, our findings corroborate existing reports [13, 26, 28] that adduce the 'serological profile', i.e. the combination of these serological markers, of a patient is an important contributor to radiographic progression during early RA (e.g. increase in radiographic progression with higher RF when all other risk factors are stable).

Using the results from ASPIRE, we generated two alternate risk models for early RA, one excluding CRP and another excluding ESR. To perform an initial assessment of whether the risk factors selected for the models were generalizable to other RA population samples, we applied data from the established RA patients in ATTRACT to the ASPIRE-based models and generated two very similar matrix risk models. A few important differences between the two data sets are of note. First, RF contributed less to the ATTRACT-based models than to the ASPIRE-based models, possibly due to the differences between the study populations (e.g. disease duration and treatment history). Another explanation may be that 'serological factors' are less important in established disease than in early disease and that the progression of joint damage is primarily influenced by current disease activity in patients with established disease. Secondly, differences in the effect of aggressive combination therapy between the ASPIRE- and ATTRACT-based models should be considered in light of the distinct patient sample populations (ATTRACT patients had longer disease duration, higher X-ray scores and disability, etc.), and their treatment history (i.e. MTX-failure *vs* -naïve), as delayed treatment itself is likely to have played a role in disease progression [6]. Thirdly, RRP in all risk groups may not be surprising in ATTRACT, since all patients were refractory to MTX and those assigned to MTX monotherapy essentially received placebo. Regardless, the risk profiles of patients on aggressive therapy in both ASPIRE and ATTRACT were similarly influenced by all selected baseline risk factors.

The utility and widespread success of the SCORE chart [17] motivated us in part to develop a similar risk model for RA. Whereas our matrix risk models predict the risk of joint destruction using correlated risk factors rather than cardiovascular mortality using independent risk factors, they also incorporate treatment as a contributor to the risk of RRP. In the context of the data sets used to build our models, MTX monotherapy can be considered conservative management, whereas infliximab plus MTX can be considered aggressive management. Although our matrix risk models should not be used to determine the appropriateness of initiating biological therapy before a conservative regimen, such as MTX monotherapy, in any individual patient, differential radiographic outcomes resulting from these two treatments were clearly observed and might warrant initiation of an aggressive regimen that includes several DMARDs in combination with corticosteroids. Our models identified subgroups of patients with low predicted risk of RRP in whom conservative management provides effective treatment (**Figure 16B**) as well as subpopulations of RA patients in whom it had a high risk of failure to prevent RRP (**Figure**

16A). Moreover, patients with values for the selected baseline risk factors exceeding the upper limits of the matrix models (e.g. CRP >3 mg/dl in combination with high values for the other factors) had an even higher likelihood of RRP with an NNT that approached 1. It is specifically in these very high-risk subpopulations that aggressive therapy demonstrated improved treatment benefit, and in whom early combination therapy may be warranted in light of the worse prognosis.

For a risk model to be broadly applicable, it should be easy to use, reflective of current clinical practice, and representative of the range of patients seen in the real-life clinical setting from those with DMARD-naïve, early RA to DMARD-refractory, established RA. An overview of the selected variables in a number of recent publications of large early RA cohorts (**Table 17**) suggests that the number of swollen joints is lower in clinical practice than in ASPIRE. However, the medians and quartiles of CRP and ESR in ASPIRE (**Table 15**), i.e. the most important predictors of RRP, do appear representative of what are seen in daily practice (**Table 17**).

Our study has several important limitations. First, the ASPIRE study was not specifically designed to create a matrix risk model. Unlike the goal-driven strategies used in current clinical practice, treatment assignment was fixed for 1 year for patients in the ASPIRE study to allow for true placebo control. The entry criteria selected a specific group of early RA patients in ASPIRE; it is certain that in daily rheumatology practice the proportion of patients at high risk is smaller than it was in the ASPIRE study.

Further, the selected risk factors for RRP were limited to the variables collected and analysed for the ASPIRE study, which may limit their applicability to other data sets. Introducing novel 'disease activity-related risk factors' for radiographic progression, such as MMP-3 and IL-8 [38], or 'serological factors', such as HLA-DR shared epitope [39], may have improved the predictive value of our models. However, the limited accessibility of tests for some of these parameters restricts their utility in routine practice.

Additionally, although anti-cyclic citrullinated peptide antibodies (ACPAs) are now considered one of the most important risk factors for joint progression in RA [40, 41] and their use is becoming increasingly routine in clinical practice, we were unable to include this predictive marker in our models because only a small number of ASPIRE patients had ACPA assessments available. Research on the relationship between levels of RF and ACPA, separately and combined, has shown that the prognostic value of high-titre RF and ACPAs for erosive disease are comparable. Testing patients with high-titre RF additionally for ACPAs, however, appears to be of limited prognostic benefit. Despite the excellent performance of high-titre RF overall, ACPAs proved slightly better for prognostic value [42]. In practice, ACPA testing is considerably more expensive and less available in clinical practice than RF. However, as with CRP and ESR, ACPAs and RF can likely be interchanged in our model and clinicians can use the marker they are most familiar with.

Lastly, due to a lack of available RA patient data sets with placebo-controlled treatment regimens similar to ASPIRE, we could not test our preliminary matrix models in another early RA cohort and, instead, tested the models using the ATTRACT established RA sample population. Therefore, the differences between the ASPIRE- and ATTRACT-based matrix risk models should be interpreted with caution, especially in light of the much smaller sample size in ATTRACT.

Study	Duration	(Sub) cohort, n	CRP, mg/dl, mean (range)	ESR, mm/h, mean (range)	SJC, mean (range)	RF+, %	Treatment
Kiely et al. [43]	2002–07	808	1.2 (0.5, 2.7)	25 (13, 43)	4 (2, 10)	58	51% MTX, 41% SSZ, 8% other DMARD, 9% combination
Welsing et al. [44]	1985–90	167	NA	40.5 (22, 60)	12 (8, 17)	79	2% MTX, 60% SSZ, other
	1990–95	132	NA	34 (13.5, 49)	11 (6, 17)	74	9% MTX, 82% SSZ, other
	1995–2000	114	NA	24.5 (9.5, 38.5)	10 (5, 13)	76	10% MTX, 76% SSZ, other
	2000–05	112	NA	19 (10, 34)	9 (6, 14)	67	NA
Gossec et al. [45]	1993–94	191	3.4 ± 4.3	40.2 ± 28.5	9.0 ± 5.9	81	30% MTX, 31% SSZ, 7% other DMARD, 25% combination
Nikolaisen et al. [46]	2000–06	820	2.6 (0, 25.2)	30.2 (2, 112)	8.8 (0, 32)	57	78% MTX, 19% SSZ, 2% other DMARD, 2% combination
Combe et al. [47]	2002–05	814	2.2 ± 3.4	29.4 ± 24.5	7.2 ± 5.4	44.2	NA
Carbonell et al. [48]	2004–05	111 male	1.0 (0.3, 2.7)	28 (16, 51)	NA	48	NA
	2004–05	251 female	0.7 (0.3, 2.1)	32 (17, 55)	NA	56	NA
Carli et al. [49]	1997–2001	2584	3.1 ± 3.4	35.4 ± 25.4	9.3 ± 5.3	69	DMARD

TABLE 17. *Disease status and treatment in recently published early-RA cohort . Data are presented as median (interquartile range) or mean ± s.d. unless noted otherwise. aN = 71 fulfilled ACR criteria for RA.*

In summary, using the radiographic data from the ASPIRE study, we developed two novel models for the risk of RRP in patients with early RA. Our preliminary risk models use some of the established disease characteristics (SJC, ESR, CRP and RF) that are readily available in routine clinical setting to generate easy-to-use, visual matrices that, once refined through future development, can be used to predict the risk of joint damage progression in RA patients, particularly those with DMARD-naïve early disease. Additional exploratory development and testing of the matrix risk models in other populations and with other therapies is needed to finalize a single risk model that can be used to guide rheumatologists in making treatment decisions for individual patients with RA.

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4.2. Validation of the poor prognosis model in RA

It is obvious that outcomes predicted with a model that is created from one clinical trial with selected patients may not accurately predict outcome in patients that were not selected in accordance with the same in- and exclusion criteria. Validation of the model in other RA population is therefore needed to increase the generalizability of the results. In order to investigate the value of this methodology for prediction of rapid radiographic progression, a number of groups that that have access to databases of randomized clinical trials were approached and were asked to apply the modeling in their dataset. The results of these efforts are briefly described.

In the BeSt Study conducted in the Netherlands [1], data from 465 patients with recent-onset RA randomized to receive initial monotherapy or combination therapy were used to develop a matrix model for the prediction of RRP defined identically as above mentioned. The presence of autoantibodies, baseline CRP level, erosion score and treatment group were significant independent predictors of RRP in the matrix. The proportion of patients with RPP ranged from 5% to 78% in patients on initial monotherapy and from 1% to 42% and 1% to 34% in patients with initial combination therapy with prednisone or infliximab respectively (**Figure 18**).

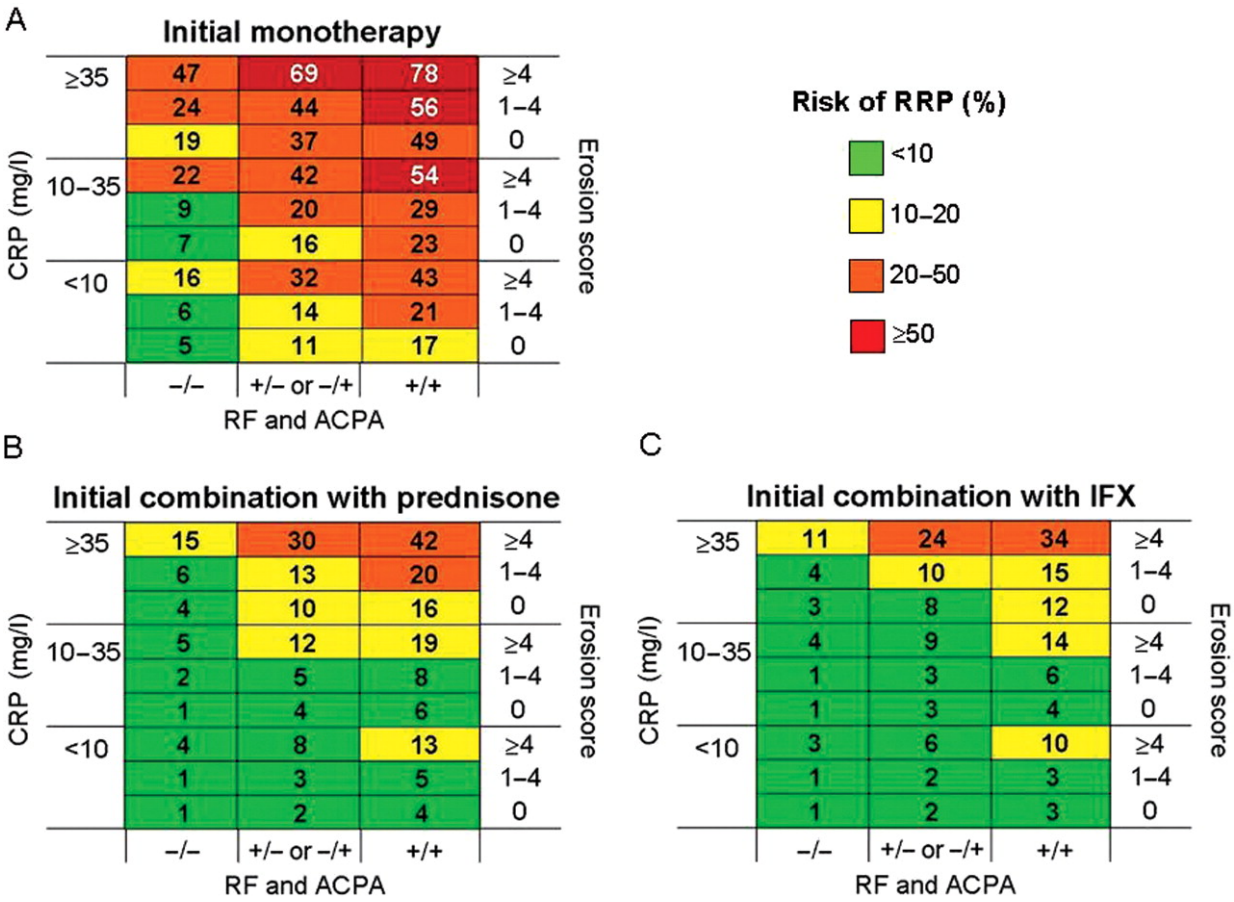

FIG.18: *Matrix predicting rapid radiographic progression in the BeSt study. From Visser et al. Ann Rheum Dis. 2010 Jul; 69(7):1333-7.*

Combination therapy was thus associated with a markedly reduced risk of RRP especially in patients with (a combination of) high CRP, baseline erosions and presence of RF and/or ACPA. The NNT with initial combination therapy to prevent one patient from RRP with monotherapy was in the range 2–3, 3–7 and 7–25 for patients with a high (i.e. >=50%), intermediate (i.e. 20%-50%) and low predicted risk (<20%), respectively. Positive and negative predictive values of the matrix were 62% and 91%, respectively. They concluded that the model, having a better negative predictive (NPV) value than a positive predictive value (PPV), is a better tool to help decide who should not rather than who should undergo a more intensive treatment strategy.

In the SWEFOT study from Sweden [2], radiological data of 277 DMARD naïve patients who were initially started on methotrexate (MTX, target dose 20 mg/week) were used for a similar analysis. In this study, patients who achieved a low disease activity after 3-4 months continued on MTX, while the other patients were randomized to add either SSZ and hydroxychloroquine (HCQ) or infliximab. Sixty five patients had RRP. Different combinations of predictors of RRP were combined in 3-parameter matrices and the results compared for overall differentiation between low-risk versus high-risk as well as for clinical feasibility and ease of use. The model which included CRP, baseline erosions and current cigarette smoking differentiated best between RA patients with and without risk of RRP. Rheumatoid factor (RF)/anti-cyclic citrullinated peptide (anti-CCP) positivity did not significantly predict radiographic progression using the definition of RRP with ≥5 units increase on the SHS score as cut-off. In a secondary exploratory analysis using cut-off >1 for radiographic progression, both RF and anti-CCP positivity were significant predictors in unadjusted, but not adjusted analyses. A step-up gradient was observed, where 63% of the patients carrying all the predictors had developed RRP after 1 year in comparison to only 12 % of patients without these predictors. The risk ratio for highest versus lowest risk was 5.88 (95% CI 2.36-14.62).

Researchers from France [3] used a registry to quantify RRP in daily practice and evaluated whether matrix models incorporating characteristics that are associated with radiographic progression could be used for risk stratification. In the ESPOIR cohort RRP was measured in 11.1% of 370 early RA patients who had received a DMARD during the first year of follow up and combining autoantibodies, CRP, swollen joint counts and baseline erosions allowed predicting a risk of RRP that ranged from 2% to 64% (**Figure 19**).

		Absence of typical RA erosion on radiographs			Presence of typical RA erosions on radiographs		
		SJC < 14	14 ≤ SJC < 20	SJC ≥ 20	SJC < 14	14 ≤ SJC < 20	SJC ≥ 20
ACPA positivity	CRP ≥ 35	0.12 [0.05; 0.23]	0.16 [0;0.91]	0.33 [0.10; 0.84]	0.34 [0.17; 0.54]	0.40 [0.16; 0.67]	0.64 [0.28; 0.88]
	4 ≤ CRP < 35	0.12 [0.07; 0.19]	0.16 [0;0.9]	0.32 [0.09; 0.63]	0.33 [0.19; 0.50]	0.40 [0.18; 0.52]	0.64 [0.24; 0.88]
	CRP < 4	0.06 [0.01; 0.13]	0.07 [0.01; 0.24]	0.17 [0.03; 0.52]	0.18 [0.04; 0.35]	0.22 [0.04; 0.52]	0.43 [0.07; 0.82]
ACPA negativity	CRP ≥ 35	0.04 [0.01; 0.10]	0.06 [0.01; 0.16]	0.14 [0.03; 0.33]	0.15 [0.04; 0.31]	0.18 [0.05; 0.43]	0.37 [0.08; 0.68]
	4 ≤ CRP < 35	0.04 [0.01; 0.08]	0.06 [0.01; 0.15]	0.14 [0.03; 0.33]	0.14 [0.04; 0.28]	0.18 [0.05; 0.44]	0.37 [0.08; 0.69]
	CRP < 4	0.02 [0; 0.04]	0.03 [0; 0.08]	0.07 [0.01; 0.19]	0.07 [0.02; 0.15]	0.08 [0.01; 0.24]	0.20 [0.02; 0.52]

RRP Risk
≥ 50%
25 ≤ < 50%
10 ≤ < 25%
< 10%

FIG.19: *Matrix predicting RRP in early RA patients in clinical practice in France. From Arthritis Res Ther. 2012; 14(6): R249.*

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4.3. Prediction of Remission and Low Disease Activity in DMARD-refractory Patients with Rheumatoid Arthritis Treated with Golimumab

4.3.1. Abstract

Objective

To create a tool to predict probability of remission and low disease activity (LDA) in patients with rheumatoid arthritis (RA) being considered for anti-TNF treatment in clinical practice.

Methods

We analyzed data from GO-MORE, an open-label, multinational, prospective study in biologic-naïve patients with active RA (28-joint disease activity score based on erythrocyte sedimentation rate [DAS28-ESR] ≥3.2) despite DMARD therapy. Patients received 50-mg subcutaneous golimumab (GLM) once monthly for 6 months. In secondary analyses, regression models were used to determine the best set of baseline factors to predict remission (DAS28-ESR <2.6) at month 6 and LDA (DAS28-ESR ≤3.2) at month 1.

Results

In 3280 efficacy-evaluable patients, of 12 factors included in initial regression models predicting remission or LDA, 6 were retained in final multivariable models. Greater likelihood of LDA and remission was associated with being male; younger age; lower Health Assessment Questionnaire (HAQ), erythrocyte sedimentation rate (or C-reactive protein), and tender joint count (or swollen joint count) scores; and absence of comorbidities. In models predicting 1-, 3-, and 6-month LDA or remission, area under the receiver operating curve was 0.648 to 0.809 (R^2=0.0397 to 0.1078). The models also predicted 6-month HAQ and EuroQoL-5-Dimension scores. A series of matrices were developed to easily show predicted rates of remission and LDA.

Conclusions

A matrix tool was developed to show predicted GLM treatment outcomes in patients with RA, based on a combination of 6 baseline characteristics. The tool could help provide practical guidance in selection of candidates for anti-TNF therapy.

4.3.2. Introduction

To make best use of resources for biologic treatment in patients with rheumatoid arthritis (RA), it would be useful to identify a set of predictors that enable selection of patients who will benefit most from such treatment and avoid treatment of patients who are unlikely to respond. Several studies have evaluated predictors of outcomes during anti-tumor necrosis factor (TNF) treatment (for a review, see Callaghan, 2014 [1]; Katchamart, 2010 [2]). One limitation of some of these studies [3] is that the predictive capacity of single predictors is low (vs combinations of predictors), and they are less useful when making practice decisions for individual patients.

Although there is variability in which factors have predictive ability, some of the baseline characteristics that have been found to predict anti-TNF outcomes include baseline age (e.g., Hetland, 2010;[4] Radovits, 2009[5]), smoking (eg, Barnabe, 2014 [6]; Hyrich, 2006 [7]; Mattey, 2009 [8]), gender (eg, Barnabe, 2014 [6]; Mancarella, 2007[9]), disease activity (eg, Kristensen, 2008 [10]; Listing, 2006 [11]) and functional ability (eg, Hetland, 2010[4]). Predictors that are significant across studies may depend on factors such as the patient population, type of treatment, the outcome being evaluated, and whether the outcome is a state measure or an improvement measure.

Current European League Against Rheumatism (EULAR) recommendations emphasize low disease activity (LDA) or remission as the treatment goal in RA and advocate the use of poor prognostic factors to guide treatment decisions [12]. If a patient does not attain remission or LDA with disease-modifying anti-rheumatic drugs (DMARDs) and if poor prognostic factors are present (eg, high disease activity, rheumatoid factor [RF] positivity, and anti-cyclic citrullinated peptide [CCP] antibodies, erosive disease), EULAR recommendations suggest the addition of a biologic treatment. However, poor prognostic factors such as high baseline disease activity have also been shown to be associated with poorer anti-TNF treatment outcomes; that is, patients who begin anti-TNF treatment with high disease activity have been reported to be less likely to achieve remission or LDA than patients who begin treatment with more moderate disease activity (eg, Combe, 2014 [13]; Listing, 2006 [11]). This adds complexity to clinical decisions balancing risks and benefits to determine which patients will benefit most from anti-TNF treatment.

The goal of these analyses was to develop a tool that can be used to assist in decision making to optimize treatment goal attainment in patients with RA who have failed DMARD treatment. The tool identifies groups of patients who would most likely benefit from golimumab (GLM) therapy and presents findings in a form that is simple and can be used in daily clinical practice.

4.3.3. Methods

4.3.3.1. Design and Patients

Analysis of associations between baseline characteristics and outcomes of treatment was a key secondary objective of the GO-MORE trial. GO-MORE was an open-label, prospective study of add-on treatment with GLM in patients with active RA despite DMARD treatment in 40 countries (protocol P06129; NCT00975130). Details of the study procedures have been previously reported (Combe et al, 2014) and are only briefly described here. The study received approval from appropriate research ethics committees and was conducted in accordance with the Declaration of Helsinki and standards of good clinical research practice. All patients consented to participate. Data were collected from October 29, 2009, to July 21, 2011.

Patients in GO-MORE were biologic-naïve with active RA (28-joint disease activity score based on the erythrocyte sedimentation rate [DAS28-ESR] ≥3.2) despite DMARD therapy and had no contraindications for TNF inhibitor treatment.

4.3.3.2. Study Procedures

In the first 6 months of GO-MORE, all patients received monthly subcutaneous GLM 50 mg administered by autoinjector and had efficacy and safety assessments at month 1, 3, and 6. At month 6, patients who had good or moderate EULAR response but were not in remission were able to continue to part 2 of the study, an extension phase which is described in length elsewhere [13].

4.3.3.3. Statistical Analyses

A sequence of steps was used to develop an optimal model to predict remission. The main outcomes to be predicted were DAS28-ESR LDA at end of month 1 (after 1 injection) and remission at the end of month 6. The model's ability to predict DAS-28-ESR remission, DAS28-ESR LDA, Simple Disease Activity Index (SDAI) remission (SDAI ≤3.3) and LDA (SDAI ≤11=LDA), and DAS28 based on C-reactive protein (CRP) (cutoff criteria: <2.6 and ≤3.2) at different time-points during treatment was also explored.

Baseline predictors included in the initial univariate analyses were gender, age, disease duration, smoking status, comorbidities, number of previously failed DMARDs, 28-joint tender joint count (TJC28), 28-joint swollen joint count (SJC28), patient global assessment of disease activity (PGA; measured on a 100-mm visual analog scale [VAS]), health assessment questionnaire (HAQ) score, methotrexate dose, and log ESR. Characteristics that predicted DAS28-ESR remission at month 6 and LDA at month 1 at the $p<0.10$ level were retained and used in multivariable models. Stepwise selection was used as a sensitivity analysis to confirm the factors selected for the model.

To determine whether TJC and SJC or ESR and CRP could be used interchangeably with no loss in predictive power, multivariable models switching out these components were compared. Area under the receiver operating characteristic curve (AUC-ROC) analysis and R^2 were used to evaluate the models.

To create the matrix tool, continuous variables were transformed to categorical variables, using tertiles or quartiles. Models with 3- and 4-level categories were evaluated using AUC-ROC analysis. The predicted LDA/remission rates were displayed in an easily readable color-coded matrix.

Additional analyses were performed to explore the model's usefulness and limitations. First, the associations between the predictors and outcomes of physical function (HAQ) and quality of life (EuroQol-5-dimension [EQ-5]) were explored. Next, the association between the predictors and DAS28 improvement (as opposed to DAS28 disease state) over 6 months was investigated. Finally, the association between the predictors and EULAR response was evaluated, because EULAR response included measures of both disease state and amount of improvement from baseline. For these additional analyses, patients were divided into subgroups of DAS28 predicted remission at 6 months (patients predicted to have <10% chance of DAS28 remission, 10%–<20%, 20%–<30%, 30%–<40%, 40%–<50%, and ≥50%) For patients in each prediction subgroup, median and interquartile ranges for DAS28, HAQ, and EQ-5D at baseline and 6 months and the change in value from baseline to 6 months were calculated.

4.3.4. Results

4.3.4.1. Disposition and baseline characteristics.

Of 3366 patients enrolled in GO-MORE, 3280 were included in the efficacy evaluable population. The patient disposition and baseline characteristics are fully reported in Combe et al, 2014. A summary of baseline characteristics is shown in Table 18.

Patient Characteristics	N=3280
Demographic Characteristics	
Female, n (%)	2716 (82.8%)
Age, y	
Mean (SD)	52.3 (12.8)
Median (min, max)	53.0 (18, 88)
Disease Characteristics	
Disease duration (y)	n=3279
Mean (SD)	7.6 (7.9)
Median (min, max)	4.9 (0.01, 56.6)
TJC28, Mean (SD)	13.0 (6.81)
SJC28, Mean (SD)	9.6 (5.56)
DAS28-ESR	n=3270
Moderate Disease Activity (3.2–5.1), n (%)	698 (21.3)
High Disease Activity (>5.1), n (%)	2572 (78.7)
Mean (SD)	5.97 (1.095)
DAS28-CRP	n=3236
Mean (SD)	5.41 (0.998)
CRP (mg/L)	n=3236
Mean (SD)	14.48 (20.376)
ESR (mm/hr)	n=3280
Mean (SD)	34.9 (24.64)
Anti-CCP	n=3225
Positive (≥20 U/mL), n (%)	2318 (71.9)
Rheumatoid Factor	n=3234
Positive (≥15 IU/mL), n (%)	2344 (72.5)
HAQ-DI, Mean (SD)	1.44 (0.67)

Table adapted from Combe et al, 2014. *Ann Rheum Dis* 2014 Aug;73:1477–86 [13].

TABLE 18: *Demographics & Baseline Characteristics of Patients in the Efficacy Population of GO-MORE.*

A majority of patients were female (82.8%, 2716/3280) and the mean age was 52.3 years (SD=12.8). A majority of patients 78.7% (2572/3280) had high disease activity (DAS28-ESR >5.1) at baseline; the remaining patients had moderate disease activity (DAS28-ESR of 3.2–5.1) at baseline. At least 1 comorbidity was reported by 76.2% of patients (2499/3280). See Table 19 for a list of the comorbidities that were reported in ≥2% of patients.

System Organ Class	Preferred Term	n (%)
Blood and lymphatic system disorders	Anemia	113 (3.45)
Endocrine disorders	Hypothyroidism	270 (8.23)
Gastrointestinal disorders	Gastritis	156 (4.76)
	Gastrooesophageal reflux disease	86 (2.62)
	Dyspepsia	72 (2.20)
Immune system disorders	Drug hypersensitivity	112 (3.41)
Infections and infestations	Latent tuberculosis	244 (7.44)
Metabolism and nutrition disorders	Hypercholesterolemia	266 (8.11)
	Diabetes mellitus	167 (5.09)
	Hyperlipidemia	108 (3.29)
	Dyslipidemia	103 (3.14)
	Obesity	87 (2.65)
Musculoskeletal & connective tissue disorders	Osteoporosis	336 (10.24)
	Osteoarthritis	276 (8.41)
	Osteopenia	135 (4.12)
	Spinal osteoarthritis	96 (2.93)
	Back pain	74 (2.26)
	Sjogren's syndrome	69 (2.10)
Psychiatric disorders	Depression	197 (6.01)
	Insomnia	78 (2.38)
Respiratory, thoracic & mediastinal disorders	Asthma	133 (4.05)
Social circumstances	Postmenopause	89 (2.71)
	Menopause	84 (2.56)
Vascular disorders	Hypertension	962 (29.33)
	Varicose vein	77 (2.35)

Note: Patients were excluded from the trial for the following conditions:

1. Evidence of active TB or latent TB that is untreated
2. History of lymphoproliferative disease or any unknown malignancy or history of malignancy within the previous 5 years, with the exception of non-melanoma skin cancer that has been treated with no evidence of recurrence.
3. History of moderate to severe heart failure even if medically controlled.
4. An inflammatory rheumatic disease other than RA that might confound the evaluations of safety and toxicity such as, but not limited to, ankylosing spondylitis and psoriatic arthritis.
5. Any systemic inflammatory condition with signs and symptoms that might confound the evaluations of safety and toxicity from GLM therapy, including, but not limited to: active Lyme disease, systemic lupus erythematosus, infectious or reactive arthritis, Reiter's syndrome, non-rheumatoid vasculitis, or parvovirus infection.
6. Allergy/sensitivity to investigational product(s) or its/their excipients, including latex.
7. Pregnant or intending to become pregnant.
8. Any clinically significant condition or situation, other than the condition being studied that, in the opinion of the investigator, would interfere with the trial evaluations or optimal trial participation.

TABLE 19: *Comorbidities Reported in at Least 2% of Patients (N=3280).*

4.3.4.2. Regression model for prediction of remission and LDA.

At the end of month 6, 23.9% of patients had achieved DAS28-ESR remission and 37.4% achieved LDA; at the end of month 1, 16.6% of patients had achieved LDA (Combe et al, 2014). Initial univariate analyses narrowed the set of factors that were candidates for the multivariable models predicting remission and LDA. Factors retained (those that had significant relationships [*P* <.10] with DAS28 remission at month 6 and LDA at month 1) were analyzed in a multivariable model predicting DAS28-ESR remission at month 6 (Table 20). Factors retained after this step were gender, HAQ, presence of comorbidities, age, TJC, and ESR. Smoking was associated with remission at 6 months but not with LDA at 1 month, and therefore was not retained.

Baseline Variable	Wald Chi-square	*P* value
	Remission at Month 6	
Gender	13.1130	.0003
Smoking history	7.0247	.0298
MTX category	1.2557	.7397
HAQ category	14.5097	.0007
Comorbidities	9.4939	.0021
Age	18.4272	<.0001
TJC28	48.2602	<.0001
SJC28	0.6006	.4384
Disease duration, y	0.2943	.5875
Patient VAS	2.5396	.1110
ESR (log)	109.9716	<.0001
	Low Disease Activity at Month 1	
Gender	9.3505	.0022
Age	8.1473	.0043
MTX category	2.1650	.5389
HAQ category	6.2534	.0439
Comorbidities	10.0289	.0015
TJC28	103.1994	<.0001
SJC28	5.5348	.0186
Patient VAS	9.8722	.0017
ESR (log)	150.1696	<.0001

TABLE 20: Initial Multivariate Model Predicting DAS28-ESR Remission at Month 6 and Low Disease Activity at Month 1

Overall, the predictive value of the model (Table 21) was slightly weakened by replacing TJC with SJC or by replacing CRP with ESR in the models predicting DAS28. The patterns were similar for models predicting SDAI and DAS28-CRP outcomes at months 1, 3, and 6. Prediction of outcomes at month 1 was slightly better than for outcomes at month 6.

Outcome predicted	Baseline Predictor Set[a]	Month 1		Month 3		Month 6	
		AUC	R^2	AUC	R^2	AUC	R^2
DAS28-ESR remission	With TJC, ESR	0.809	0.0954	0.738	0.1002	0.717	0.1078
	With SJC, CRP	0.729	0.0521	0.694	0.0696	0.687	0.0815
	With TJC, CRP	0.758	0.0660	0.707	0.0788	0.702	0.0949
DAS28-ESR LDA	With TJC, ESR	0.795	0.1565	0.734	0.1372	0.710	0.1261
	With SJC, CRP	0.724	0.0937	0.682	0.0874	0.665	0.0807
	With TJC, CRP	0.757	0.1202	0.702	0.1057	0.690	0.1052
SDAI remission	With TJC, ESR	0.708	0.0168	0.664	0.0282	0.655	0.0394
	With SJC, CRP	0.703	0.0153	0.648	0.0226	0.648	0.0353
	With TJC, CRP	0.706	0.0158	0.663	0.0288	0.658	0.0409
SDAI LDA	With TJC, ESR	0.707	0.0145	0.661	0.0266	0.660	0.0397
	With SJC, CRP	0.705	0.0144	0.649	0.0224	0.651	0.0352
	With TJC, CRP	0.701	0.0142	0.662	0.0281	0.664	0.0418
DAS28-CRP <2.6	With TJC, ESR	0.738	0.0777	0.687	0.0785	0.674	0.0820
	With SJC, CRP	0.698	0.0536	0.658	0.0570	0.661	0.0711
	With TJC, CRP	0.737	0.0780	0.687	0.0795	0.683	0.0924
DAS28-CRP ≤3.2	With TJC, ESR	0.751	0.1448	0.700	0.1152	0.683	0.0995
	With SJC, CRP	0.712	0.1063	0.681	0.0954	0.661	0.0791
	With TJC, CRP	0.753	0.1473	0.705	0.1209	0.689	0.1071

[a]All factor sets include continuous HAQ and categorical gender and comorbidity. Inclusion of ESR, CRP, TJC, and SJC varied as indicated. TJC, SJC, ESR, and CRP were all continuous variables. CRP was used in logarithm scale.

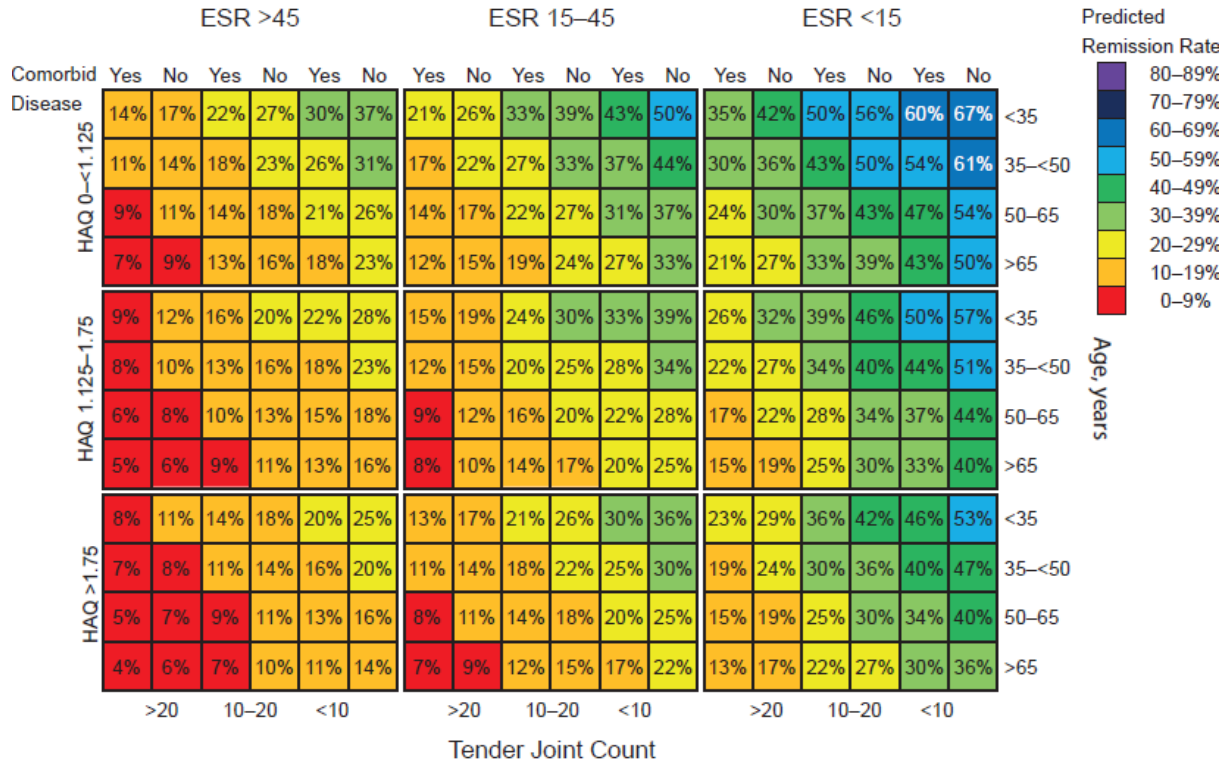
TABLE 21: *AUC and R^2 for Prediction of Several Different Outcomes With 3 Different Sets of Baseline Factors.*

To translate the data into the prediction matrix tool, continuous predictor variables (age, ESR, and TJC) had to be transformed to categorical variables with either 3 or 4 levels. AUC and R^2 values for models with the continuous versus categorical variables indicated that little predictive power was lost moving from continuous to categorical variables (data not shown). Categorical variables with 3 levels were selected for all but age because this resulted in a simpler matrix tool.

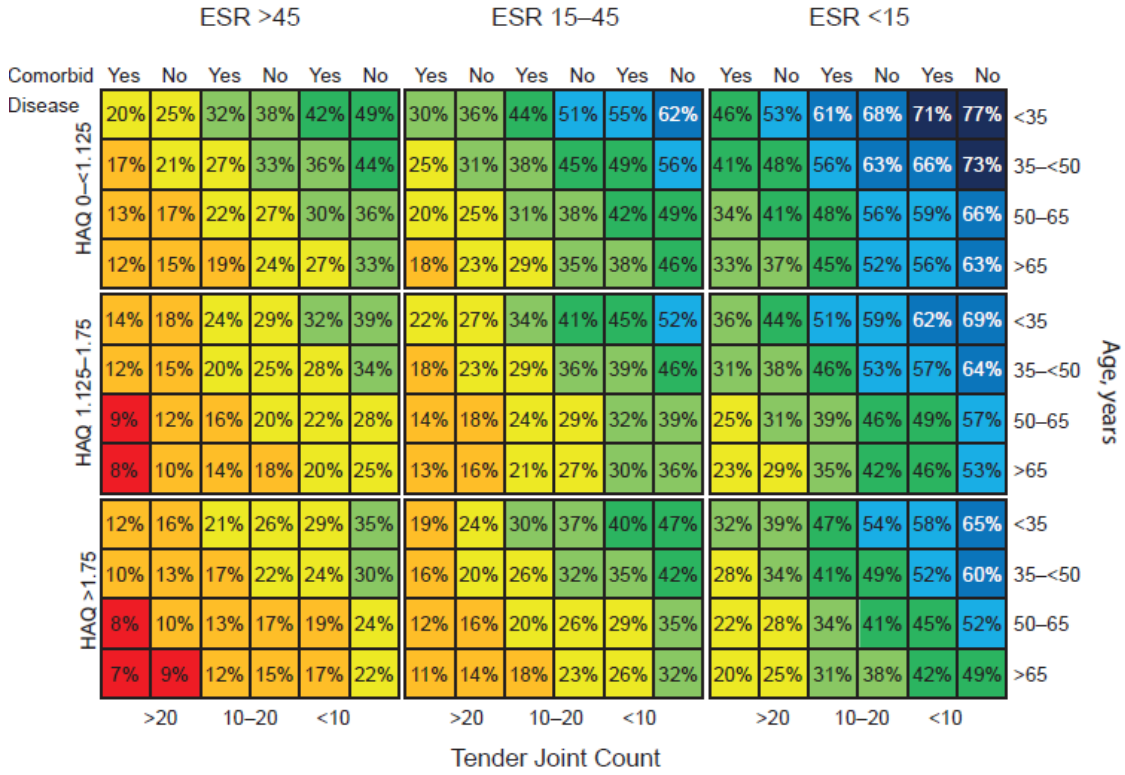
4.3.4.3. Prediction matrix tool

Predicted remission and LDA rates from the final multivariable models were used to create a series of matrix tools, as shown in Figure 20 and Figure 21. Figures for males and females were generated separately (the impact of each predictor was similar in each gender group, but males had better outcomes overall). Separate models were generated to predict DAS28 remission and LDA, and for SDAI remission and LDA. In addition, separate models were created for use with ESR versus CRP as the inflammatory marker.

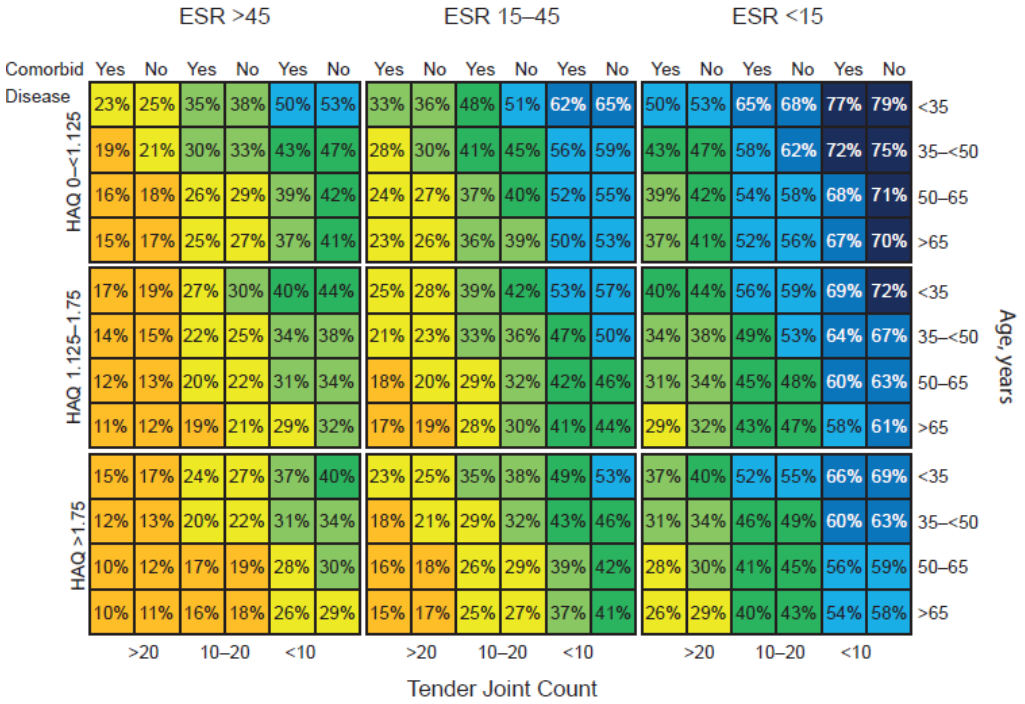
A. 6-Month DAS28-ESR remission in females



B. 6-Month DAS28-ESR remission in males



C. 6-Month DAS28-ESR LDA in females



D. 6-Month SDAI LDA with CRP instead of ESR as a predictor in females

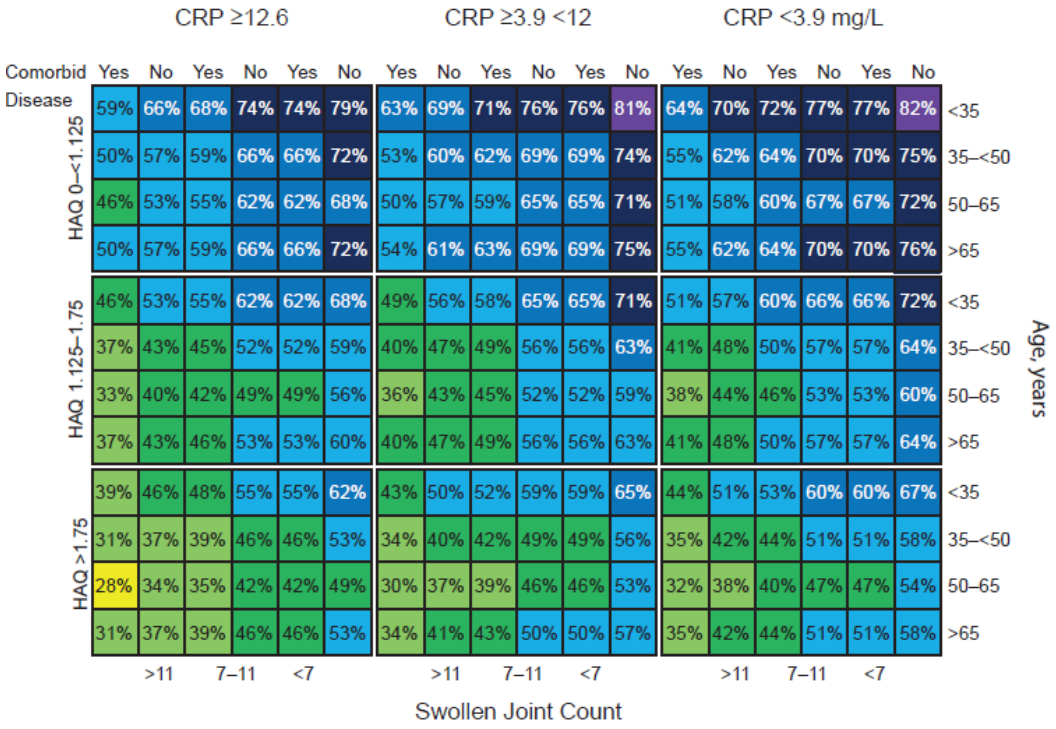
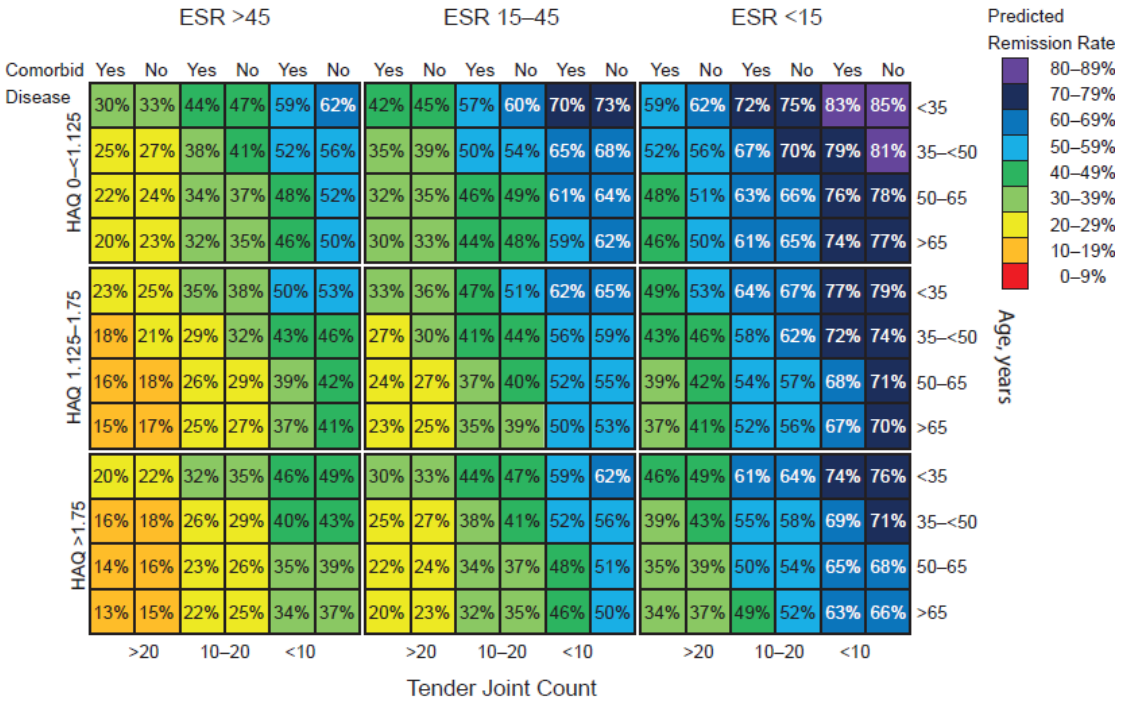


FIG. 20: Matrix model estimates of outcomes at month 6 of golimumab treatment by each combination of predictor variables. Predicted rates shown for DAS28-ESR remission in female (A) and male (B) patients, DAS28-ESR LDA in female patients (C), and SDAI low disease activity in female patients using CRP instead of ESR as a predictor (D).

A. 6-Month DAS28-ESR LDA in males



B. DAS28-ESR LDA in male patients with CRP instead of ESR as a predictor

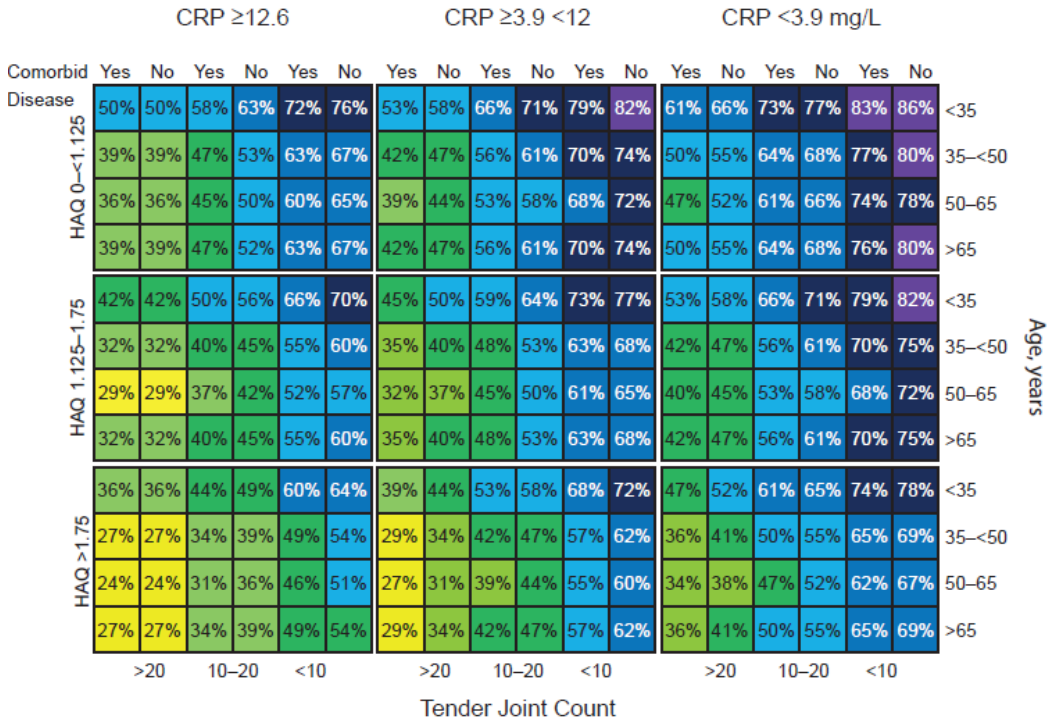


FIG. 21: *Matrix model for prediction of DAS28-ESR LDA in male patients (A) and DAS28-ESR LDA in male patients using CRP instead of ESR as a predictor (B).*

	OR (95% CI)		
	DAS28-ESR Remission		
Variable	**Month 1**	**Month 3**	**Month 6**
ESR			
<15 vs ≥45	9.18 (5.62–15.01)	4.71 (3.45–6.42)	3.43 (2.66–4.41)
≥15 to <45 vs ≥45	2.62 (1.60–4.29)	2.20 (1.64–2.94)	1.68 (1.33–2.11)
Gender			
Male vs female	1.58 (1.16–2.15	1.73 (1.37–2.19)	1.64 (1.33–2.02)
HAQ			
0 to 1.125 vs ≥1.75	1.70 (1.18–2.45)	1.40 (1.09–1.80)	1.79 (1.44–2.22)
≥1.125 to <1.75 vs ≥1.75	1.48 (0.99–2.19)	1.19 (0.91–1.56)	1.20 (0.95–1.51)
Age, y			
<35 vs ≥65	1.71 (1.02–2.87)	2.00 (1.33–2.99)	1.92 (1.35–2.73)
≥35 to <50 vs ≥65	1.15 (0.74–1.78)	1.59 (1.14–2.21)	1.54 (1.16–2.04)
≥50 to <65 vs ≥65	0.88 (0.57–1.34)	1.23 (0.90–1.70)	1.14 (0.88–1.49)
Comorbidities			
No vs yes	1.51 (1.11–2.04)	1.44 (1.15–1.81)	1.34 (1.10–1.65)
TJC			
<10 vs ≥20	5.12 (2.92–9.00)	2.81 (2.02–3.92)	2.87 (2.14–3.84)
≥10 to <20 vs ≥20	2.09 (1.18–3.70)	1.43 (1.03–1.99)	1.85 (1.39–2.45)
	DAS28-ESR Low Disease Activity		
	Month 1	**Month 3**	**Month 6**
ESR			
<15 vs ≥45	5.92 (4.32–8.11)	4.35 (3.40–5.55)	3.34 (2.67–4.18)
≥15 to <45 vs ≥45	2.13 (1.58–2.87)	1.78 (1.44–2.21)	1.67 (1.38–2.02)
Gender			
Male vs female	1.65 (1.30–2.10)	1.46 (1.18–1.80)	1.44 (1.18–1.76)
HAQB			
0 to 1.125 vs ≥1.75	1.79 (1.38–2.32)	1.59 (1.30–1.96)	1.68 (1.39–2.03)
≥1.125 to <1.75 vs ≥1.75	1.34 (1.01–1.79)	1.25 (1.00–1.56)	1.16 (0.95–1.41)
Age, y			
<35 vs ≥65	1.58 (1.07–2.33)	1.47 (1.05–2.06)	1.65 (1.20–2.26)
≥35 to <50 vs ≥65	1.07 (0.78–1.46)	1.24 (0.96–1.61)	1.27 (1.00–1.62)
≥50 to <65 vs ≥65	0.82 (0.61–1.11)	1.02 (0.80–1.30)	1.07 (0.86–1.34)
Comorbidities			
No vs yes	1.49 (1.18–1.89)	1.36 (1.11–1.65)	1.15 (0.95–1.39)
TJC			
<10 vs ≥20	6.13 (4.13–9.08)	3.65 (2.77–4.81)	3.35 (2.62–4.28)
≥10 to <20 vs ≥20	2.04 (1.37–3.03)	1.85 (1.42–2.42)	1.85 (1.46–2.33)

TABLE 22: *Odds Ratios for Associations of Individual Predictor Variables with DAS28-ESR Remission and LDA at Months 1, 3, and 6*

Each matrix shows the predicted remission or LDA rate for every combination of the 6 baseline factors, representing a total of 432 different RA subpopulations. Across all the models, the highest remission rates are in the cells at the upper right and the lowest rates in the cells at the lower left. The color codes have been added for easier visual perception use of the matrix, with each color representing an estimated range of 10% likelihood of remission or LDA; warmer colors (e.g., red, yellow) indicate worse predicted outcomes and cooler colors (e.g., blue, purple) indicate better predicted outcomes. Odds ratios associated with each factor are shown in **Table 22.**

Overall, higher remission rates are predicted for patients with male gender, absence of comorbidities, younger age, and who have lower baseline HAQ. Low baseline TJC and ESR were the strongest predictors in the model.

4.3.4.4. Additional analyses to explore the matrix model's usefulness and limitations.

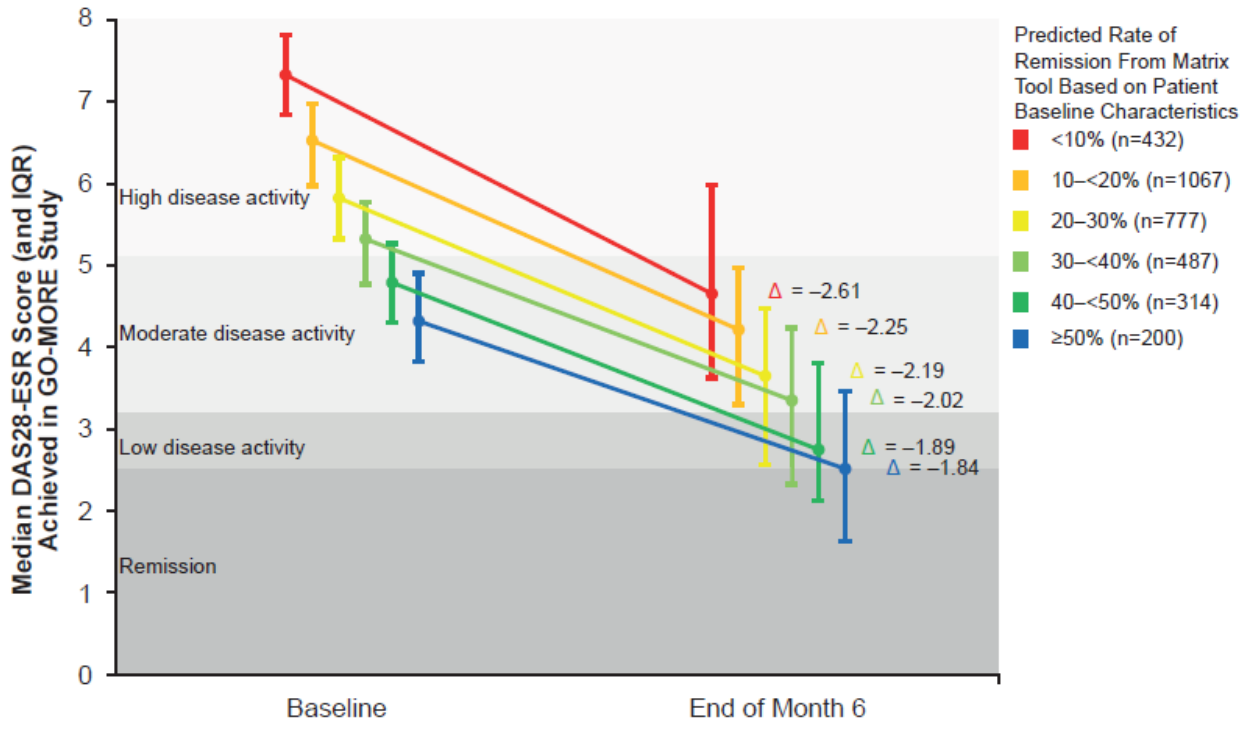
The factors in the model built to predict DAS28 remission or LDA also were associated with attainment of meaningful EQ-5D and HAQ cutoffs (Table 23). Of all the factors included in the model, baseline HAQ was most strongly related to attainment of cutoff levels for EQ-5D (≥.7 and ≥.8) and HAQ (<.5) at month 6 (ORs from 2.38 to 6.55 for the lowest vs highest HAQ score categories).

	Month 6 Response OR (95% CI)		
	EQ-5D		HAQ
Baseline predictor variable	**≥0.7**	**≥0.8**	**≤0.5**
ESR			
<15 vs ≥45	1.06 (0.85–1.33)	0.83 (0.65–1.08)	0.80 (0.63–1.02)
≥15 to <45 vs ≥45	0.98 (0.81–1.18)	0.99 (0.80–1.22)	0.80 (0.66–0.98)
Gender			
Male vs female	0.80 (0.65–0.99)	0.96 (0.77–1.21)	1.47 (1.19–1.81)
HAQ			
0 to 1.125 vs ≥1.75	5.86 (4.81–7.13)	2.38 (1.91–2.96)	6.55 (5.31–8.09)
≥1.125 to <1.75 vs ≥1.75	1.62 (1.32–2.00)	1.26 (0.99–1.60)	1.60 (1.28–2.01)
Age, y			
<35 vs ≥65	1.36 (0.99–1.87)	1.36 (0.97–1.92)	2.91 (2.06–4.12)
≥35 to <50 vs ≥65	0.90 (0.71–1.15)	0.94 (0.71–1.24)	2.18 (1.65–2.87)
≥50 to <65 vs ≥65	0.93 (0.75–1.17)	0.94 (0.75–1.22)	1.75 (1.35–2.27)
Comorbidities			
No vs yes	1.29 (1.06–1.56)	1.63 (1.33–1.99)	1.70 (1.39–2.07)
TJC			
<10 vs ≥20	1.51 (1.19–1.92)	1.44 (1.09–1.89)	1.23 (0.96–1.59)
≥10 to <20 vs ≥20	1.36 (1.09–1.71)	1.21 (0.93–1.57)	1.10 (0.86–1.39)

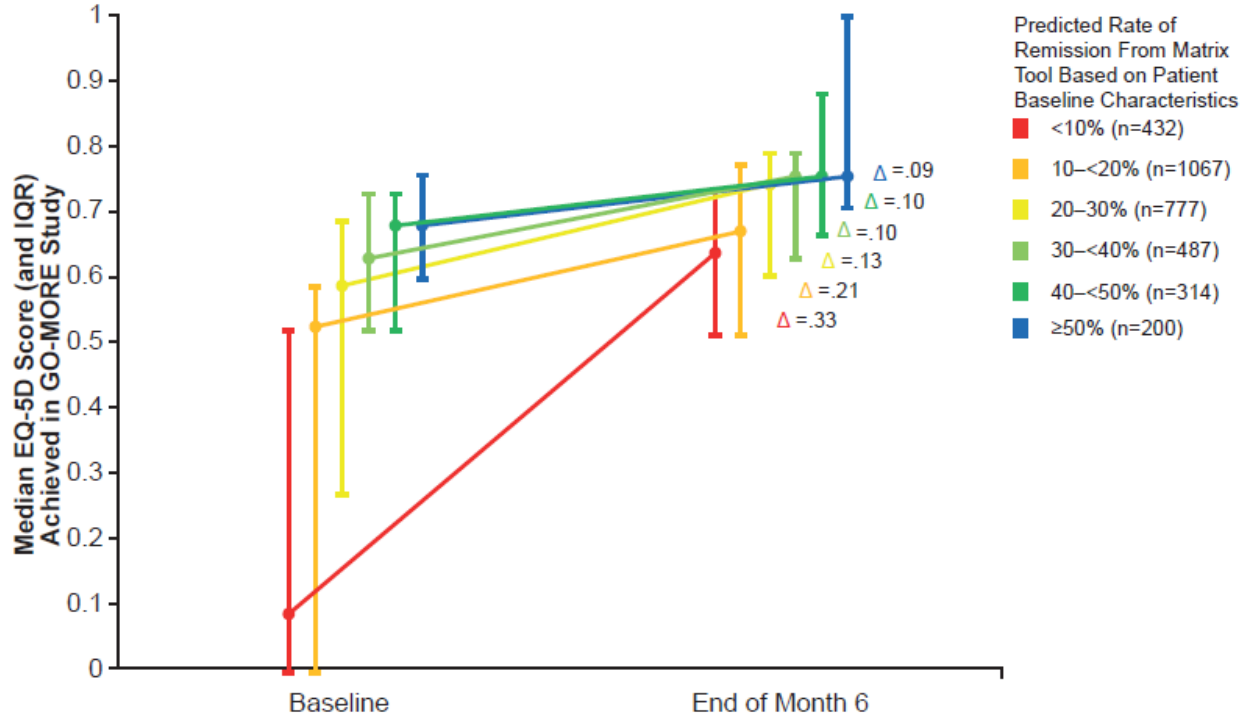
TABLE 23: Relationships Between Baseline Predictor Variables and 6-Month Outcomes of HAQ and EQ-5D scores

In Figure 22, patients are divided by their predicted rate of remission from the matrix tool, which is determined by their baseline characteristics. For each category of predicted remission (eg, patients with 10% predicted rate of remission, shown in red in both the matrix model and Figure 22), the median and IQR for baseline and month 6 DAS28-ESR are shown.

A.


Median DAS28-ESR Score (and IQR) Achieved in GO-MORE Study
8
7
6
5
4
3
2
1
0
High disease activity
Moderate disease activity
Low disease activity
Remission
Δ = –2.61
Δ = –2.25
Δ = –2.19
Δ = –2.02
Δ = –1.89
Δ = –1.84
Baseline
End of Month 6
Predicted Rate of Remission From Matrix Tool Based on Patient Baseline Characteristics
<10% (n=432)
10–<20% (n=1067)
20–30% (n=777)
30–<40% (n=487)
40–<50% (n=314)
≥50% (n=200)

B.


Median EQ-5D Score (and IQR) Achieved in GO-MORE Study
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Δ =.09
Δ =.10
Δ =.10
Δ =.13
Δ =.21
Δ =.33
Baseline
End of Month 6
Predicted Rate of Remission From Matrix Tool Based on Patient Baseline Characteristics
<10% (n=432)
10–<20% (n=1067)
20–30% (n=777)
30–<40% (n=487)
40–<50% (n=314)
≥50% (n=200)

C.

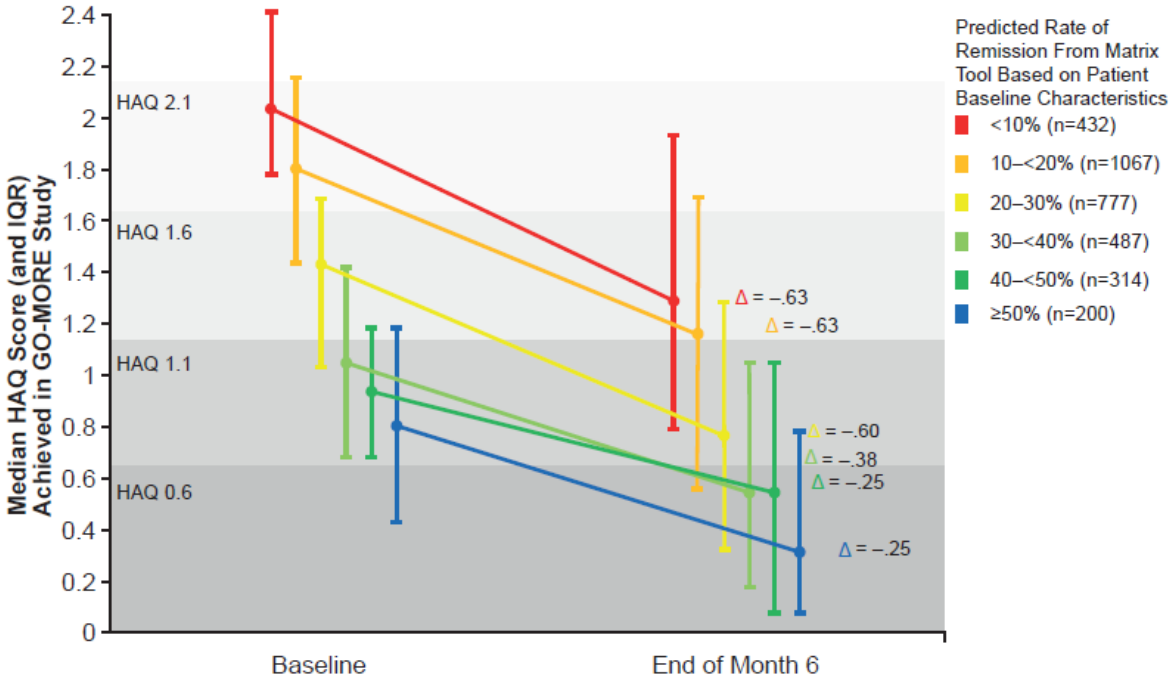


FIG. 22: *Relationship between remission rate category predicted by the matrix model and observed DAS28 (A), EQ-5D (B), and HAQ (C) scores in the GO-MORE study. The figure shows, for example, that for the patients who were predicted by the matrix tool to have a remission rate of less than 10% (red line), the actual mean DAS28 score at baseline was 7.36, with improvement of 2.61 at month 6. For patients predicted by the matrix tool to have ≥50% remission rate (blue line), their mean baseline DAS28 ESR score was 4.43, with improvement of 1.81 at month 6. Note that improvement is positive change for EQ-5D; improvement is negative change DAS28 and HAQ. Δ refers to median change.*

The data reveal that patients who were predicted to have the lowest chance of remission (ie, those in the <10% group; the red line in the figure, who also have the highest disease activity at baseline) also had the greatest change in DAS28-ESR score between baseline and month 6 (Figure 22A). That is, the patients who had the worse values of their predictors improved the most but were still the least likely to attain remission. A similar pattern was seen for HAQ and EQ-5D scores (Figure 22B and Figure 22C).

Figure 23 shows the relationship between the categories of predicted response rates from the matrix model and the attainment of EULAR response at month 6. EULAR response is a measure of both disease state and improvement over time, and it was not related to the predicted probability of remission. EULAR response was about 82%, regardless of the rate of remission predicted by the matrix tool.

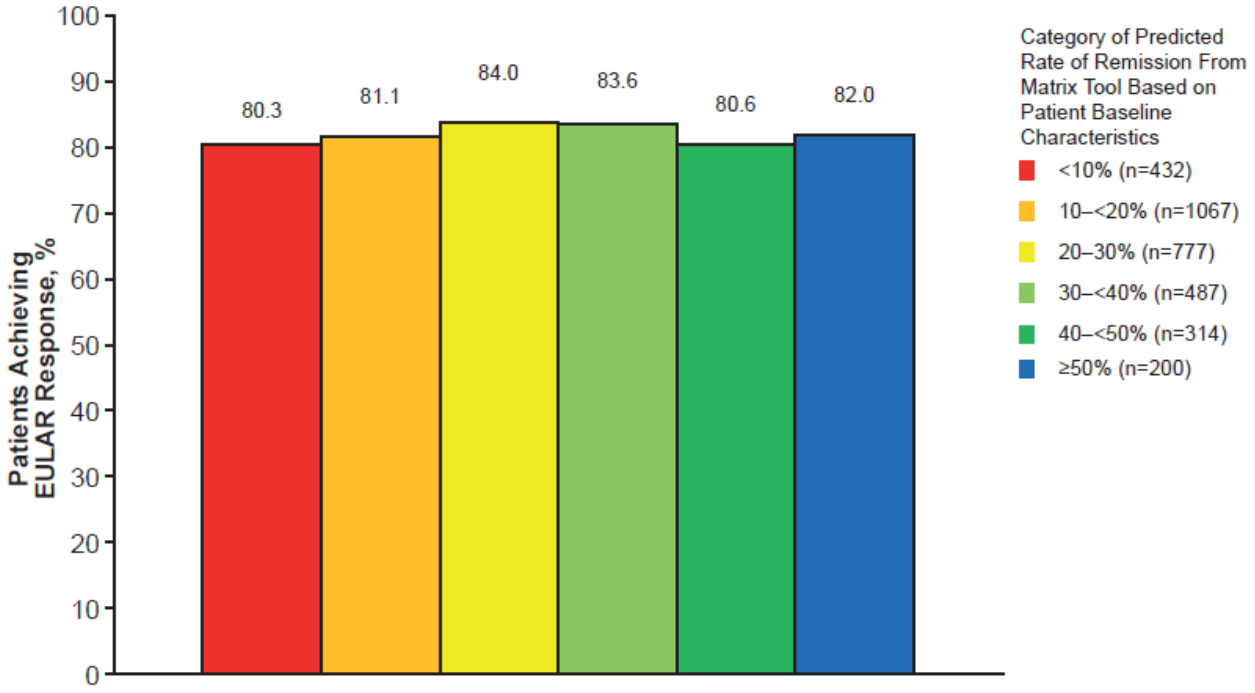


FIG 23: *For each category of predicted DAS28-ESR remission rate from the matrix model, percentage of patients who attained good or moderate EULAR response after 6 months of GLM treatment.*

4.3.5. Discussion

Tools that determine which patients with RA might benefit from biologic treatment can help make value-based decisions. We have developed a tool derived from data collected in a large trial of GLM treatment in more than 3000 patients with active RA despite DMARD treatment. The matrix tool predicts outcomes of 432 sub-populations of RA patients identified by combinations of 6 characteristics (gender, HAQ, presence of comorbidities, age, TJC, and ESR) that are associated with LDA and remission in the early treatment phase. It can assist clinicians in identification of patients for treatment, aid in establishing a treatment goal for an individual patient, and provide guidance to policy-makers for the selection of RA patient populations that are likely to achieve good disease states from anti-TNF treatment. The model can be used to predict outcomes at several time points during treatment, and the predictions for disease activity are also relevant to physical function and quality-of-life outcomes. A similar matrix model approach to visualizing prediction of remission and response has been developed for patients with ankylosing spondylitis treated with biologics [14].

The data are important when considering the implications of treatment recommendations and reimbursement criteria on both patient selection criteria and patient outcomes as patients are considered for anti-TNF treatment. For example, in the United Kingdom (UK), reimbursement for biologic treatment in RA is limited to patients who have a DAS28 >5.1. In Belgium, the threshold for reimbursement is DAS28 >3.7. The GO-MORE study included patients from both of these countries, and we compared treatment efficacy based on these eligibility criteria. For patients from the UK, 185/263 (70%) had DAS28ESR >5.1 at baseline. For patients from Belgium, 114/123 (93%) had DAS28ESR >3.7. In these subgroups of patients who would have been eligible for reimbursement, the selection-criterion

based on DAS28 led to large differences in the HAQ score, ESR, and SJC of selected patients at baseline. As a result, remission was obtained by 20% of UK patients and 43% of Belgian patients. LDA was obtained by 35% of UK patients and 55% of Belgian patients. In this analysis, because of different policy regarding access to treatment in the UK and Belgium, the Belgian population had a doubled rate of remission.

Although patients with lower baseline disease activity were more likely to achieve remission and LDA, patients with high baseline disease activity demonstrated greater improvement. The differences in remission rates and improvement rates in the different sub-populations counterbalanced each other and resulted in nearly equal EULAR response rates across the population (**figure 23**). This may suggest that, at least for some DMARD refractory populations, response is a more appropriate goal of treatment than LDA or remission. At the same time, the excellent remission rates that can be obtained in patients with moderate disease activity may be a convincing argument to open up that patient population for treatment.

Health Technology Assessments tend to be based on change-scores between 2 treatments compared in randomized, controlled trials and resulting in cost of quality-adjusted life-years. However, when clinicians make treatment choices or adjustments to treatments, they tend to rely on disease state rather than level of improvement. Elevated disease activity in RA patients receiving anti-TNF treatment is associated with dose increases [15], and also the other direct and indirect costs of care of RA patients are significantly lower in patients with LDA or remission as opposed to those who have moderate or high disease activity [16, 17]. Physical function, and to a lesser extent disease activity state, have been shown to be the major drivers of cost of RA management. **Tables 24** and **25** summarize cost associated with different levels of HAQ, DAS28, and SDAI, and indicate that, even for biologic treated patients, function and disease activity drive health care utilization costs of patients maintained on treatment. Therefore, not only the cost associated with change of disease state but also the disease state that is achieved is of importance for value-based decision making. Once the decision to treat is made, the eventual disease state achieved will be the driver of cost and further decision making. Even if larger improvements are seen in patients with the worst values of predictors at baseline, this may be an argument to value achievement of good disease state more than improvement. Another consideration for payers is that cost of treatment may be reduced if patients, as per EULAR recommendations, can taper or stop therapy after achieving sustained remission (EULAR recommendation 12) [12]. Better selection of patients who are likely to achieve remission may increase the likelihood of tapering or stopping therapy. Early achievement of remission appears to be an important component to successfully stopping therapy, which points to the relevance of the 1- and 3-month time points we chose for prediction of disease state in our analysis [18].

Most of the factors included in the matrix model are validated by a number of studies that have analyzed individual predictors of RA treatment outcomes in studies of other biologics [1, 2], thereby increasing the face-validity of the model. Some characteristics, such as smoking, were not predictive in this dataset, but may be predictors in the overall RA population. The presence of comorbidities as a prognostic indicator has been shown previously [19], and it has also been shown that greater comorbidity is associated with greater physical disability in RA patients [3]. Because collection of comorbidity data in GO-MORE was not rigorous, and comorbidities were likely to have been underreported in this study, future work should further explore the nature of the relationship between comorbidities and RA outcomes.

HAQ score range	Sweden (n=183)[1] None on biologic			United Kingdom (n=916)[1] None on biologic			Canada (n=1086)[2] On biologic	HAQ score range	Germany[3]	Sweden[4]	Netherlands[5,6]
	Direct	Indirect	Total	Direct	Indirect	Total	Total		Sick leave	Disability (HCA)	Disability (FCA)
<0.6	$723	$0	$723	$1,228	$148	$1,376	$4,157	=1.2	€ 856	€ 4,731	€ 752
0.6– <1.1	$1,293	$5,997	$7,290	$3,152	$2,524	$5,676	$5,073				
1.1– <1.6	$1,924	$8,524	$10,448	$2,091	$3,474	$5,565	$5,645	1.2–1.7	€ 3,212	€ 12,707	€ 2,019
1.6– <2.1	$3,672	$15,588	$19,260	$3,087	$5,300	$8,387	$9,861				
2.1– <2.6	$3,363	$24,838	$28,201	$3,401	$8,070	$11,471	$14,225	>1.7	€ 7,619	€ 18,894	€ 3,002
=2.6	$1,782	$27,067	$28,849	$2,697	$8,407	$11,104					

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TABLE 24: *Mean annual cost per patient with rheumatoid arthritis by health assessment questionnaire (HAQ) score category.*

Disease state	Mean (95% CI) total health care service utilization costs in Canadian dollars[1] 87% on biologic (total n=1086)		Mean Costs (SD) in Euros [2] 36.2% on biologic (total n=356)			
			Resource use	Sick leave	Work disability (HCA)	Work disability (FCA)
	DAS28	SDAI	SDAI	SDAI	SDAI	SDAI
Remission	n=175 $3130 (2644–3617)	n=46 $2945 (1771–4120)	€828.28 (2,491.24)	€1,285.2 (1,502.1)	€5,772.8 (3,388.7)	€917.5 (538.3)
Low disease activity	n=911 $5992 (5333–6652)	n=1040 $5670 (5075–6266)	€1,039.02 (2,561.41)	€1,874.2 (2,185.9)	€7,186.6 (4,864.9)	€1,142.1 (772.8)
Median or high disease activity			€1,702.39 (3,500.74)	€3,291.9 (2,871.3)	€10,525.7 (6,129.2)	€1,672.5 (973.7)

1. Barnabe C, Thanh NX, Ohinmaa A et al. Effect of remission definition on healthcare cost savings estimates for patients with rheumatoid arthritis treated with biologic therapies. J Rheumatol 2014;41:1600–6.
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TABLE 25: *Mean annual cost per patient with rheumatoid arthritis by disease activity level measured by DAS28 or SDAI.*

Further research will be helpful to validate this model in other populations, improve its predictive ability, or expand its usefulness to include prediction of other outcomes. Although AUC in the ROC analysis of the prediction models was relatively high, not all factors that may affect response were included in the model. For example, patient expectations about effectiveness of treatment have been shown to be associated with remission [20].

4.3.6. Conclusions

A matrix tool was developed to predict GLM treatment outcomes in patients with RA, based on a combination of 6 baseline demographic and disease characteristics of patients. Value of the outcome of therapy may be the amount of improvement in disease activity or the eventual disease state achieved. It is expected that such a tool will assist physicians, guideline committees, and payers in providing practical guidance on identification and selection of appropriate candidates for anti-TNF therapy.

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4.4. Predicting the outcome of ankylosing spondylitis therapy

4.4.1. Abstract

Objectives

To create a model that provides a potential basis for candidate selection for anti-tumor necrosis factor (TNF) treatment by predicting future outcomes relative to the current disease profile of individual patients with ankylosing spondylitis (AS).

Methods

ASSERT and GO–RAISE trial data (n=635) were analysed to identify baseline predictors for various disease-state and disease-activity outcome instruments in AS. Univariate, multivariate, receiver operator characteristic and correlation analyses were performed to select final predictors. Their associations with outcomes were explored. Matrix and algorithm-based prediction models were created using logistic and linear regression, and their accuracies were compared. Numbers needed to treat were calculated to compare the effect size of anti-TNF therapy between the AS matrix subpopulations. Data from registry populations were applied to study how a daily practice AS population is distributed over the prediction model.

Results

Age, Bath ankylosing spondylitis functional index (BASFI) score, enthesitis, therapy, C-reactive protein (CRP) and HLA-B27 genotype were identified as predictors. Their associations with each outcome instrument varied. However, the combination of these factors enabled adequate prediction of each outcome studied. The matrix model predicted outcomes as well as algorithm-based models and enabled direct comparison of the effect size of anti-TNF treatment outcome in various subpopulations. The trial populations reflected the daily practice AS population.

Conclusion

Age, BASFI, enthesitis, therapy, CRP and HLA-B27 were associated with outcomes in AS. Their combined use enables adequate prediction of outcome resulting from anti-TNF and conventional therapy in various AS subpopulations. This may help guide clinicians in making treatment decisions in daily practice.

Ankylosing spondylitis (AS) is characterised by back pain caused by inflammation of the sacroiliac joints and spine. The management of AS includes non-pharmacological, pharmacological, invasive and surgical interventions that should be tailored to each patient's disease manifestations, current symptoms, clinical findings and prognostic indicators [1]. Non-steroidal anti-inflammatory drugs (NSAID) are recommended as first-line pharmacological treatment, and anti-tumour necrosis factor (TNF) agents are recommended in the case of NSAID failure [2–6].

Predictors of response to therapy may enable improved patient selection, outcomes and resource utilization [7, 8]. The recommendations for anti-TNF use in AS are, however, based primarily on inadequate response to conventional therapies and less on the expectation that an anti-TNF agent will be effective in a particular patient [2]. The literature continues to establish predictors of response [9–14], which are also associated with anti-TNF use in AS [15]. Ideally, these may help clinicians to make evidence-based decisions that maximise the benefits from treatment by targeting subsets of patients most likely to respond [16]; however, single predictors are too weak to be useful for decision-making in the individual patient.

This paper describes the predictor selection and construction of a model that identifies AS subpopulations likely to respond optimally to anti-TNF therapy. In the absence of a 'hard outcome' parameter that can be predicted in AS, such as mortality in cardiovascular disease, the ability and robustness of the predictor model to predict the results of a variety of AS outcome instruments were explored.

In addition, the distribution of AS registry populations encountered in daily rheumatology practice over the prediction model was evaluated.

4.4.2. Patients and methods

This is a post-hoc analysis of the ASSERT and GO–RAISE trials in adult patients with active AS despite NSAID or disease-modifying antirheumatic drugs (DMARD) and naive to anti-TNF therapy.

In ASSERT, patients were randomly assigned to receive infusions of placebo or 5 mg/kg infliximab at weeks 0, 2, 6, 12 and 18 and were allowed to receive concurrent NSAID but not DMARD or systemic corticosteroids [5]. In GO–RAISE, patients were randomly assigned to receive subcutaneous injections of placebo or 50 or 100 mg golimumab every 4 weeks and could continue concurrent NSAID, DMARD and systemic corticosteroids. For our analysis, week 16 data from GO–RAISE were carried forward to week 24 for placebo patients who received golimumab starting at week 16 [4]. Week 24 data were collected between November 2002 and September 2003 in ASSERT and between December 2005 and May 2007 in GO–RAISE.

4.4.2.1. Outcome instruments

The Bath ankylosing spondylitis disease activity index (BASDAI) score measures disease activity based on six questions on fatigue, spinal pain, joint pain/swelling, areas of localised tenderness and morning stiffness [17]. BASDAI50 response is defined as a 50% or greater improvement in the BASDAI score.

Assessment of spondyloarthritis (ASAS) 20 response is an improvement of 20% or more in the patient global assessment (PGA), patient assessment of pain, Bath ankylosing spondylitis functional index (BASFI) score and assessment of inflammation. ASAS partial remission is achieved when the value of each of these domains is less than 2 cm on a 10-cm visual analogue scale [18].

The ankylosing spondylitis disease activity score (ASDAS) measures disease activity state using an algorithm comprising assessment of back pain, morning stiffness duration, joint pain/swelling, PGA and C-reactive protein (CRP) [19, 20]. Clinically important and major ASDAS improvements are defined as a decrease of 1.1 units or more and 2.0 units or more, respectively. ASDAS less than 1.3 is the threshold for an inactive disease state [21].

The association of the following characteristics at baseline with BASDAI50 response and partial remission was studied: age, gender, HLA-B27 status, disease duration, CRP, BASFI, Bath ankylosing spondylitis metrology index (BASMI) score, chest expansion, intermalleolar distance, tragus to wall distance, modified Schobers index, lateral spinal flexion, cervical rotation, PGA, pain assessment, BASDAI, inflammation score, Berlin enthesitis score index and treatment group. MRI, x-rays of the spine and peripheral joint counts were not available for the analysis.

4.4.2.2. Statistics

4.4.2.2.1. Study population

The ASSERT and the GO–RAISE datasets were summarised using means±SD and were also combined into a third dataset.

4.4.2.2.2. Outcome predictor selection

Predictors of week 12 BASDAI50 response and week 24 partial remission were identified by comparing the values of the aforementioned baseline characteristics between responders and non-responders and between remitters and non-remitters using Student's t test and $\chi 2$ tests. Variables that differed at p=0.1 were explored further.

Multivariate regression and stepwise selection procedures were used to narrow the number of predictors. The area under the receiver operating characteristics curve (ROC–AUC) and the maximum rescaled R^2 were calculated. The ROC–AUC measures the accuracy of a prediction model as: 90–100% excellent prediction; 80–90% good prediction; 70–80% fair prediction; 60–70% poor prediction and 50–60% failed prediction [22]. The R^2 compares how competing models fit the dataset [23].

Spearman correlation coefficients were calculated for continuous baseline characteristics, and associations between variables were explored. A variable was selected for the final prediction model if it was retained in stepwise selection in any dataset and for either BASDAI50 response or the partial remission model, provided it did not have a correlation coefficient of 0.4 or greater with another variable. Final predictors were categorised into tertiles or according to a clinically relevant threshold in the matrix model.

4.4.2.2.3. Associations of predictors with outcomes

Associations of predictor variables with BASDAI50, ASAS20, ASDAS clinically important and major improvement, ASAS partial remission and ASDAS inactive disease state were explored using OR and 95% CI of outcomes relative to the categorised predictor variables. OR was interpreted as: 1.5 to 1 weak association; 2.5 to 1 moderate association; 4 to 1 strong association and 10 to 1 very strong association [24].

4.4.2.2.4. Matrix model construction

Fitted logistic regression was used to calculate the predicted proportion of patients meeting the outcome criterion according to each subpopulation's value category for the predictors at baseline. These results were organised into a matrix model showing increasing predicted rates of achieving each

outcome from left to right, bottom to top [25]. Patient subpopulations with high predicted outcome rates are shown in yellow, those with low rates are shown in red, and those with intermediate rates are shown in orange. The numbers needed to treat (NNT) to realise a target beneficial outcome following anti-TNF treatment was calculated as follows: NNT=1/(predicted outcome rate with anti-TNF–predicted outcome rate with conventional therapy) and are presented in matrix models using a white, grey and black colour scheme.

4.4.2.2.5. Algorithm-based models

For each outcome instrument, logistic regression with stepwise selection was used to calculate the model yielding the highest ROC–AUC and R^2 using numeric values for CRP, BASFI, age and enthesitis score; categorical values for treatment and HLA-B27 genotype and their interaction terms. In a similar approach using linear regression, models predicting week 12 ASDAS and BASDAI scores were also calculated. The multiple correlation coefficient (R), which represents the correlation between the observed and the predicted values, and the R^2 were calculated, with R of 0.1 or less being 'small', R of 0.1–0.3 being 'medium', and R of 0.3–0.5 being 'large' [26]. The predicted versus the observed change in ASDAS and BASDAI scores were plotted.

4.4.2.2.6. Distribution of two registry AS populations over the prediction model

The ASPECT and the Regisponser studies [15, 27, 28] conducted in 2004–5 in Belgium and Spain, respectively, were used to study the distribution of a daily practice AS population over the model. Cross-sectional data were used from AS patients who had complete data for BASDAI, BASFI, CRP, the presence of enthesitis, age and HLA-B27 status. The percentage of the ASPECT/Regisponser populations falling within each of the predictor value categories in the matrix model is shown for all patients, irrespective of BASDAI score (total registry population), and only for patients with a BASDAI score of 4 or greater (active registry population). The proportion of registry patients corresponding with the NNT categories in the matrix models for various outcome instruments is reported. The OR of BASDAI50 response in the combined dataset were compared with those reported for AS populations treated with anti-TNF therapy in clinical practice [10–12].

4.4.3. Results

4.4.3.1. Study population

Four hundred and seventy-nine patients treated with anti-TNF agents and 156 treated with placebo in ASSERT or GO–RAISE were included. The characteristics of the datasets are presented in **Table 26**. The mean (SD) ASDAS at baseline was 4.0 (0.8) and median ASDAS (IQR) was 3.9 (3.4–4.5).

Variables at baseline	ASSERT	GO–RAISE	Combined
N	279	356	635
Male (%)	80.6	71.6	75.6
Age (years)	39.8±10.2	39.3±12.1	39.5±11.3
BASDAI score	6.4±1.6	6.7±1.5	6.6±1.5
BASFI score	5.8±2.0	5.1±2.4	5.4±2.2
BASMI score	4.0±2.1	3.5±2.2	3.7±2.1
Cervical rotation (°)	45.8±21.9	48.8±20.3	47.5±21.0

Variables at baseline	ASSERT	GO–RAISE	Combined
Intermalleolar distance (cm)	95.3±30.6	100.8±24.8	98.3±27.7
Lateral flexion (cm)	11.2±11.0	11.0±5.8	11.1±8.5
Tragus to wall distance (cm)	17.0±6.3	14.2±5.7	15.4±6.1
CRP (mg/dl)	2.4±2.7	1.8±2.0	2.1±2.4
Enthesitis, presence of (%)	63.3	63.7	63.5
HLA-B27 positive (%)	87.1	83.4	85.0
PGA (cm)	6.8±1.8	7.0±1.8	6.9±1.8
Concomitant medications for placebo patients			
NSAID (%)	90.7	92.3	–
Methotrexate (%) (mean dose (mg/week))	–	19.2 (14.2)	–
Sulphasalazine (%) (mean dose (g/day))	–	30.8 (1.8)	–
Oral corticosteroids (%) (mean dose (mg/day))	–	16.7 (7.2)	–
Anti-inflammatory/antirheumatic drugs (%)	38.5	–	–

TABLE 26: *Characteristics at baseline of the ASSERT, the GO–RAISE and the combined datasets. Values are mean±SD for continuous variables or percentages for categorical variables unless otherwise specified.*

4.4.3.2. Outcome predictor selection

Age, CRP, HLA-B27, PGA, BASFI, BASDAI, BASMI, cervical rotation, tragus to wall distance, intermalleolar distance, Berlin enthesitis score and treatment differed significantly ($p<0.1$) between BASDAI50 responders and non-responders and between partial remitters and non-remitters in ASSERT, GO–RAISE or the combined dataset (see Table 27).

	Week-12 BASDAI50			Week-24 ASAS Partial Remission		
Variables	ASSERT	GO-RAISE	Combined	ASSERT	GO-RAISE	Combined
Age	<0.0001	0.0371	<0.0001	0.0027	0.0511	0.0007
BASDAI score	>0.1	0.0126	>0.1	>0.1	0.0021	0.0343
BASFI score	0.0037	<0.0001	<0.0001	0.0143	<0.0001	<0.0001
BASMI score	>0.1	>0.1	0.0909	0.0006	0.0792	0.0003
Cervical	0.032	>0.1	0.0983	0.0013	0.0150	<0.0001
Intermalleolar	0.0172	0.0216	0.0014	0.0234	0.0251	0.0011
Tragus to wall	>0.1	>0.1	>0.1	0.0046	0.0318	0.0002
CRP	0.0159	0.0102	0.0004	0.0388	>0.1	>0.1
Berlin Enthesitis	0.0264	0.0030	0.0002	0.0495	0.0053	0.0007
PGA	>0.1	0.0052	>0.1	>0.1	0.0037	>0.1

Treatment	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
HLA-B27	0.0882	0.0106	0.0021	0.0583	>0.1	0.0479

TABLE 27: *Exploration of predictors of BASDAI50 response at week 12 and ASAS partial remission at week 24 using Student t-test for continuous variables and χ^2 test for categorical variables.*

These variables were further investigated. In stepwise multiple regression analysis (T), age, BASFI, enthesitis score, CRP, HLA-B27 and treatment were identified as predictors of BASDAI50 response and ASAS partial remission. BASMI and cervical rotation were identified as predictors of partial remission but not of BASDAI50 response (Table 28).

	ASSERT			GO–RAISE			Combined			
	All	Select	Final	All	Select	Final	All	Select	Final	Final category
Age	√, x	√, x	√, x	√, x		√, x	√, x		√, x	>/≤40 years
BASDAI score	√, x			√, x			√, x			
BASFI score	√, x	√	√, x	√, x	√, x	√, x	√, x	√, x	√, x	Tertiles
BASMI score	√, x	x		√, x			√, x			
Cervical rotation	√, x			√, x			√, x	x		
Intermalleolar distance	√, x			√, x			√, x			
Tragus to wall distance	√, x			√, x			√, x			
Enthesitis score	√, x		√, x	√, x	x	√, x	√, x	√, x	√, x	0/≥1
CRP	√, x	√, x	√, x	√, x	√	√, x	√, x	√, x	√, x	Tertiles
PGA	√, x			√, x			√, x			
HLA-B27	√, x		√, x	√, x	√	√, x	√, x	√, x	√, x	+/–
Treatment	√, x	√, x	√, x	√, x	√, x	√, x	√, x	√, x	√, x	Anti-TNF/placebo
R^2	0.40, 0.34	0.36, 0.27	0.37, 0.27	0.27, 0.24	0.23, 0.18	0.24, 0.22	0.29, 0.26	0.27, 0.25	0.28, 0.24	0.32, 0.28
ROC–AUC (95% CI)	0.83, 0.84	0.81, 0.80	0.82, 0.80	0.77, 0.78	0.75, 0.74	0.75, 0.77	0.78, 0.79	0.77, 0.79	0.77, 0.78	0.80 (0.76–0.83), 0.77 (0.73–0.82)

TABLE 28: *Multivariate regression models for BASDAI50 response and ASAS partial remission using variables with p<0.1 on univariate screening, stepwise selection and final selection of variables for both the ASSERT and the GO–RAISE datasets. R^2 and the area under the receiver operating characteristics curve (ROC–AUC) are presented for the different models. √ represents Bath ankylosing spondylitis disease activity index (BASDAI) 50, x represents assessment of spondyloarthritis (ASAS) partial remission. R^2 and ROC–AUC values are presented for BASDAI50 response, ASAS partial remission.*

High correlation was observed between BASMI, its subcomponents and BASFI scores but not when other variables were compared (see Table 29).

	BASDAI score	BASFI score	BASMI score	Cervical Rotation	Intermalleollar Distance	Tragus to Wall Distance	CRP	Enthesitis Score	PGA
Age	-0.01	0.20	0.26	-0.25	-0.31	0.23	-0.15	0.18	0.02
BASDAI score		0.45	0.07	-0.08	-0.12	0.05	0.14	0.25	0.64
BASFI score			0.42	-0.37	-0.37	0.33	0.13	0.23	0.39
BASMI score				-0.58	-0.55	0.68	0.25	0.07	0.10
Cervical					0.31	-0.44	-0.26	-0.07	-0.11
Intermalleolar distance						-0.23	-0.07	-0.27	-0.00
Tragus to wall distance							0.21	-0.03	0.09
CRP								-0.09	0.13
Enthesitis									0.07

TABLE 29: *Spearman correlation coefficients between baseline factors.*

Age and BASFI score were significantly higher for HLA-B27-negative than HLA-B27-positive patients, but numeric differences were small and not clinically significant (see Table 30).

Variables	HLA-B27	N	Mean	SD	P-value
Age	–	95	42.8	12.0	0.0016
	+	538	38.9	11.1	
Berlin enthesitis score	–	94	2.9	3.2	0.0948
	+	538	2.4	2.8	
BASFI total score	–	94	5.8	1.9	0.0427
	+	536	5.3	2.3	
CRP	–	92	2.0	2.5	0.8113
	+	530	2.1	2.3	

TABLE 30: *Relationship between HLA-27 status and continuous variables of interest at baseline in the combined dataset.*

Due to the high correlation between BASMI and BASFI and to limit the total number of predictors to six (which is a reasonable maximum, considering the total number of patients included in the analysis; n=635), BASMI and cervical rotation were not retained in the final model. Age, BASFI, CRP, enthesitis score, treatment and HLA-B27 were retained in at least one of the different stepwise selection models and were therefore retained in the final model.

BASFI was categorised into 4.5 or less (35%), 4.5–6.5 (31%) and over 6.5 (34% of patients). CRP was categorised into 0.6 mg/dl or less (corresponding with the upper limit of normal (ULN) 32%), ULN to 2 mg/dl (34%) and over 2 mg/dl (33%). An age cut-off of 40 years yielded the highest ROC–AUC; 46% of patients were 40 years old or less and 54% were over 40 years old. Enthesitis was present (enthesitis score >0) in 64% and absent (enthesitis score 0) in 36%. Additional information leading to the selection of age and enthesitis categories is provided in Table 31.

	Week-12 BASDAI50				Week-24 ASAS partial remission			
Berlin Enthesitis Index Score	≤0 vs. >0		≤2 vs. >2		≤0 vs. >0		≤2 vs. >2	
Age (yrs)	R^2	ROC-AUC	R^2	ROC-AUC	R^2	ROC-AUC	R^2	ROC-AUC
≤30 vs. >30	0.3001	78.8	0.2925	78.2	0.2304	77.2	0.2373	77.5
≤35 vs. >35	0.3010	78.8	0.2936	78.5	0.2292	77.2	0.2360	77.7
≤40 vs. >40	0.3168	79.7	0.3117	79.3	0.2370	77.4	0.2439	78.2
≤45 vs. >45	0.3128	79.4	0.3076	78.8	0.2352	77.4	0.2420	78.0
≤50 vs. >50	0.3015	79.0	0.2945	78.2	0.2387	77.8	0.2445	78.3

TABLE 31: *Area under the Receiver Operator Characteristic (ROC-AUC) curve and R^2 for different dichotomous categorizations of Berlin Enthesitis Index score and age.*

The ROC–AUC and R^2 of the different models presented in table 2 indicate that the accuracy of the predicted BASDAI50 response and predicted partial remission was similar when models with many predictor variables were compared with models with few variables. In addition, they show that the final set of predictors predicts BASDAI50 response and partial remission in the three datasets reasonably well. The relationship between the week 12 BASDAI50 response and week 24 partial remission is shown in Table 32.

		Wk-24 BASDAI50		Wk-24 ASAS partial remission	
		No (%)	Yes (%)	No (%)	Yes (%)
Wk-12 BASDAI50	No	326 (86.0)	53 (14.0)	372 (98.2)	7 (1.9)
	Yes	31 (13.4)	201 (86.6)	122 (52.6)	110 (47.4)

TABLE 32: *2x2 table relating BASDAI50 response at week 12 to BASDAI50 response and ASAS partial remission at week 24.Chi-square test. All p-values <0.0001.*

4.4.3.3. Associations of predictor variables with outcomes

The OR (95% CI) of achieving an outcome relative to the value category of a predictor variable is presented in Table 33.

HLA-B27 was more strongly associated with large improvements and disease states (BASDAI50, ASDAS major improvement, ASAS partial remission, ASDAS inactive disease) than with small improvements (ASAS20, ASDAS clinically important improvement). Age was more strongly associated with improvement than with disease states. Enthesitis showed weak associations with all outcome instruments. The BASFI score was strongly associated with disease state and BASDAI50 improvement but less so with ASDAS and ASAS20 improvements. The very strong association between CRP and ASDAS improvement is striking, albeit reasonable given that CRP is an intrinsic component of ASDAS. A strong association was also seen between CRP and BASDAI50. Finally, very strong associations between anti-TNF therapy and all outcomes were seen with OR ranging from 5.8 to 46.5.

4.4.3.4. Matrix model construction

Matrix models using the six predictor variables were created for all outcome instruments (Figure 24A–F) and show a good spread of outcome rates over the different subpopulations defined by the predictor value categories. The strength of associations between predictor and outcome instrument is reflected in the differences between outcome rates in these subpopulations. Differences of 22% or less were seen when rates of large improvement and disease states were compared between similar HLA-B27-positive versus negative patients. Differences of 14% or less were seen when small improvements were compared between genotypes. Differences in improvement rates were larger than differences in rates of disease state when older and younger patients were compared, whereas the association of BASFI led to larger differences in disease state. Differences in outcome rates related to the presence of enthesitis were small. The association of CRP with ASDAS improvement led to major differences in outcomes; for example, ASDAS major improvement in HLA-B27-positive patients aged 40 years or less who had BASFI of 4.5 or less and no enthesitis was 81% if their CRP was over 2 mg/dl but only 22% if their CRP was normal.

	ASDAS clinically important improvement 3 months			ASAS20 response 3 months		
	OR	Lower 95% CI	Upper 95% CI	OR	Lower 95% CI	Upper 95% CI
Anti-TNF vs conventional	17.7	10.0	31.3	5.8	3.7	9.0
HLA-27+ vs HLA-27−	1.3	0.7	2.2	1.7	1.1	2.9
Age ≤40 vs >40 years	2.2	1.5	3.4	1.7	1.2	2.4
CRP high vs low	9.3	5.5	16.0	2.2	1.4	3.4
CRP moderate vs low	3.5	2.2	5.7	1.2	0.8	1.9
Berlin enthesitis score 0 vs >0	0.9	0.6	1.3	1.2	0.8	1.6
BASFI low vs high	2.2	1.3	3.6	1.5	1.0	2.4
BASFI moderate vs high	2.2	1.3	3.6	1.9	1.2	3.0
	ASDAS major improvement 3 months			BASDAI50 response 3 months		
	OR	Lower 95% CI	Upper 95% CI	OR	Lower 95% CI	Upper 95% CI
Anti-TNF vs conventional	14.2	6.5	31.1	8.7	4.9	15.6
HLA-27+ vs HLA-27−	2.4	1.2	4.7	2.5	1.4	4.5
Age ≤40 or >40 years	1.8	1.2	2.9	1.9	1.3	2.8
CRP high vs low	15.0	7.9	28.6	3.6	2.2	5.8
CRP moderate vs low	4.1	2.2	7.8	2.3	1.4	3.7
Berlin enthesitis score 0 vs >0	1.6	1.0	2.5	1.4	1.0	2.1
BASFI low vs high	1.635	0.9	2.8	3.4	2.1	5.5
BASFI moderate vs high	1.4	0.8	2.4	3.0	1.8	4.8
	ASDAS inactive disease 6 months			ASAS partial remission 6 months		
	OR	Lower 95% CI	Upper 95% CI	OR	Lower 95% CI	Upper 95% CI
Anti-TNF vs conventional	46.5	6.4	339.6	16.8	5.2	54.4
HLA-27+ vs HLA-27−	2.4	1.0	5.5	2.2	1.0	5.0
Age ≤40 or >40 years	1.6	1.0	2.6	1.6	1.0	2.6
CRP high vs low	2.3	1.3	4.2	2.1	1.2	3.7
CRP moderate vs low	1.6	0.9	3.0	1.3	0.8	2.4
Berlin enthesitis score 0 vs >0	1.5	0.9	2.4	1.3	0.8	2.1
BASFI low vs high	3.2	1.7	5.9	4.1	2.2	7.6
BASFI moderate vs high	1.8	1.0	3.5	2.6	1.4	4.8

TABLE 33: *Associations of predictor variables with selected outcome instruments.*

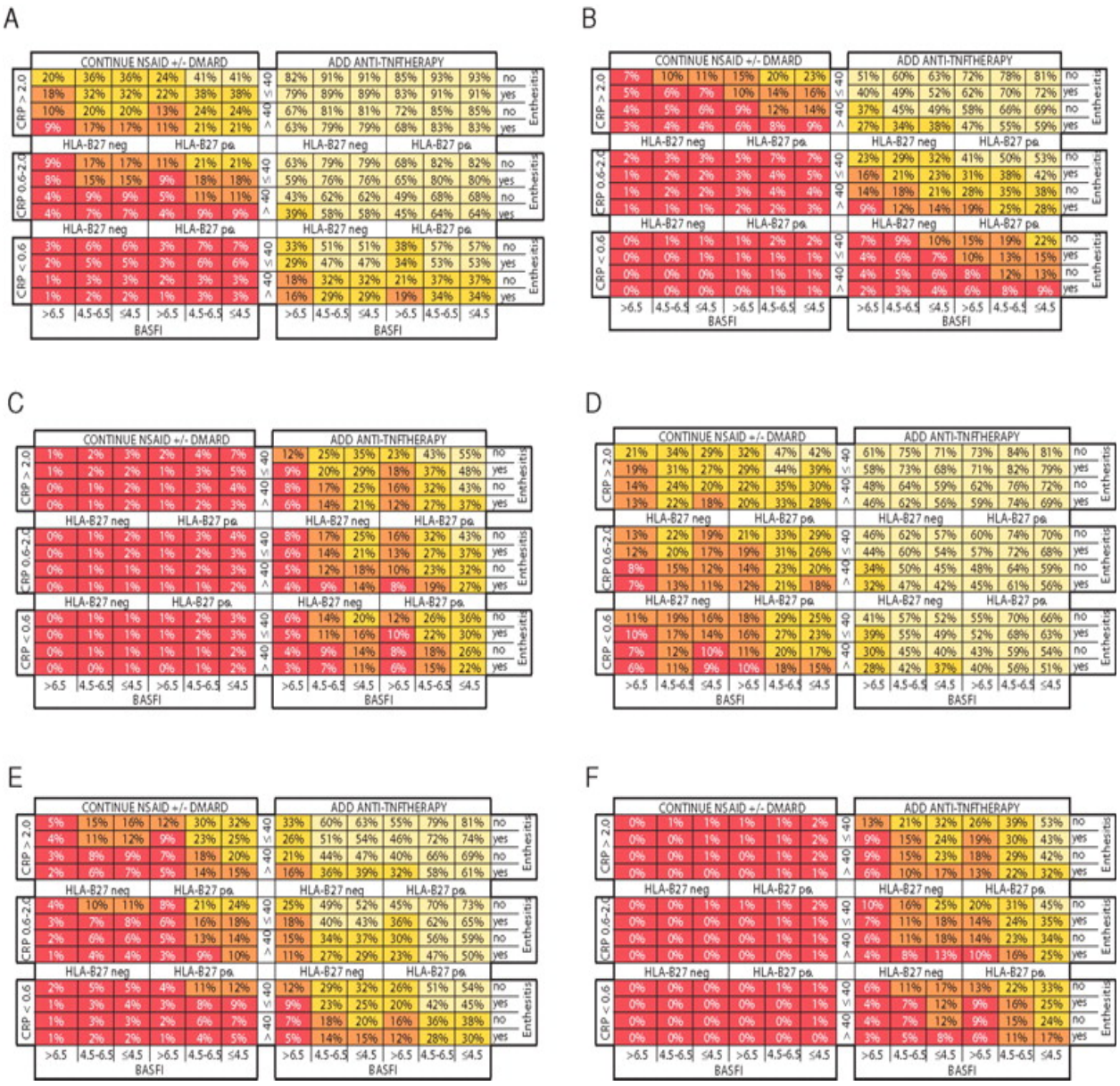

FIG 24: *Matrix presentation of outcome rates of different patient subpopulations (%) defined by the categorised predictor variables: (A) ankylosing spondylitis disease activity score (ASDAS) clinically important improvement, (B) ASDAS major improvement, (C) assessment of spondyloarthritis (ASAS) partial remission, (D) ASAS 20 response, (E) Bath ankylosing spondylitis disease activity index (BASDAI) 50 response and (F) ASDAS inactive disease.*

Differences in response rates exceeding 50% were observed when anti-TNF was compared with conventional therapy. The robustness of response to anti-TNF therapy is further highlighted by **Figure 25A–F**, which indicates that almost all subpopulations have a NNT of less than five to achieve small improvements.

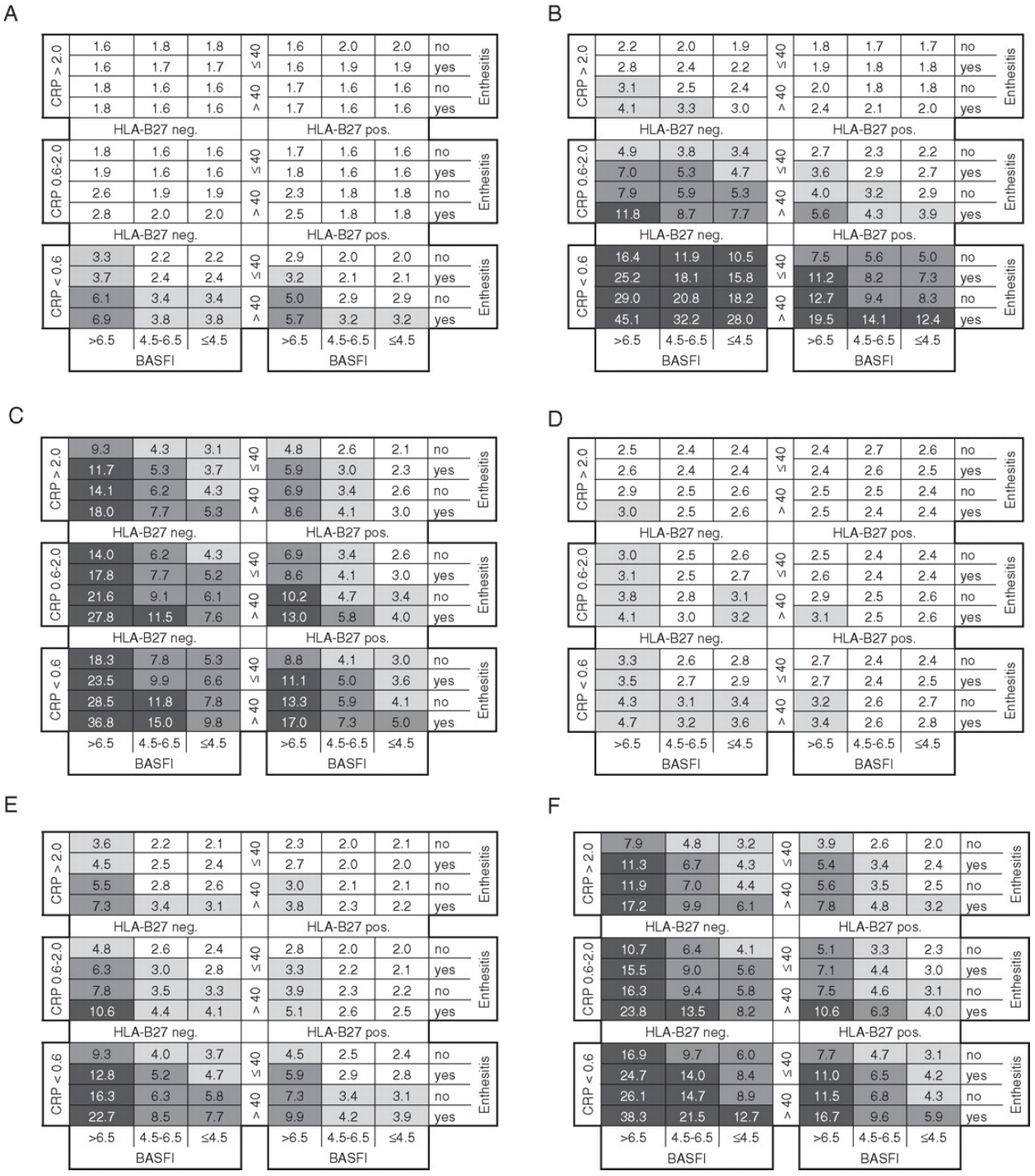

FIG 25: *Matrix presentation of numbers needed to treat for one patient to respond to anti-tumour necrosis factor treatment according to different outcome instruments at 12 or 24 weeks: (A) ankylosing spondylitis disease activity score (ASDAS) clinically important improvement, (B) ASDAS major improvement, (C) assessment of spondyloarthritis (ASAS) partial remission, (D) ASAS 20 response, (E) Bath ankylosing spondylitis disease activity index (BASDAI) 50 response, and (F) ASDAS inactive disease.*

High NNT indicate that large improvements and inactive disease states are difficult to achieve in some subpopulations. The ROC–AUC (R^2) for the matrix model of ASAS20 response, BASDAI50 response, ASAS

partial remission, ASDAS clinically important and major improvement, and ASDAS inactive disease was 0.74 (0.28), 0.80 (0.32), 0.77 (0.28), 0.84 (0.44), 0.84 (0.39) and 0.79 (0.25), respectively.

4.4.3.5. Algorithm-based models

The formulae of the models using selected predictor variables and/or their interaction terms are presented in Table 34.

Predicted outcome	ROC-AUC	R^2	Prediction formula *
% ASAS20 response – week 12	0.75	0.244	P=1/(1+exp(-(β0+ (β1.4)*(X1X4)+(β1.6)*(X1X6)+β2*X2 +(β2.5)*(X2X5)+ (β3.5)*(X3X5)+ (β4.5)*(X4X5))))
% BASDAI50 response – week 12	0.79	0.326	P=1/(1+exp(-(β0+ β1*X1+(β1.3)*(X1X3)+(β2.4)*(X2X4) +(β2.6)*(X2X6)+ (β3.5)*(X3X5)+ (β3.6)*(X3X6)+ (β4.5)*(X4X5))))
% ASDAS clinically important improvement – week 12	0.86	0.480	P=1/(1+exp(-(β0+ β1*X1+(β1.6)*(X1X6)+β2*X2+ (β2.5)*(X2X5)+(β3.5)*(X3X5)+ (β3.6)*(X3X6))))
% ASDAS major improvement – week 12	0.85	0.427	P=1/(1+exp(-(β0+ (β1.4)*(X1X4)+(β1.5)*(X1X5)+ (β2.6)*(X2X6)+ (β3.5)*(X3X5)+(β3.6)*(X3X6)+ β4*X4)))
Unit ASDAS change – week 12	0.697[1]	0.486	Y=β0+ β1*X1+(β1.6)*(X1X6)+(β2.6)*(X2X6)+(β3.5)*(X3X5)+ (β3.6)*(X3X6)+ (β4.5)*(X4X5)+ (β4.6)*(X4X6)+ β5*X5
% BASDAI change – week 12	0.517[1]	0.267	Y=β0+X1*β1+(X1X6)*(β1.6)+(X2X6)*(β2.6)+(X3X4)*(β3.4)+ (X3X5)*(β3.5) +(X3X6)*(β3.6)
% ASDAS remission – week 24	0.78	0.257	P=1/(1+exp(-(β0+ β1*X1+(β2.3)*(X2X3)+ (β3.5)*(X3X5)+β4*X4+β4.6)*(X4X6))))
% AS partial remission – week 24	0.79	0.254	P=1/(1+exp(-(β0+ (β1.6)*(X1X6)+(β2.3)*(X2X3) +(β3.6)*(X3X6)+ (β4.5)*(X4X5)+β5*X5)))

TABLE 34: *Area under the ROC curve, R^2, and algorithms for the prediction of different outcome instruments.* P = predicted probability of outcome, Y = predicted outcome, X1 = Treatment, X2 = HLA-B27, X3 = Age, X4 = Enthesitis, X5 = BASFI, X6 = ln(1+CRP). [1] multiple correlation coefficient (R) is provided.*

The values for ROC–AUC and R^2 were very similar to those of the matrix models. Comparisons of R^2 show that the model to predict week 12 ASDAS fitted the combined dataset best. Values for R indicate that the association of the algorithm-based model with week 12 ASDAS was higher than that with BASDAI. Figures 26A and B show the predicted versus the observed changes in ASDAS and BASDAI scores and also illustrate that the prediction of ASDAS is more accurate than the prediction of BASDAI.

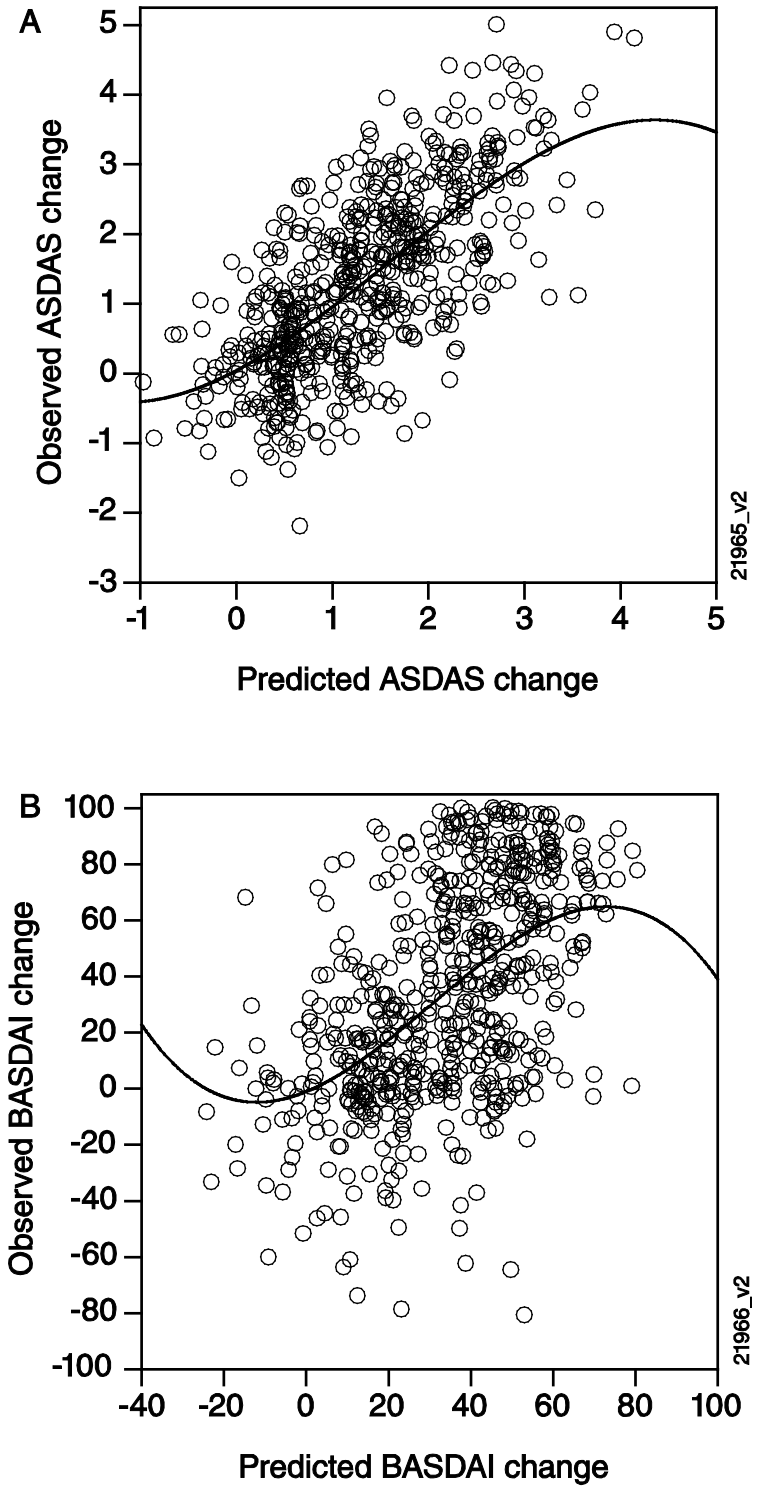

FIG.26: *Observed versus predicted change in ASDAS score (A) and BASDAI score (B).*

4.4.3.6. Distribution of a cross-sectional AS registry population over the model

Of the 1760 AS patients in the total registry population, 1051 (59.7%) had an elevated BASDAI score of 4 or greater (ie, the active registry population). The distribution of CRP in the total/active populations,

respectively, was: 56.6%/51.0% for patients with CRP less than ULN; 29.8%/33.6% for those with a CRP level of ULN to 2 mg/dl; and 13.6%/15.3% for those with CRP greater than 2 mg/dl. The distribution of BASFI was: 53.9%/32.9% for patients with a score less than 4.5; 22.5%/30.4% for those with a score of 4.5–6.5; and 23.6%/36.7% for those with a score greater than 6.5. Approximately 83% of patients were HLA-B27 positive, and approximately 33% of patients were 40 years old or younger in both the total and the active populations. Enthesitis was present in 16% and 21% of the total and the active registry populations, respectively. The percentage of the total and the active registry patients falling into each cell of the matrix is shown in **Figure 26A , B**. The percentage of registry patients falling into the different NNT categories for each outcome instrument (**Figure 25A–F**) is reported in **Table 35**.

Total registry population	ASAS20	BASDAI50	ASAS partial remission	ASDAS clinically important improvement	ASDAS major improvement	ASDAS inactive disease
NNT<3	81.8%	45.2%	10.9%	82.2%	27.3%	10.7%
NNT 3-5	18.2%	38.6%	45.3%	9.3%	11.7%	45.5%
NNT 5-10	0.0%	14.1%	26.0%	8.5%	40.7%	29.8%
NNT>10	0.0%	2.2%	17.8%	0.0%	20.3%	14.0%
Active registry population	ASAS20	BASDAI50	ASAS partial remission	ASDAS clinically important improvement	ASDAS major improvement	ASDAS inactive disease
NNT<3	75.5%	40.8%	8.4%	79.4%	26.3%	8.4%
NNT 3-5	22.5%	38.7%	34.7%	7.9%	16.8%	34.7%
NNT 5-10	0.0%	16.9%	29.9%	12.7%	33.6%	36.1%
NNT>10	0.0%	3.5%	27.0%	0.0%	23.3%	20.8%

TABLE 35: *Percentages of patients of the total and active registry population that fall within the patient subpopulations as categorized by the NNT for each outcome instrument. See also* **Figures 25A-F**.

For example, for ASDAS clinically important improvement, 82.2%, 9.3% and 8.5% of the active registry population fell into the NNT less than three, three to five and five to 10 categories, respectively. NNT greater than 10 was not observed for this outcome (F), therefore 0% of registry patients fell into this category.

A

		HLA-B27 neg.				HLA-B27 pos.			
CRP > 2.0	≤ 40	0.1%	0.1%	0.3%	≤ 40	0.7%	1.0%	1.8%	no
		0.1%	0.1%	0.0%		0.2%	0.3%	0.2%	yes
	> 40	0.3%	0.1%	0.8%	> 40	2.0%	1.8%	2.4%	no
		0.2%	0.1%	0.1%		0.6%	0.2%	0.2%	yes
CRP 0.6-2.0	≤ 40	0.1%	0.1%	0.4%	≤ 40	0.8%	1.4%	4.2%	no
		0.1%	0.2%	0.1%		0.3%	0.2%	1.1%	yes
	> 40	0.9%	0.3%	1.2%	> 40	4.3%	4.1%	6.5%	no
		0.2%	0.2%	0.2%		1.2%	1.0%	0.7%	yes
CRP < 0.6	≤ 40	0.5%	0.6%	1.3%	≤ 40	2.0%	2.0%	10.2%	no
		0.2%	0.1%	0.4%		0.3%	0.7%	1.5%	yes
	> 40	1.3%	0.9%	3.8%	> 40	5.6%	6.0%	14.0%	no
		0.6%	0.1%	0.3%		1.1%	1.0%	2.2%	yes
		>6.5	4.5-6.5	≤4.5		>6.5	4.5-6.5	≤4.5	
		BASFI				BASFI			

Enthesitis

B

		HLA-B27 neg.				HLA-B27 pos.			
CRP > 2.0	≤ 40	0.2%	0.1%	0.2%	≤ 40	1.1%	1.6%	1.0%	no
		0.1%	0.1%	0.0%		0.4%	0.6%	0.1%	yes
	> 40	0.5%	0.1%	0.6%	> 40	3.0%	2.0%	1.5%	no
		0.3%	0.2%	0.2%		1.0%	0.4%	0.0%	yes
CRP 0.6-2.0	≤ 40	0.2%	0.0%	0.2%	≤ 40	1.1%	2.0%	3.0%	no
		0.1%	0.3%	0.0%		0.6%	0.4%	1.0%	yes
	> 40	1.5%	0.5%	0.9%	> 40	6.6%	6.0%	4.3%	no
		0.3%	0.3%	0.1%		2.0%	1.5%	0.9%	yes
CRP < 0.6	≤ 40	0.8%	0.9%	1.0%	≤ 40	3.4%	2.8%	5.3%	no
		0.3%	0.1%	0.5%		0.6%	1.1%	1.3%	yes
	> 40	2.0%	0.9%	2.2%	> 40	7.9%	7.3%	6.7%	no
		1.0%	0.1%	0.3%		1.8%	1.2%	1.6%	yes
		>6.5	4.5-6.5	≤4.5		>6.5	4.5-6.5	≤4.5	
		BASFI				BASFI			

Enthesitis

FIG. 27: *Cross-sectional application of the ASPECT/Regisponser populations over the matrix grid: percentage of (A) the total registry population (including all patients irrespective of Bath ankylosing spondylitis disease activity index (BASDAI) score), and of (B) the active registry population (including only patients with a BASDAI score of ≥4) defined by the categorised predictor variables.*

A detailed comparison of associations between predictors and outcomes reported from comparable analyses performed in AS populations treated with anti-TNF therapy in clinical practice [10-12] is provided in **Table 36**.

Predictor	Odds of BASDAI50 response at 3 months			
	ASSERT/ GO-RAISE	Lord et al.[11]	Rudwaleit et al.[12]	Glintborg et al.[10]*
CRP: OR/mg/dL increase	1.21	1.4 (raised vs. not)	1.23	0.45 (> vs. ≤14 mg/L)
BASFI: OR/unit increase	0.82	0.94	0.89	0.87
Age: OR/year increase	0.97	0.97	0.97	0.98
HLA-B27: OR + vs. –	2.47	-	1.77	-

TABLE 36: *Comparison of associations between predictor variables and BASDAI50 response at 3 months. * Response was defined as BASDAI50 improvement or an improvement of at least 2 cm in the BASDAI score.*

4.4.4. Discussion

Our analyses show that CRP, HLA-B27 genotype, BASFI, age, enthesitis and choice of therapy are independent predictors of a variety of outcome instruments, and that the combination of these six variables adequately predicted clinical improvement following therapy and subsequent disease states in the ASSERT and the GO–RAISE datasets separately and combined.

4.4.4.1. Model validity

The goal of our analysis was to create a practical, evidence-based model that can help guide clinicians in making informed treatment choices for AS patients. The predictive variables identified in these randomised studies have been shown to be associated with response and remission in other datasets and outside of a randomised controlled setting, which lends support to the external validity of the model [8-14].

The associations of age, CRP, HLA-B27 and BASFI with BASDAI50 response in ASSERT/GO–RAISE are very similar to those in previous reports [10-12]. **Figure 27** further indicates that the 72 subpopulations characterised by the baseline values for predictors reasonably represent the AS population in clinical practice. This may support the value of our model in daily practice.

There are, however, several weaknesses of our data indicating that validation of the model is necessary. The association of the enthesitis score with outcomes was not investigated in previous reports, and comparisons between anti-TNF and conventional treatment were not performed. Our algorithms and models originate from studies designed and powered to show the superiority of anti-TNF therapy over placebo, and identifying predictors of response was not a formal endpoint of those studies. The blinded, controlled design of the trials may have led to outcomes different from those observed in clinical practice, and other data sources may have led to the development of different models. Finally, the cross-sectional registry data do not provide any insight into the model's ability to predict outcomes adequately in daily practice.

The predictors retained in the step-wise selection procedures differed between ASSERT and GO–RAISE (**Table 28**), and enthesitis was not associated with ASAS20 response (**Table 33**, **Table 34**). As such, some final predictor variables are redundant for certain datasets or for certain outcomes. However, independent of the dataset used and the outcome instrument predicted, the ROC–AUC of the six selected predictors combined remains close to 0.80, indicating good accuracy of prediction.

4.4.4.2. Comparison of different outcome instruments

Interestingly, although final predictors were selected for their ability to predict BASDAI50 response and ASAS partial remission, these predictors were more accurate in predicting week 12 ASDAS improvement and inactive disease. Our single component analysis shows that this is due to a stronger association of CRP and therapy with the ASDAS scoring system (**Table 28**). The difference in strength of association between predictors and outcome instruments is relevant for trial design in AS. The stronger association of anti-TNF therapy with ASDAS than with traditional outcomes indicates that the ASDAS scoring system may be a more powerful tool than current outcome instruments in showing the efficacy of biological agents. The associations identified may also improve patient selection in studies.

The inclusion of CRP as a component in the ASDAS formula may explain partly why outcomes assessed with ASDAS were very strongly associated with baseline CRP. However, although BASFI is a component of ASAS20 response and ASAS partial remission criteria, the association between BASFI and these outcomes was not as strong as that between CRP and ASDAS outcomes.

In subpopulations with normal CRP, BASDAI50 response and ASAS partial remission rates following anti-TNF treatment were higher than ASDAS major improvement and ASDAS inactive disease rates, and absolute differences with response to conventional therapy led to higher NNT. Differences between ASAS20 response and ASDAS clinically important improvement were also present but smaller. This may indicate that outcomes in patients with normal CRP may be better assessed with an outcome instrument based only on patient-reported outcomes. These findings are in concordance with validation sets of the ASDAS in which discrimination of ASDAS was better than that of BASDAI in patients with elevated CRP and equal to BASDAI in patients with normal CRP [20].

4.4.4.3. Selected predictors

Although BASDAI was not a predictor of response in our datasets, it was in previous reports [8, 11]. This may be due to a homogeneous selection of study patients based on elevated BASDAI scores as part of the inclusion criteria. BASFI was retained as a predictor in this and previous studies [10-12]. The correlation between BASDAI and BASFI is relevant for selecting candidates for anti-TNF therapy in AS, as shown in the AS registries. The proportion of patients in the lowest BASFI category is much higher in the total than the active registry population. The high correlation between BASFI and BASDAI is due to the exclusion of patients with low BASDAI in the active registry population. Patients with a BASDAI less than 4, however, may still have other clinical characteristics that are associated with response and remission in addition to a low BASFI score. For example, 658 (37.4%) of all registry patients were HLA-B27 positive and had CRP elevation greater than ULN; of these, 214 (32.5%) had a BASDAI less than 4. These patients have not been studied in clinical trials and are currently not recommended for anti-TNF therapy.

Our data show that somewhat worse outcomes can be expected in patients with an elevated enthesitis score. Because of the lack of agreement on how enthesitis should be measured [29], enthesitis was assessed only as present or absent and was not scored in the registries. This explains why enthesitis is present in the majority of patients in randomised studies but only in a minority of patients in registries. The differences in response and remission to anti-TNF therapy were not large when similar patients with and without enthesitis were compared. As anti-TNF agents are very effective in patients with well-defined enthesitis [30] patients with peripheral manifestations having worse enthesitis may be a reflection of more severe disease in general [31, 32].

HLA-B27-positive patients responded better to anti-TNF treatment in our study and in previous reports [8, 12]. It is unclear whether this is a function of HLA-B27 facilitating earlier and correct diagnosis or the disease biology differing in HLA-B27-positive versus negative AS patients.

Age was an independent predictor of outcome in the ASSERT study, and significant differences were seen when age was compared between responders and remitters in the GO–RAISE study and the combined dataset. The importance of age in response prediction has been shown previously [8, 10, 11]. Although disease duration has been shown to be relevant for outcome prediction [8] disease duration was not retained in our dataset because age can be more precisely determined than disease duration and may be more useful for prediction.

Our data confirm the association of elevated CRP levels with good response to anti-TNF therapy [9-14]. As the registry data show that AS patients with normal CRP constitute approximately half the AS population, recognising suitable candidates for anti-TNF treatment among such patients may be challenging. Other inflammatory biomarkers and MRI may help in predicting response to therapy [14, 29], and may be especially useful in distinguishing responders from non-responders in patients with low CRP [14, 33].

4.4.4.4. Subpopulations with robust response to anti-TNF treatment

Anti-TNF therapy is recommended for patients who have sustained elevated disease activity despite conventional therapy and should be prescribed based on expert opinion [2]. Our prediction model may help guide that expert opinion. The data show that the continuation of conventional therapy in the face of sustained elevated disease activity will be unlikely to result in improvement. The differential responses in ASAS20 and ASDAS clinically important improvement rates from using anti-TNF versus continued conventional treatment and the resulting low NNT indicate that anti-TNF treatment is a clinically sound choice in all subpopulations with elevated disease activity. Given the lack of good alternatives, the treating physician should therefore consider a defined trial period with an anti-TNF agent if disease activity is not controlled with NSAID [2]. Large improvements and remission may, however, not be achievable therapeutic goals for all patients.

In conclusion, our analysis shows that a model combining age, HLA-B27 genotype, CRP level, functional status and the presence of enthesitis at baseline enables a good prediction of the response to anti-TNF or conventional therapy in AS, as measured by various outcome instruments. This may help clinicians choose more appropriate therapies for patients in daily practice and also help improve patient selection and protocol design for clinical studies.

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4.5. ASDAS high disease activity versus BASDAI elevation in patientswith ankylosing spondylitis as selection criterion for anti-TNF therapy

4.5.1. Abstract

Objective

To investigate which of the 2 ankylosing spondylitis (AS) disease activity instruments identifies better those patients with characteristics that have been associated with positive response to anti-TNF therapy.

Methods

Data from patients with AS in the REGISPONSER registry were analyzed. Patients were categorized by disease activity using 3 different selection criteria: elevated Bath Ankylosing Spondylitis Disease Activity Index criteria (BASDAI ≥ 4), high Ankylosing Spondylitis Disease Activity Score (ASDAS ≥ 2.1), or very high ASDAS (ASDAS ≥ 3.5). To determine which criterion selects for patients most likely to respond to anti-TNF therapy, the groups of patients selected with each criterion were compared on five disease characteristics that are associated with good response to anti-TNF therapy: lower age, lower function score, less enthesitis, higher C-reactive protein (CRP), and HLA-B27-positive status.

Results

50.9%, 66.3%, and 24.9% of 1156 patients had elevated BASDAI, high ASDAS, or very high ASDAS, respectively. Compared to patients selected with elevated BASDAI, more patients selected with high ASDAS had characteristics associated with good response to anti-TNF therapy. Patients with very high ASDAS had higher CRP and were younger, but more frequently had enthesitis and had higher function scores when compared to those with elevated BASDAI.

Conclusions

Selection of AS patients with the ASDAS instrument results in patient sub-populations with different characteristics than those selected with the BASDAI instrument. Since some of these characteristics have been associated with response to anti-TNF therapy, further study should establish if the choice of selection instrument improves the outcome of therapy in the selected populations.

4.5.2. Introduction

For patients with axial spondyloarthritis and patients with ankylosing spondylitis (AS) failing 2 or more nonsteroidal anti-inflammatory drugs (NSAIDs), recommendations for anti-tumor necrosis factor (anti-TNF) therapy require presence of elevated Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and positive expert opinion using clinical disease characteristics [1–3]. Even though clinical activity and physician judgment are still the main drivers for starting anti-TNF therapy, different studies suggest that demographic and disease characteristics, such as age, C-reactive protein (CRP), functionality, and HLA-B27 genotype may influence response to anti-TNF and therefore could help in the selection of candidates for treatment with these drugs [4–9].

The reason elevated BASDAI is used for patient selection in treatment recommendations is because elevated BASDAI has also been used as a selection criterion in efficacy studies [10, 11] How-ever, because a higher BASDAI score has been associated with nonresponse and anti-TNF treatment discontinuation [5, 7] selection with elevated BASDAI score may be a recipe for poor outcomes. As elevated disease activity is indispensable for patient selection, we investigated whether use of the newly developed Ankylosing Spondylitis Disease Activity Score (ASDAS) as selection instrument results in a different population of patients than those selected with BASDAI, and whether the populations could be characterized through characteristics that have been associated with response to anti-TNF therapy in published literature [9, 12].

4.5.3. Methods

4.5.3.1. Disease activity instruments.

The BASDAI measures disease activity using six patient-reported questions pertaining to fatigue, spinal pain, joint pain/swelling, areas of localized tenderness and morning stiffness [13]. Patients have an elevated disease activity if the BASDAI score is ≥4 on a10-point scale.

The ASDAS measures disease activity using an algorithm comprising 3 BASDAI questions (spinal pain, morning stiffness, and joint pain/swelling), the patient global assessment, and CRP [11]. ASDAS ≥ 1.3 indicates moderate, ≥2.1 indicates high, and ≥3.5 indicates very high disease activity [14].

4.5.3.2. Characteristics associated with treatment outcome

Lower age, lower Bath Ankylosing Spondylitis Functional Index (BASFI), lower enthesitis score, higher CRP, and presence of HLA-B27 have been associated with good outcomes to anti-TNF therapy [3–8]. Samples selected with the various disease activity measures/cutoffs were compared for their profile of these 5 characteristics.

4.5.3.3. Patient population

Patients with AS according to the modified New York criteria included in the Spanish national registry of spondyloarthropathies (REGISPONSER), who had complete data for BASDAI, ASDAS, age, CRP, BASFI, presence of enthesitis, and HLA-B27 status, were included in this analysis [15].

4.5.3.4. Analysis

Two-by-two cross-tabulation reflecting patient samples selected with BASDAI and ASDAS were created. Each sample's characteristics are reported using the following categories: BASFI ≤ 4.5, 4.5–6.5, and >6.5; CRP <upper limit of normal (ULN),>ULN but <2 mg/dL, and >2 mg/dL; age ≤40 and >40 years; and enthesitis present or absent. The different combinations of these variables and categories allowed the identification of 72 subpopulations, which were represented in a matrix grid that situates

subpopulations that have been associated with the best outcomes (i.e., high CRP, no enthesitis, HLA-B27-positive, low age, and low BASFI) in the upper right corner and those associated with lower response rates in the lower left corner [8].

The difference between the numbers of patients selected with ASDAS versus BASDAI is reported for each subpopulation. Subpopulations that had a net increase or decrease when selected with ASDAS are presented in green and red, respectively. The proportion of patients falling into each of the 72 subpopulations, relative to the total population selected with BASDAI or ASDAS are reported.

4.5.4. Results

A total of 1156 patients had complete data for all variables (mean age: 48 years [SD 13], 74.5% male and 25.5% female). Mean disease duration was 21.5 years (SD: 13), 84.9% had positive HLA-B27 and 34.6% had history of enthesitis. A total of 17.0% was being treated with anti TNF agents, 9.2% was taking steroids, 8.6% methotrexate, 14.2% sulphasalazine and 0.6% leflunomide. CRP value was<0.6 mg/dL in 53.2% of the sample, whilst 11.6% had ≥2.0 mg/dL.

Table 37 shows the distribution of ASDAS and BASDAI values. Almost all patients had at least moderate ASDAS (Table 37A), two-thirds had at least high ASDAS (Table 37B), and one-quarter had very high ASDAS (Table 37C). Approximately half of the patients had elevated BASDAI. Among those with high ASDAS or high BASDAI, 14.3%and 15.1% were treated with anti TNF drugs respectively. Of 568patients with a low BASDAI score, 210 patients had high disease activity as measured by ASDAS (37%, Table 37B), and only 16 had very high disease activity on ASDAS (2.8%, Table 37C). Of 390 patients with ASDAS <2.1, only 32 had elevated BASDAI (8.2%, Table 37B). There were no patients with ASDAS <1.3 and elevated BASDAI (Table 37C).

A.

	BASDAI <4	BASDAI ≥4 (elevated activity)	Total
ASDAS <1.3	142	0	142 (12.3%)
ASDAS ≥1.3 (moderate activity)	426	588	1014 (87.7%)
Total	568 (49.1%)	588 (50.9%)	1156 (100%)

B.

	BASDAI <4	BASDAI ≥4 (elevated activity)	Total
ASDAS <2.1	358	32	390 (33.7%)
ASDAS ≥2.1 (high activity)	210	556	766 (66.3%)
Total	568 (49.1%)	588 (50.9%)	1156 (100%)

C.

	BASDAI <4	BASDAI ≥4 (elevated activity)	Total
ASDAS <3.5	552	316	868 (75.1%)
ASDAS ≥3.5 (very high activity)	16	272	288 (24.9%)
Total	568 (49.1%)	588 (50.9%)	1156 (100%)

TABLE 37: *Percentage of patients who met each criterion and characteristics of patients selected with each criterion. Two-by-two cross-tabulations of disease activity state as determined by the BASDAI*

criterion for elevated disease activity versus ASDAS criteria for moderate (A), high (B), and very high disease activity (C).

Table 38 shows that more patients selected with high ASDAS have disease characteristics that have been associated with positive outcomes of anti-TNF treatment in reported literature (markedly higher CRP and lower BASFI; slightly lower age, fewer patients with enthesitis, and more patients with HLA-B27 positive status) when compared to patients selected with elevated BASDAI. Patients with very high ASDAS had much higher CRP levels and were younger (both associated with positive outcomes in literature), but more frequently had enthesitis and had markedly higher BASFI scores (inversely associated with positive outcomes) when compared to those with elevated BASDAI. Characteristics of patients with moderate ASDAS were nearly identical to the total cohort (not shown).

		Patients with High Disease Activity, as Determined by Each Selection Criterion		
	All patients (n=1156)	ASDAS ≥2.1 (n=766)	ASDAS ≥3.5 (n=288)	BASDAI ≥4 (n=588)
Age ≤40 years	28.6%	26.4%	24.0%	23.1%
HLA-B27–positive	84.9%	85.1%	83.0%	83.5%
Never had enthesitis	65.4%	61.7%	53.3%	58.2%
BASFI				
≥6.5	19.8%	27.3%	44.4%	34.2%
4.5–6.5	20.0%	26.1%	26.4%	28.7%
<4.5	60.2%	46.6%	29.2%	37.1%
CRP (mg/dL)				
≥2	11.6%	17.4%	30.2%	12.9%
0.6–2	34.9%	45.0%	54.9%	41.5%
<0.6	53.2%	37.6%	14.9%	45.6%

TABLE 38: *Percentage of patients who had each characteristic that has been associated with positive anti-TNF treatment outcomes, by patient groups selected with ASDAS or BASDAI criteria.*

Relative to the total population included in this analysis, the pro-portion of patients in subpopulations identified with characteristics that have been associated with positive outcomes (i.e. expected to respond well and located to the right and top of the matrix grid) increases when selection is done with high ASDAS instead of BASDAI (**Figure 28B, D, and E**). At the same time, few sub-populations are numerically decreasing when BASDAI is replaced by high ASDAS. These sub-populations are located at the bottom left of the matrix grid (i.e., associated with worse outcomes related to anti-TNF therapy) and the size of these subgroups relative to the total population goes down. If BASDAI is replaced by very high ASDAS, few subpopulations in the highest CRP category have a small increase, whereas most subpopulations show decreases in population size (**Figure 28A, C, and D**).

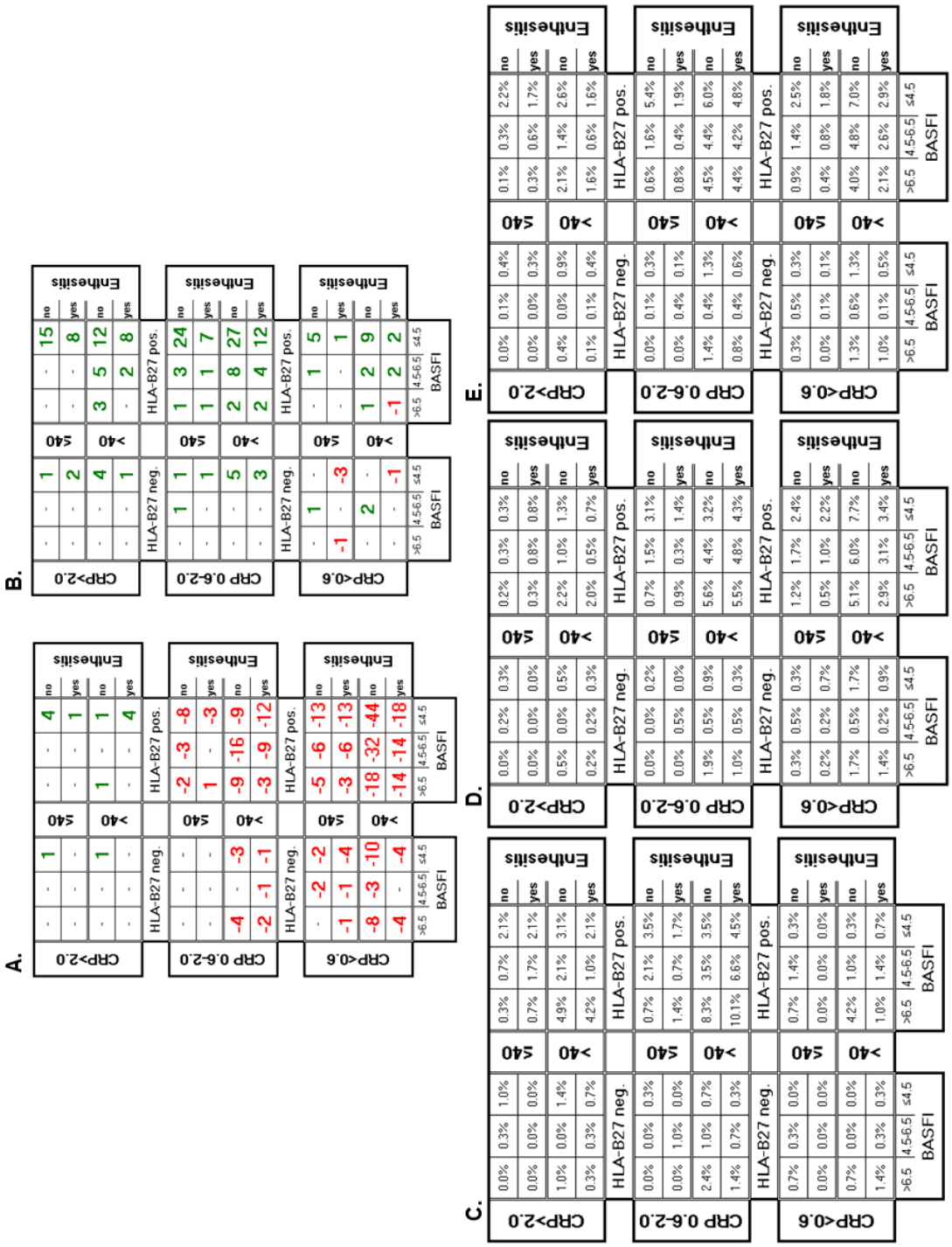

FIG. 28: *Matrix representation of characteristics of patients selected with each criterion. Net numeric increase (green) or decrease (red) within each of the various subpopulations when the measure of disease activity used to select patients changes from elevated Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) to (A) Ankylosing Spondylitis Disease Activity Score (ASDAS) very high disease activity and (B) ASDAS high disease activity. Size of each of the 72 subpopulations, relative to the total population selected with the following disease activity measure: (C) very high ASDAS, (D) elevated BASDAI, and (E) high ASDAS.*

4.5.5. Discussion

This analysis of cross-sectionally evaluated patients with AS in daily clinical practice describes the profile of patients who would be selected for anti-TNF therapy if different disease activity instruments were used. The purpose of this hypothesis-generating research was to evaluate which disease activity measure and threshold criterion would select the population that is most likely to have characteristics that have been associated with response to anti-TNF treatment in the literature. The data show that more patients have high ASDAS than elevated BASDAI, and compared to those selected with high BASDAI, patients selected with high ASDAS more frequently have disease characteristics that have a documented association to good response to anti-TNF therapy [9].

The selection of patients for anti-TNF therapy is not an easy decision. The BASDAI instrument is currently the main driver to select candidates to receive anti-TNF therapy in AS, but positive expert opinion clinical based in clinical judgment based on disease characteristics is also very important [1–3] In this study, we highlight that the BASDAI instrument may exclude a certain proportion of patients that (1) have high disease activity according to another instrument (i.e. the ASDAS activity index), (2) show characteristics that have been associated to good outcome to anti-TNF therapy in the literature, and (3) may correspond with a patient profile that a clinician may think is appropriate for anti-TNF treatment (e.g., a young patient with high disease activity, high CRP, and HLA-B27-positive status). In the current study, 37% of patients who had low disease activity according to the BASDAI criterion had high disease activity according to the ASDAS; if BASDAI was used as a strict criterion for determining eligibility for treatment, none of these patients would be eligible for anti-TNF treatment. The use of high ASDAS as a selection criterion instead of elevated BASDAI would increase the number of treatment candidates. Patients selected with elevated ASDAS but not elevated BASDAI had a combination of disease characteristics that are associated with positive outcomes in published studies (represented in green in **Figure 28B**) [4–9]. Very few patients had high BASDAI and low ASDAS and would not be selected with the high ASDAS criterion (represented in red in **Figure 28B**); these patients tend to have characteristics that may not be associated with good outcomes. Good selection criteria for treatment in clinical practice would ideally select future responders as treatment candidates, and select against patients who are not likely to respond to treatment.

Whether selection is based on elevated BASDAI or high ASDAS, a number of patients who would be selected have combined characteristics that are associated with low probability of response. This indicates that the recommendation to use clinical characteristics (in addition to a disease activity criterion) to guide choice of therapy remains important. Predictors of response such as the ones described can be helpful tools to complement the elevated ASDAS criterion for patient selection. In clinical practice, a rheumatologist may wonder whether there is a good reason to use anti-TNF treatment in an older HLA-B27-negative patient who reports poor function and high disease activity, despite absence of objective signs of inflammation (i.e., CRP < 0.6 mg/dL); this profile corresponds with that of 24/1156 REGISPONSER patients. From a societal perspective, payers may want to evaluate whether it is worth excluding patients with such characteristics to allow treating a group of HLA-B27-positive patients younger than 40 years of age with high disease activity and CRP greater than 2 mg/dL who still have preserved function (this profile corresponds with 23/1156 REGISPONSER patients). Thus, using BASDAI as the only criterion to decide anti-TNF treatment could exclude the latter group to be treated with anti-TNF therapy in many European countries, and this is why expert opinion and clinical judgment based on patient's characteristics and biochemical markers like CRP levels or HLA-B27status is critical in the decision.

Compared to selection with BASDAI, more patients are selected for anti-TNF treatment when high ASDAS is used and fewer patients are selected when very high ASDAS is the selection criterion. Because BASDAI and BASFI are highly correlated, selection with high BASDAI automatically leads to a selection of patients who fall in the higher categories for BASFI. Replacing BASDAI with ASDAS leads to an increase of the proportion of patients in the lower BASFI category, which is associated with better response. The advantageous CRP profile (higher CRP is associated with better response) that is seen for a population with very high ASDAS is largely offset by the disadvantageous BASFI profile (higher BASFI is associated with worse response). The data show that patients with very high ASDAS also have a higher likelihood of enthesitis, which is associated with slightly worse outcomes [9]. In addition to leading to a more favorable CRP and BASFI profile, selection with high and very high ASDAS also results in a younger population, even though age is not an explicit component of the ASDAS. Because younger patients tend to respond better, this finding is relevant for patient selection in practice. The overall decrease in number of patients who can be treated and the profile of patients no longer selected if BASDAI is replaced by very high ASDAS indicates that the latter selection criterion may not be an improvement over the former. However, replacing BASDAI with high ASDAS may need to be considered for future recommendations. In fact, in a recent study, a small group of patients with high ASDAS and normal BASDAI (n = 48) have shown to respond to anti-TNF therapy [16], and these patients would have been excluded from anti-TNF therapy if high BASDAI would have been used as strict selection criterion.

The main limitation of the study is its cross-sectional design with no follow-up, which precludes validating the findings of the study by assessing the response to anti-TNF therapy in groups of patients with the abovementioned characteristics. We did not get specific information on individual components of BASDAI and ASAS indexes; thus, we cannot display BASDAI and ASAS component-per-component values to check which items contribute to the discordance in the high ASAS/low BASDAI group. Another limitation is that some 15% of patients were already treated with anti-TNF agents, and this may have had an influence on BASDAI and ASDAS as well as some of the relevant disease characteristics (e.g. CRP and BASFI). It is difficult to say how this has an influence on the results. Although higher ASDAS has been associated with better outcomes [8] it is important to emphasize that the database did not allow confirmation of whether the response was indeed higher inpatients selected with ASDAS versus BASDAI. Because the efficacy of anti-TNF treatment in patients with high ASDAS and BASDAI less than 4 has never been studied, except in a small group of patients [16] it is not certain whether the favorable disease characteristic profile described here is also related to better outcomes in that patient group. Further investigation on the response to anti-TNF in a larger population with high ASDAS/low BASDAI is needed.

In conclusion, in this cross-sectional study, selection of AS patients with the ASDAS instrument results in patient sub-populations that have different characteristics than those selected with the BASDAI instrument. Since some of these characteristics have been associated with good outcome to anti-TNF therapy, the hypothesis generated through this research is that replacing the disease activity measure in anti-TNF treatment recommendations from BASDAI to ASDAS may lead to better outcomes of therapy. This hypothesis should be tested in prospective studies.

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Chapter 5: Anti-TNF alpha Treatment Discontinuation following Remission

Includes 3 publications from the '*Infliximab as First Line Therapy in Patients with Early Active Axial Spondyloarthritis Trial' (INFAST).*

Efficacy and safety of infliximab plus naproxen versus naproxen alone in patients with early, active axial spondyloarthritis: results from the double-blind, placebo-controlled INFAST study, Part 1.

Sieper J, Lenaerts J, Wollenhaupt J, Rudwaleit M, Mazurov VI, Myasoutova L, Park S, Song Y, Yao R, Chitkara D, Vastesaeger N; All INFAST Investigators.
Ann Rheum Dis. 2014 Jan; 73(1):101-7. Epub 2013 May 21.

Maintenance of biologic-free remission with naproxen or no treatment in patients with early, active axial spondyloarthritis: results from a 6-month, randomised, open-label follow-up study, INFAST Part 2.

Sieper J, Lenaerts J, Wollenhaupt J, Rudwaleit M, Mazurov VI, Myasoutova L, Park S, Song Y, Yao R, Chitkara D, Vastesaeger N; All INFAST Investigators.
Ann Rheum Dis. 2014 Jan; 73(1):108-13. Epub 2013 Jun 5.

Partial Remission in Ankylosing Spondylitis and Non-Radiographic Axial Spondyloarthritis and Associations between Partial Remission and Baseline Disease Characteristics during Treatment with Infliximab plus Naproxen or Naproxen alone.

Sieper J, Lenaerts J, Wollenhaupt J, Rudwaleit M, Mazurov VI, Myasoutova L, Park S, Song Y, Yao R, Chitkara D, Vastesaeger N; All INFAST Investigators.
Submitted manuscript.

5.1. Efficacy and safety of infliximab plus naproxen versus naproxen alone in patients with early, active axial spondyloarthritis: results from the double-blind, placebo-controlled INFAST study, Part 1

5.1.1. Abstract

Objectives

To assess whether combination therapy with infliximab (IFX) plus nonsteroidal anti-inflammatory drugs (NSAIDs) is superior to NSAID monotherapy for reaching Assessment of SpondyloArthritis international Society (ASAS) partial remission in patients with early, active axial spondyloarthritis (SpA) who were naïve to NSAIDs or received a submaximal dose of NSAIDs.

Methods

Patients were randomised (2 : 1 ratio) to receive naproxen (NPX) 1000 mg daily plus either IFX 5 mg/kg or placebo (PBO) at weeks 0, 2, 6, 12, 18 and 24. The primary efficacy measure was the percentage of patients who met ASAS partial remission criteria at week 28. Several other measures of disease activity, clinical symptoms and patient-rated outcomes were evaluated. Treatment group differences were analysed with Fisher exact tests or analysis of covariance.

Results

A greater percentage of patients achieved ASAS partial remission in the IFX+NPX group (61.9%; 65/105) than in the PBO+NPX group (35.3%; 18/51) at week 28 ($p=0.002$) and at all other visits ($p<0.05$, all comparisons). Results of most other disease activity and patient-reported endpoints (including Ankylosing Spondylitis Disease Activity Score, Bath Ankylosing Spondylitis Disease Activity Index, Bath Ankylosing Spondylitis Functional Index, multiple quality of life measures and pain measures) showed greater improvement in the IFX+NPX group than the PBO+NPX group, with several measures demonstrating early and consistent improvement over 28 weeks of treatment.

Conclusions

Patients with early, active axial SpA who received IFX+NPX combination treatment were twice as likely to achieve clinical remission as patients who received NPX alone. NPX alone led to clinical remission in a third of patients.

5.1.2.Introduction

The term axial spondyloarthritis (SpA) is the umbrella term for patients with ankylosing spondylitis (AS) according to the modified New York criteria [1] and for patients who do not yet show signs of structural damage in the sacroiliac (SI) joint that are visible as radiographic sacroiliitis and, therefore, categorised as non-radiographic axial SpA. Recently, new classification criteria for axial SpA have been developed, which cover both subgroups [2]. There are currently only two treatments with proven efficacy available for these patients with axial SpA: nonsteroidal anti-inflammatory drugs (NSAIDs) and tumour necrosis factor (TNF)-α–targeted therapy [3]. Until now, TNF antagonists have only been investigated and are only recommended for patients with axial SpA who fail previous NSAID therapy [3 , 4]. Although data are limited, studies have demonstrated up to 50% remission rate with TNF-α antagonist therapy in NSAID-refractory patients with axial SpA who are treated in the first 3–5 years of their disease [5-7]. This raises the question of whether even earlier treatment of axial SpA in patients who are not refractory to NSAID therapy would result in even higher response rates and potentially even in biologic drug-free remission, as has been recently investigated in great detail in patients with rheumatoid arthritis [8, 9].

The Infliximab (IFX) as First Line Therapy in Patients with Early Active Axial Spondyloarthritis Trial (INFAST) evaluated whether combination therapy with the TNF antagonist IFX and naproxen (NPX) was superior to treatment with NPX alone in patients who had active moderate-to-severe axial SpA and who were naïve to NSAIDs or had only been treated with a submaximal dose of NSAIDs. All patients had to fulfil the Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axial SpA, thus including patients both with AS and with non-radiographic axial SpA; had to have a disease duration ≤3 years; and had to have evidence of inflammatory SI lesions on MRI at baseline. Thus, this study is the first investigation of the potential benefits of early TNF-antagonist treatment in active axial SpA patients who are not yet refractory to NSAID therapy.

5.1.3.Methods

5.1.3.1. Design and patients

INFAST was a Phase 3b, randomised, parallel-group, multisite, double-blind, placebo (PBO)-controlled study of IFX in adults with moderate-to-severe, active axial SpA who were not refractory to NSAIDs (Protocol P05336, NCT00844805). Patients were recruited consecutively by rheumatologists in hospitals or private practice settings. Patients were enrolled in 47 centres in nine countries (Austria, Belgium, Denmark, France, Germany, Hungary, Russia, South Korea and Ukraine). The study protocol was reviewed by appropriate institutional review boards for each study site. All patients gave written informed consent to participate. Data were collected between 22 October 2009, and 20 September 2011.

Patients were 18–48 years of age with a diagnosis of active axial SpA according to the local investigator and disease duration of ≤3 years. All patients had to fulfil the imaging portion of the ASAS criteria for axial SpA,2 with active inflammation of the SI joints (defined as bone oedema within or adjacent to the SI joints) as shown by short tau inversion recovery MRI. For inclusion into the study, the MRI scans were read locally. All patients had active disease at screening and baseline, defined as a total back pain evaluation of ≥40 mm (visual analogue scale (VAS) of 0–100 mm) and a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥4 cm (0–10 cm VAS). Patients were either NSAID-naïve at baseline or had been treated with not more than two-thirds of the maximal recommended dose10 during the 2 weeks prior to screening and had undergone a washout period of ≥3 days before baseline, during which they had an increase in total back pain of ≥30%.

5.1.3.2. Study treatment

During Part 1 of INFAST patients were randomised in double-blind fashion at a 2 : 1 ratio to receive either intravenous (IV) IFX 5 mg/kg or IV PBO at weeks 0, 2, 6, 12, 18, and 24 (Figure 29). Both groups also received oral NPX 1000 mg daily. A computer-generated randomisation list was created by the sponsor and held by the central randomisation centre, which was contacted by the site to assign treatment to each patient as he or she enrolled. Patients who met ASAS partial remission criteria at week 28 were eligible to participate in Part 2 of INFAST, which compared maintenance of partial remission with two follow-up regimens (NPX alone or no treatment); this portion of the study is reported separately.

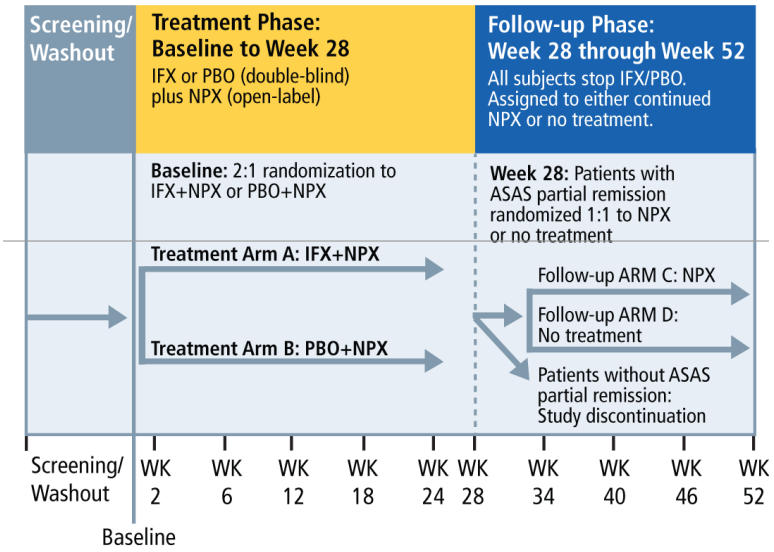

FIG. 29: *INFAST study design.*

5.1.3.3. Outcome measures

The primary efficacy measure was the percentage of patients in each treatment group who met ASAS partial remission criteria at week 28. A number of secondary measures of disease activity, clinical signs and symptoms, inflammatory markers, and patient-reported outcomes were also assessed.

Adherence to NPX treatment was measured as the percentage of days in the study that the daily dose was taken as reported on patient diary cards. Adherence to IFX and placebo was measured as the number of doses infused of the number of scheduled doses.

Adverse events (AEs) and several other safety measures were also collected.

5.1.3.4. Statistical analyses

The targeted sample size was 150 patients (100 receiving IFX+NPX and 50 receiving PBO+NPX) for 90% power to detect a 30% difference in ASAS partial remission between treatment groups, assuming a 15% withdrawal rate.

The intention-to-treat (ITT) population was used for efficacy analyses and included all patients who were randomised, received at least one dose of study medication and had at least one efficacy evaluation after baseline. Analyses included observed data. For the primary efficacy analysis, patients who withdrew before week 28 were categorised as not achieving partial remission.

Treatment group differences in categorical efficacy measures were analysed with Fisher exact tests at a two-sided significance level of 0.05. Treatment group differences in continuous measures were analysed with analysis of covariance, with baseline values as covariates.

The safety population included all patients who received at least one dose of study medication. Adverse events were analysed descriptively.

5.1.4.Results

5.1.4.1. Patient disposition

Of the 158 randomised patients, 106 were assigned to IFX+NPX and 52 to PBO+NPX (Figure 30). The ITT population included 105 patients in the IFX+NPX group (one patient did not receive study medication) and 51 in the PBO+NPX group (one patient had no post-baseline efficacy assessment). The majority of patients completed the study through week 28 (90.6% in the IFX+NPX group and 86.5% in the PBO+NPX group).

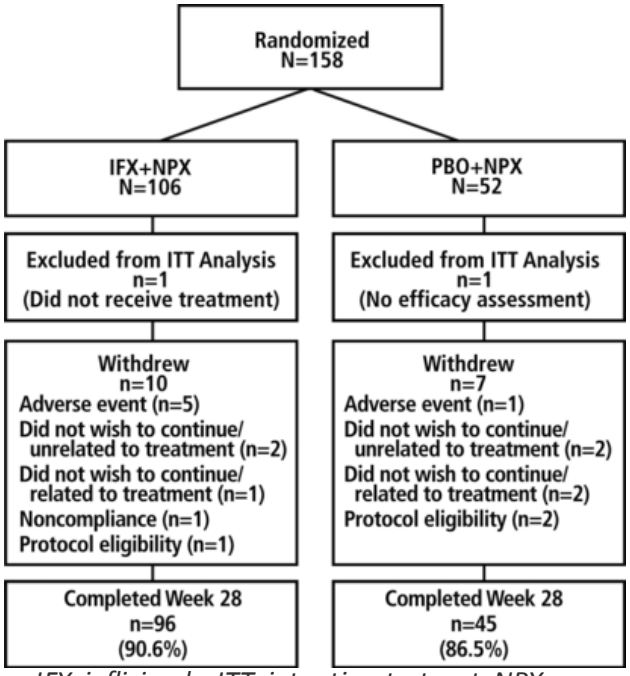

FIG. 30: *Patient disposition. IFX, infliximab; ITT, intention-to-treat; NPX, naproxen; PBO, placebo.*

5.1.4.2. Baseline characteristics

Baseline characteristics were similar in the two treatment groups (Table 39). Most patients had high or very high disease activity, as measured by Ankylosing Spondylitis Disease Activity Score (ASDAS), and mean time since axial SpA diagnosis was less than 1 year. The mean number of baseline SpA manifestations was comparable between treatment groups (3.8 vs 4.0). The incidence of arthritis appeared to be greater for the IFX+NPX arm than the PBO+NPX arm (45.3% vs 26.9%, respectively), but in both groups few joints were swollen (means, 1.49 vs 0.78, respectively) or tender (means 4.06 vs 3.80, respectively). Approximately 60% of patients had x-ray findings that met the modified New York radiographic criteria for AS (bilateral ≥grade 2 or unilateral ≥grade 3) at baseline, according to the x-ray reading by the local investigator.

5.1.4.3. Exposure and adherence

Most patients received all six infusions of IFX or PBO (90.5% and 88.5% of patients, respectively). The mean doses per infusion of IFX and PBO were 367 and 372 mg, respectively. Treatment adherence with NPX, based on total number of doses taken regardless of dosage amount, was a mean of 99.0% for IFX+NPX and 99.5% for PBO+NPX; the mean daily doses were 960.5 and 978.1 mg, respectively.

Baseline characteristics	IFX+NPX	PBO+NPX
Demographic characteristics	N=105	N=51
Gender (male), n (%)	72 (68.6)	40 (78.4)
Age (years), mean (SD)	31.7 (8.51)	30.7 (7.34)
Race, n (%)		
White	91 (86.7)	45 (88.2)
Asian	14 (13.3)	5 (9.8)
Multiracial	0	1 (2.0)
Body mass index (kg/m^2), mean (SD)	24.1 (4.35)	24.1 (3.40)
Clinical characteristics	N=106	N=52
Years since diagnosis of axial SpA, mean (SD)	0.84 (0.814)	0.69 (0.647)
Years since onset of axial SpA symptoms, mean (SD)	1.76 (0.896)	1.91 (1.439)
Number of SpA manifestations, mean (SD)	3.8 (1.4)	4.0 (1.23)
Inflammatory back pain, n (%)	95 (89.6)	48 (92.3)
Arthritis, n (%)	48 (45.3)	14 (26.9)
Dactylitis, n (%)	3 (2.8)	1 (1.9)
Psoriasis, n (%)	6 (5.7)	2 (3.8)
Family history of SpA, n (%)	16 (15.1)	11 (21.2)
Uveitis, n (%)	6 (5.7)	6 (11.5)
History of CD/UC, n (%)	0	0
Enthesitis (heel), n (%)	15 (14.2)	10 (19.2)
ASDAS, n (%)	n=105	n=51
Inactive disease: <1.3	0	0
Moderate disease activity: 1.3 to <2.1	3 (2.9)	0
High disease activity: 2.1 to ≤3.5	34 (32.4)	15 (29.4)
Very high disease activity: >3.5	63 (60.0)	34 (66.7)
HLA-B27–positive status, n (%)	87 (82.1)	47 (90.4)
X-ray sacroiliitis, according to the modified New York criteria* n (%)	61 (57.5)	33 (63.5)
Previous good response to NSAIDs, n (%)	73 (68.9)	36 (69.2)
Patients who had prior NSAID treatment, n (%)	100 (94.3)	44 (84.6)

TABLE 39: *Baseline demographic and disease characteristics. *Bilateral ≥grade 2 or unilateral ≥grade 3, as assessed by the local investigator.*

5.1.4.4. Efficacy results

The primary endpoint was met. A greater percentage of patients achieved ASAS partial remission in the IFX+NPX group (61.9% [65/105], 95% CI 52.4% to 70.6%) than in the PBO+NPX group (35.3% [18/51], 95% CI 23.6% to 49.0%; p=0.002) at week 28 (Figure 31A). The greater partial remission in the IFX+NPX group than the PBO+NPX group was statistically significant as early as week 2 and at each visit until week 28. The number of patients with partial remission increased steadily in both treatment groups over the 28 weeks. A similar pattern of treatment group differences occurred with the percentage of patients achieving 40% response in ASAS criteria (ASAS-40) (Figure 31B). The percentage of patients who achieved ASAS-20 was numerically greater in the IFX+NPX group than the PBO+NPX group, but the treatment group differences were smaller and not statistically significant after week 2 (Figure 31C).

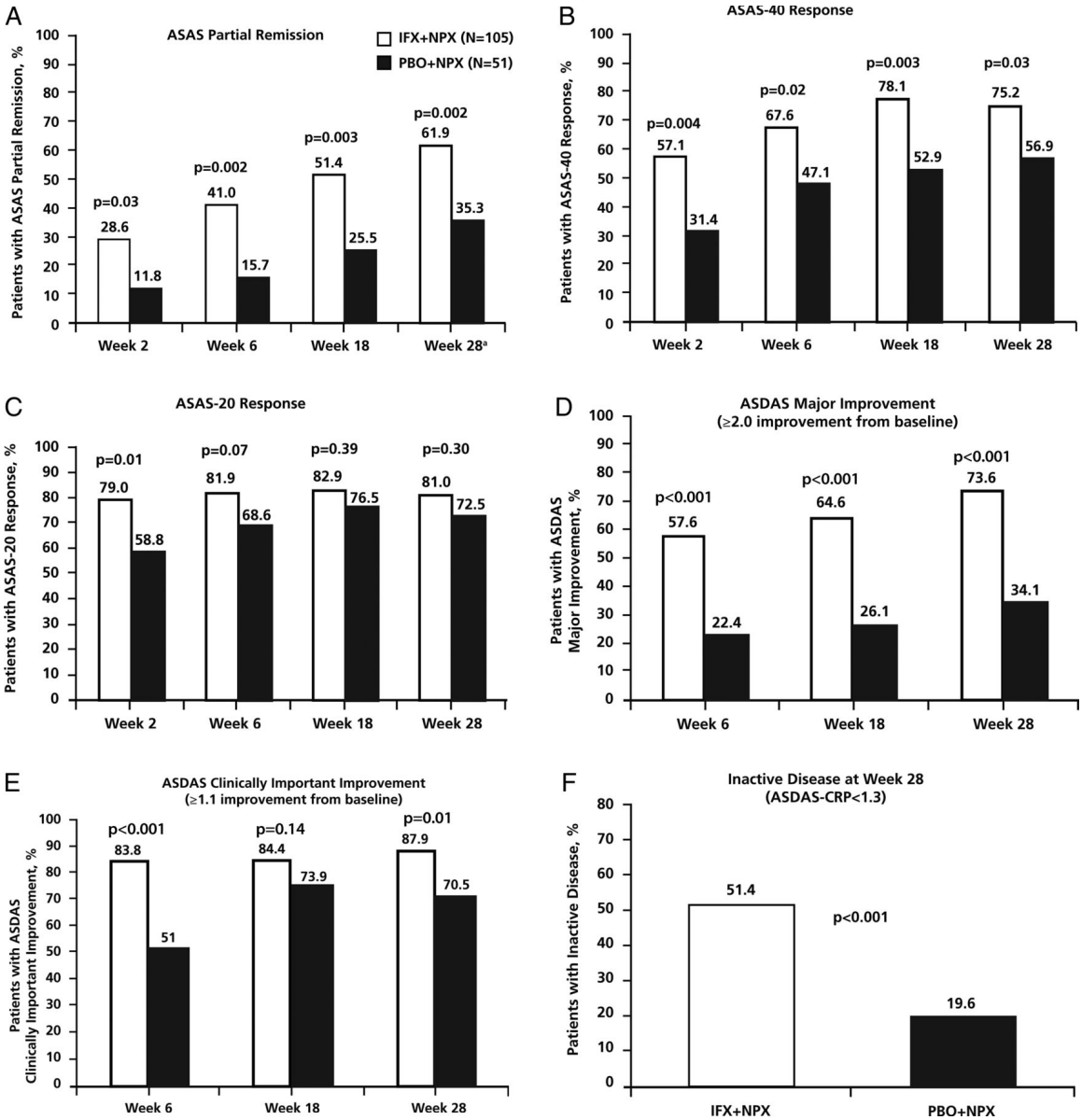

FIG.31: *Percentage of patients who achieved ASAS partial remission (A), ASAS-40 response (B), ASAS-20 response (C), ASDAS major improvement (D), ASDAS clinically important improvement (E) and ASDAS inactive disease (F). p Values are from analysis of treatment group differences in change from baseline at each visit. [a]ASAS partial remission at week 28 was the primary endpoint of the study. Subjects who*

withdrew prior to week 28 were not considered to be in partial remission. Patients who were missing more than two ASAS components at week 28 were considered not in partial remission. If a patient had data for at least two ASAS domains at week 28, missing data for the remaining ASAS domains were imputed using a last-observation-carried-forward approach

ASDAS major improvement (≥2.0-point improvement from baseline) and ASDAS clinically important improvement (≥1.1-point improvement from baseline) also showed a pattern of greater improvement in the IFX+NPX group than the PBO+NPX group at each visit (**Figure 32D and E**). The percentage of patients with ASDAS-inactive disease (ASDAS-C <1.3, using C-reactive protein (CRP) in the calculation) in the IFX+NPX group (51.4%) was much greater than in the PBO+IFX group (19.6%) at week 28 (p<0.001) (**Figure 32F**).

Efficacy measures	IFX+NPX =105				PBO+NPX N=51				p Value for treatment group difference
	Baseline (BL), mean	Week 28, mean	Change from BL, mean (SD)	% Change	Baseline, mean	Week 28, mean	Change from BL, mean (SD)	% Change	
PhGADA (100 mm VAS)	66.6	15.6	–51.3 (23.00)	–76.5	63.3	30.6	–33.0 (22.44)	–51.7	<0.001
PtGADA (100 mm VAS)	73.5	18.8	–54.5 (25.71)	–74.4	72.3	34.4	–38.1 (29.02)	–52.4	<0.001
Patient's total back pain (100 mm VAS)	76.7	18.6	–58.0 (25.61)	–75.7	76.6	30.8	–45.2 (29.27)	–59.8	0.005
Patient's nocturnal pain (100 mm VAS)	70.6	16.7	–54.0 (26.03)	–76.4	69.3	31.4	–37.4 (30.66)	–54.7	<0.001
EQ-5D index score*	0.38	0.75	0.37 (0.303)	95.4	0.33	0.60	0.27 (0.313)	81.6	0.003
EQ-5D global health status*	46.8	76.8	30.0 (29.23)	64.2	40.0	58.9	18.5 (23.11)	47.0	<0.001
SF-36 physical component*	34.0	46.6	12.6 (10.31)	42.5	32.4	40.3	8.6 (8.93)	29.4	0.003
SF-36 mental component*	40.0	49.0	9.0 (10.96)	33.5	37.7	45.7	7.6 (11.10)	27.1	0.16
BASMI	3.1	2.0	–1.1 (1.13)	–34.6	3.1	2.5	–0.6(0.72)	–18.7	<0.001
ESR (mm/h)	23.0	7.1	–16.0 (16.11)	–54.7	28.3	19.0	–9.4 (13.18)	–13.0	<0.001
CRP (mg/dL)	2.02	0.91	–1.24 (6.209)	–55.1	1.65	1.15	–0.55 (1.315)	–30.5	0.59
66-joint SJC, mean (SD)	1.49	0.15	–1.44 (4.131)	–89.6	0.78	0.40	–0.42 (0.917)	–49.0	0.06
68-joint TJC, mean (SD)	4.06	0.94	–3.29 (6.385)	–76.9	3.80	1.07	–2.93 (5.101)	–72.0	0.73

	Patients who met criterion at week 28, %	Patients who met criterion at week 28, %	
BASDAI≥50% improvement	77.3	51.1	0.003
BASDAI<3	76.3	53.3	0.01

TABLE 32: *Secondary efficacy outcomes from baseline to week 28. *An increase in scores indicates improvement on these measures. For all other measures, a decrease in score indicates improvement.*

As shown in Table 40, the IFX+NPX group had significantly greater improvement than the PBO+NPX group in most other measures of disease activity, clinical signs and symptoms and patient-reported outcomes at almost all visits. For all of the patient-reported outcomes, including quality of life and assessments of pain, both treatment groups improved substantially after baseline, with the IFX+NPX group showing significantly greater improvement at week 28 on all but one of the eight measures.

5.1.4.5. Safety

Overall, IFX was well tolerated, and the pattern of AEs in the IFX+NPX group was similar to that reported previously for TNF antagonists in comparable populations (Table 41). The AEs that occurred in ≥5% of patients in either the IFX+NPX (N=105) or PBO+NPX (N=52) group were nasopharyngitis (10.5% and 7.7%, respectively), upper abdominal pain (7.6% and 1.9%, respectively), headache (6.7% and 3.8%, respectively) and dyspepsia (2.9% and 5.8%, respectively).

No deaths occurred. Serious AEs were reported in five patients (4.8%) in the IFX+NPX group and three patients (5.8%) in the PBO+NPX group. In the IFX+NPX group, one patient experienced chest discomfort, dizziness and dyspnea; one patient had increased hepatic enzymes (alkaline phosphatase 2 times the upper limit of normal (ULN) and gamma glutamyl transpeptidase elevated greater than 10 times the ULN; at a follow-up 7 months after study discontinuation, liver enzymes were within normal range with a slight increase in GGT); one patient had breast cancer (diagnosed 6 months after start of treatment); and one patient had pneumonia and tuberculosis (patient was from the Russian Federation and had a negative tuberculin test and normal chest x-ray at screening; hospitalised for tuberculosis 5 months after the start of treatment). In addition, one case of fetal distress syndrome and uterine hypotonus occurred in a patient in the IFX+NPX group who reported pregnancy and was discontinued from the study; the baby was reported as born healthy after caesarean section. In the PBO+NPX group, one patient had anaemia and ovarian cyst rupture, one patient had worsening of AS and one patient had atopic dermatitis.

AEs leading to withdrawal from the study occurred in four patients (3.8%) in the IFX+NPX group and one patient (1.9%) in the PBO+NPX group (see details in Table 41).

Treatment-emergent infections and infestations occurred in 27/105 patients (25.7%) in the IFX+NPX group and 9/52 patients (17.3%) in the PBO+NPX group (see details in Table 41). In both treatment groups, 1.9% of patients had an increase in hepatic enzymes, including the one serious event already mentioned above in the IFX+NPX group.

Treatment-emergent AE category, n (%)	IFX+NPX N=105	PBO+NPX N=52
Any AE	61 (58.1)	26 (50.0)
Any serious AE	5 (4.8)	3 (5.8)
AE related to study medication	36 (34.3)	12 (23.1)
AE leading to early withdrawal	4 (3.8)	1 (1.9)
Dyspepsia	1 (1.0)	0
Tuberculosis	1 (1.0)	0
Hepatic enzyme increased	1 (1.0)	0
Worsening of ankylosing spondylitis	0	1 (1.9)
Breast cancer	1 (1.0)	0
Infections and infestations occurring in >1 patient in either group		
Nasopharyngitis	11 (10.5)	4 (7.7)
Localised infection	2 (1.9)	2 (3.8)
Cystitis	1 (1.0)	2 (3.8)
Bronchitis	2 (1.9)	1 (1.9)
Gastroenteritis	3 (2.9)	0
Oral herpes	2 (1.9)	0
Tonsillitis	2 (1.9)	0

TABLE 41: *Patients with treatment-emergent adverse events (AEs)*

5.1.5.Discussion

This is the first study comparing the efficacy of a combination of a TNF antagonist and an NSAID versus an NSAID alone in patients with active axial SpA who are not refractory to NSAID therapy. Nearly two-thirds of patients who received IFX+NPX combination treatment achieved ASAS partial remission at week 28, compared with about one-third of the group who received NPX alone. This pattern of greater improvement in the IFX+NPX group was apparent as early as week 2; and continued, steady improvement occurred up to week 28.

The good results in the group receiving NSAIDs alone (35% partial remission) were rather surprising. NPX and other NSAIDs have been shown to be similarly effective in AS patients [11-14] and most of these NSAID trials used a flare design similar to the design used in INFAST (ie, patients using NSAIDs before inclusion must stop treatment and demonstrate worsening symptoms to be included in the study). However, none of these trials found ASAS partial remission rates greater than about 15% [11-13]. Although the controlled phase of these studies was usually shorter (12 weeks rather than 28 weeks), response rates did not increase during trials with longer, open-label periods [12] One possible reason for the good response in the PBO+NPX group in the INFAST study may be the short symptom duration required for study entry (≤3 years, with actual mean duration <2 years) and, therefore, a mixture of patients with AS and patients with non-radiographic axial SpA; other studies have used populations with longstanding AS. In addition, all patients in INFAST had lesions seen on MRI at study entry, which was not a selection criterion for the NSAID studies. Although placebo response in the PBO+NPX group cannot be excluded, another study of patients with active axial SpA (refractory to previous NSAID therapy) with

a symptom duration of <3 years found a placebo response rate of only 12.5%.6 Our data suggest that axial SpA patients respond better to a full NSAID dose if they are treated early.

Within the first 2 weeks of NSAID therapy for patients in the PBO+NPX group, a strong improvement in disease activity was seen; mean BASDAI decreased from 6.3 to 4.4, with a continued, slower decrease up to week 28 (mean, 3.2). These data suggest that response to NSAIDs can be judged in the first 2–4 weeks of treatment, as noted in the ASAS treatment guidelines,3 and that further improvement may occur with continued treatment. Similar to the results for BASDAI, a reduction of about 50% from baseline was seen in the other continuous outcomes (**Figure 32**; **Table 40**), including CRP concentration, which has previously been shown to improve during NSAID treatment in patients with AS [13, 14]

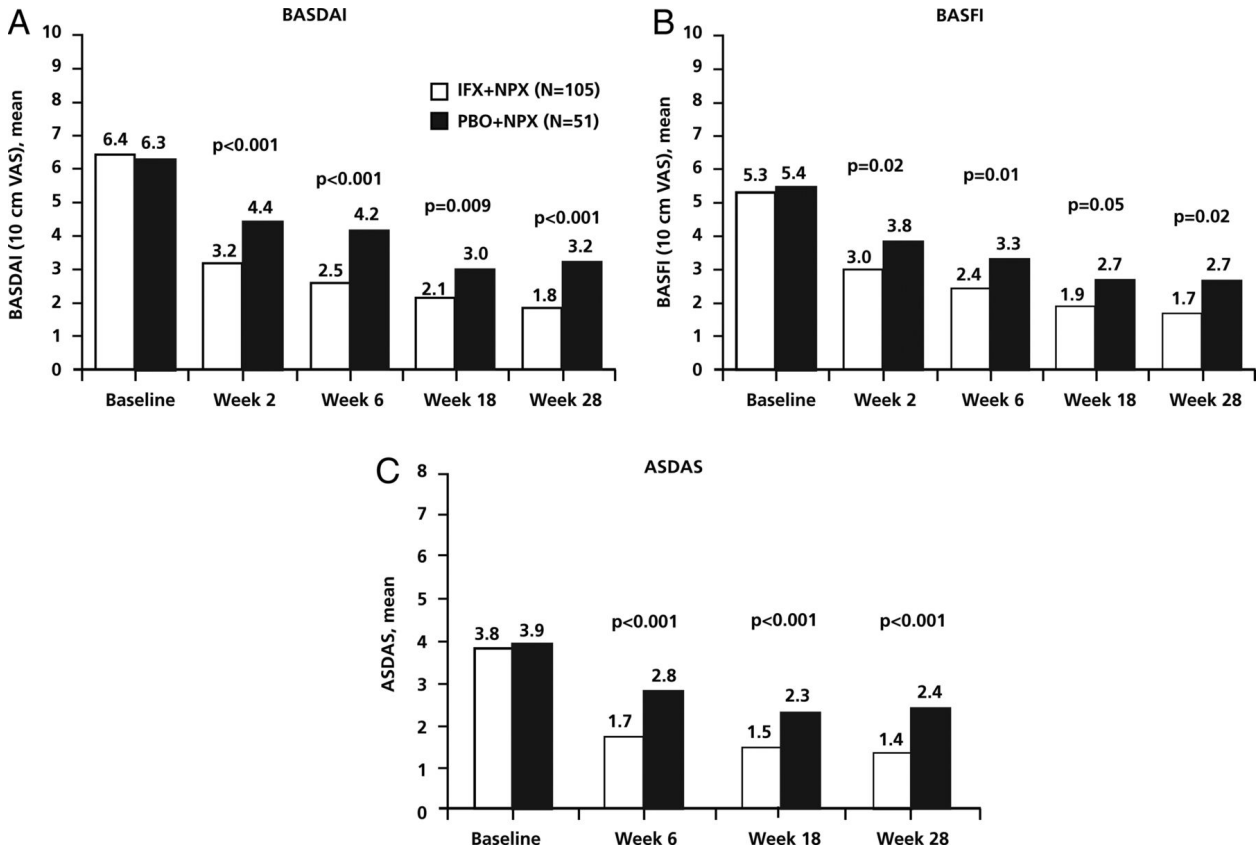

FIG.32: *Efficacy measures from baseline to week 28: BASDAI (A), BASFI (B), and ASDAS (C). p Values are from analysis of treatment group differences in change from baseline at each visit.*

Despite the better-than-expected response in the PBO+NPX group, a greater improvement in disease activity was observed in those patients who received IFX+NPX. The superiority of treatment with IFX+NPX was most obvious in the binary outcome parameters, which measured low disease activity status or major response rates (eg, ASAS partial remission and ASDAS inactive disease rate, followed by ASAS-40 response). Interestingly, there was no clear difference between the treatment groups for minor response levels such as ASAS-20. For nearly all the continuous efficacy measures, approximately 75% reductions from baseline were seen in the IFX+NPX group, and approximately 50% reductions were seen in the NPX-alone group. Whether a combination of IFX+NSAID would be superior to IFX alone cannot be determined from the INFAST study because no IFX-alone group was included. However, information about a potentially additive effect of NSAIDs and TNF antagonists for improvement of signs and

symptoms would be of interest, especially given the reported inhibitory effect of NSAIDs on radiographic progression in AS (15, 16).

The response rates in the IFX+NPX group of INFAST are comparable to those from a smaller, placebo-controlled IFX trial in active axial SpA patients with symptom duration of <3 years [6]: ASAS partial remission rates were 61.9% vs 55.6%, and ASAS-40 response rates were 67.6% vs 61.1% in the two trials, respectively. No detailed information was given in the smaller trial on the status of NSAID treatment, but these patients are likely to have been NSAID failures. The comparable response rates in the two trials and the good response rate to NSAIDs in the INFAST study support an early step-up treatment approach, with early diagnosis and treatment with NSAIDs, escalating to combination treatment after an insufficient response [3], although such an approach was not specifically tested in our trial. Currently, these two IFX studies are the only ones that limited symptom duration of axial SpA to 3 years and included a blinded control group. In a recent trial of etanercept in axial SpA, symptom duration at inclusion was limited to 5 years, and the two treatment groups, etanercept versus sulfasalazine, were not blinded for the clinical outcome assessments [7]. At week 48, ASAS partial remission was reached in 50% of the etanercept group versus 19% of the sulfasalazine group. In two trials of adalimumab in patients with non-radiographic axial SpA with no limit on symptom duration, a better response rate was reported in a subgroup of patients who had shorter symptom duration [5, 17]

Fulfillment of the ASAS criteria for axial SpA and positive MRI findings of the SI joint were, according to the ASAS definition, mandatory for inclusion into the INFAST trial. Local investigators judged whether patients had radiographic sacroiliitis according to the modified New York criteria, but these judgments were irrelevant for inclusion in the study. The percentage of patients with radiographic sacroiliitis in INFAST (59%), based on the local reading of the x-rays, was relatively high compared to the other IFX trial described above that had a similar symptom duration (12% [6]), but the percentage was not so different from other analyses of patients with axial SpA in the first 3–5 years of their disease (50% [7, 18]). Some of the variability across studies may be due to the challenge of reading x-rays of patients with early sacroiliitis; rather low sensitivity and specificity have been reported in some studies [19, 20]

Overall, the current study results, combined with evidence from other studies in which patients were already optimised on NSAID treatment, suggest that response to anti-TNF therapy may be improved with selection of patients who are young, have short disease duration and have objective evidence of inflammation (as demonstrated by MRI and elevated CRP). Evaluation of the best strategy for maintenance and/or continued improvement in patients who had achieved partial remission after 28 weeks of therapy with either IFX+NPX or NPX alone was the subject of a follow-up phase of the INFAST study that continued to week 52. Predictors of maintenance of remission were evaluated in that study, and the data will be reported in a separate manuscript.

The AE profiles for each treatment arm were as expected in patients receiving TNF-α–targeted therapy and NSAID therapy. Both treatments appeared to be well tolerated, and no new safety signals were identified. Good tolerability appears to have been reflected in the drug adherence rates, which were close to 100% in both treatment groups. Safety and good drug tolerability are especially important in this young patient population in the early phase of their disease.

In conclusion, results of the INFAST study demonstrated better outcomes on a variety of efficacy measures in patients with early axial SpA who were treated with IFX+NPX than in those treated with NPX alone. Overall, available evidence supports early diagnosis and treatment of SpA with a full dose of NSAIDs first, escalating to combination NSAID+TNF antagonist treatment in patients who have insufficient response.

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5.2. Maintenance of biologic-free remission with naproxen or no treatment in patients with early, active axial spondyloarthritis: results from a 6-month, randomised, open-label follow-up study, INFAST Part 2

5.2.1. Abstract

Objective

To investigate whether biologic-free remission can be achieved in patients with early, active axial spondyloarthritis (SpA) who were in partial remission after 28 weeks of infliximab (IFX)+naproxen (NPX) or placebo (PBO)+NPX treatment and whether treatment with NPX was superior to no treatment to maintain disease control.

Method

Infliximab as First-Line Therapy in Patients with Early Active Axial Spondyloarthritis Trial (INFAST) Part 1 was a double-blind, randomised, controlled trial in biologic-naïve patients with early, active, moderate-to-severe axial SpA treated with either IFX 5 mg/kg+NPX 1000 mg/d or PBO+NPX 1000 mg/d for 28 weeks. Patients achieving Assessment of SpondyloArthritis international Society (ASAS) partial remission at week 28 continued to Part 2 and were randomised (1:1) to NPX or no treatment until week 52. Treatment group differences in ASAS partial remission and other efficacy variables were assessed through week 52 with Fisher exact tests.

Results

At week 52, similar percentages of patients in the NPX group (47.5%, 19/40) and the no-treatment group (40.0%, 16/40) maintained partial remission, p=0.65. Median duration of partial remission was 23 weeks in the NPX group and 12.6 weeks in the no-treatment group (p=0.38). Mean Bath Ankylosing Spondylitis Disease Activity Index scores were low at week 28, the start of follow-up treatment (NPX, 0.7; no treatment, 0.6), and remained low at week 52 (NPX, 1.2; no treatment, 1.7).

Conclusions

In axial SpA patients who reached partial remission after treatment with either IFX+NPX or NPX alone, disease activity remained low, and about half of patients remained in remission during 6 months in which NPX was continued or all treatments were stopped.

5.2.2.Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are first-line treatments for patients with axial spondyloarthritis (SpA) or ankylosing spondylitis (AS). For patients who fail NSAID treatment or cannot tolerate it, tumour necrosis factor (TNF) α blockers are recommended [1] because they reduce inflammation, control disease activity and improve patient functioning and quality of life [2–5] In the Infliximab as First-Line Therapy in Patients with Early Active Axial Spondyloarthritis Trial (INFAST) study [6] patients with axial SpA who had not failed NSAIDs or were NSAID-naïve showed substantial benefit from combined treatment with NSAIDs and the TNF-antagonist infliximab (IFX). At month 6, partial remission was achieved in 62% and 35% of patients treated with IFX+naproxen (NPX) or placebo (PBO)+NPX, respectively.

For patients with axial SpA who have achieved remission, the best strategy for maintenance of remission is not known. In patients with rheumatoid arthritis (RA), several studies have shown that biologic-free remission, either with or without continuous treatment with methotrexate, can be achieved if patients are treated early enough in the course of the disease [7–9]. In patients with AS, studies have found that response to TNF antagonists may be sustained over several years, but that response is lost soon after cessation of treatment [10, 11]. Few studies have evaluated the long-term effects of TNF-antagonist treatment in patients with early axial SpA, and it is unclear how long biologic-free remission is likely to be maintained or whether NSAID treatment might aid in maintenance of remission after anti-TNF treatment is discontinued.

The primary goals of INFAST Part 2, the 6-month follow-up study reported here, were to explore whether biologic-free remission can be achieved in patients with early axial SpA and to determine whether continued treatment with NPX was superior to discontinuing all treatments in order to maintain disease control for 6 months.

5.2.3.Methods

5.2.3.1. Study design and patients

Part 1 of INFAST (Protocol P05336, NCT00844805) was a multicentre, double-blind, randomised, controlled trial of IFX+NPX vs PBO+NPX treatment in patients aged 18–48 years with early, moderate-to-severe axial SpA (see online supplementary figure S1). The design of Part 1 of the INFAST study has been reported elsewhere.6 Briefly, patients enrolled in INFAST Part 1 had been diagnosed with axial SpA of less than 3 years' duration, were naïve to biologics and were either NSAID-naïve at baseline or had been treated with not more than two-thirds of the maximal recommended dose during the 2 weeks prior to the screening visit. Patients were randomised (2:1) to receive 28 weeks of treatment with either intravenous (IV) IFX 5 mg/kg (weeks 0, 2, 6, 12, 18 and 24)+NPX 1000 mg/d or IV PBO+NPX 1000 mg/d.

In Part 2, the follow-up period of INFAST that is the focus of this report, patients who had achieved Assessment of SpondyloArthritis international Society (ASAS) partial remission at week 28 (defined as reaching ≤20 mm on a scale of 100 mm in all four ASAS domains) were eligible to continue to the follow-up phase. IFX treatment was stopped, and patients were randomised to receive either NPX or no treatment (1:1 ratio) until week 52. For the NPX group, open-label NPX was administered at the dose each patient had received prior to week 28 (1000 mg/d or 500 mg/d if the higher dose was not tolerated). A computer-generated randomisation list was created by the sponsor and held by the central randomisation centre, which was contacted by the site to assign treatment to each patient as they

enrolled. Randomisation in Part 2 was stratified by randomised treatment assignment in INFAST Part 1. Data were collected from October 2009 to September 2011.

Patients with flares, defined as Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥3 cm on a 10-cm visual analogue scale during two consecutive visits within 1–3 weeks of each other between weeks 28 and 52, had a final MRI and were discontinued from the study.

5.2.3.2. Outcome measures

The primary outcome of INFAST Part 2 was the percentage of patients who maintained ASAS partial remission until week 52. Secondary outcomes included the percentage of patients with disease flare (as defined above) and several other measures of disease activity, inflammation, clinical symptoms, functioning and quality of life (Ankylosing Spondylitis Disease Activity Score (ASDAS), BASDAI, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Metrology Index (BASMI) and EuroQoL 5D Health Questionnaire (EQ-5D)) were assessed at several points throughout the study.

Adverse events and other safety measures were also collected.

5.2.3.3. Statistical analysis

No sample size calculation was done for this exploratory follow-up study because the sample was determined by the number of patients in remission at the end of Part 1 of INFAST. Anticipating that approximately 60 patients would be in remission at the end of Part 1, with 30 patients per group, the study had an estimated 87% power to detect a 42% absolute difference between the treatment groups in the percentage of patients with ASAS partial remission at week 52 using a Fisher exact test with α set at 0.05. This was considered acceptable because a small effect of NPX would probably not justify continued use of NPX to maintain remission after stopping a biologic treatment.

The intent-to-treat (ITT) population for INFAST Part 2 included all subjects who were randomised in the follow-up phase and had at least one efficacy assessment after week 28. The safety population included all patients who were randomised in the follow-up phase. Adverse events were analysed descriptively.

Treatment group differences in categorical efficacy measures, including the primary efficacy outcome, were analysed using Fisher exact tests. α was set at 0.05. Patients who discontinued early were considered to be non-responders in the analysis of ASAS partial remission. No other data were imputed. Continuous measures were analysed using analysis of covariance with baseline values as covariates. Duration of ASAS partial remission (in weeks) was assessed using the Kaplan–Meier method with a log-rank test of the difference between treatment groups. Predictors of duration of remission were explored using Cox regression models.

5.2.4. Results

5.2.4.1. Patient disposition

In Part 1 of INFAST, 158 patients were randomised, and 141 completed the study to week 28. In Part 2, the follow-up phase that included only patients who achieved ASAS partial remission at week 28, 41 patients were randomised to NPX and 41 to no treatment (Figure 1). The ITT population included 40 patients in each treatment group; 1 patient was excluded from each treatment group because they had no efficacy data after week 28. Each treatment group in Part 2 had 31 patients from the IFX+NPX arm

and 9 patients from the PBO+NPX arm in Part 1; the greater number of patients from the IFX+NPX arm reflected the 2:1 randomisation ratio to IFX+NPX vs PBO+NPX in Part 1, and also the greater number of patients who reached partial remission in the IFX+NPX arm in Part 1. Most patients (32/41, 78%) in each of the treatment arms in Part 2 completed week 52 of the trial.

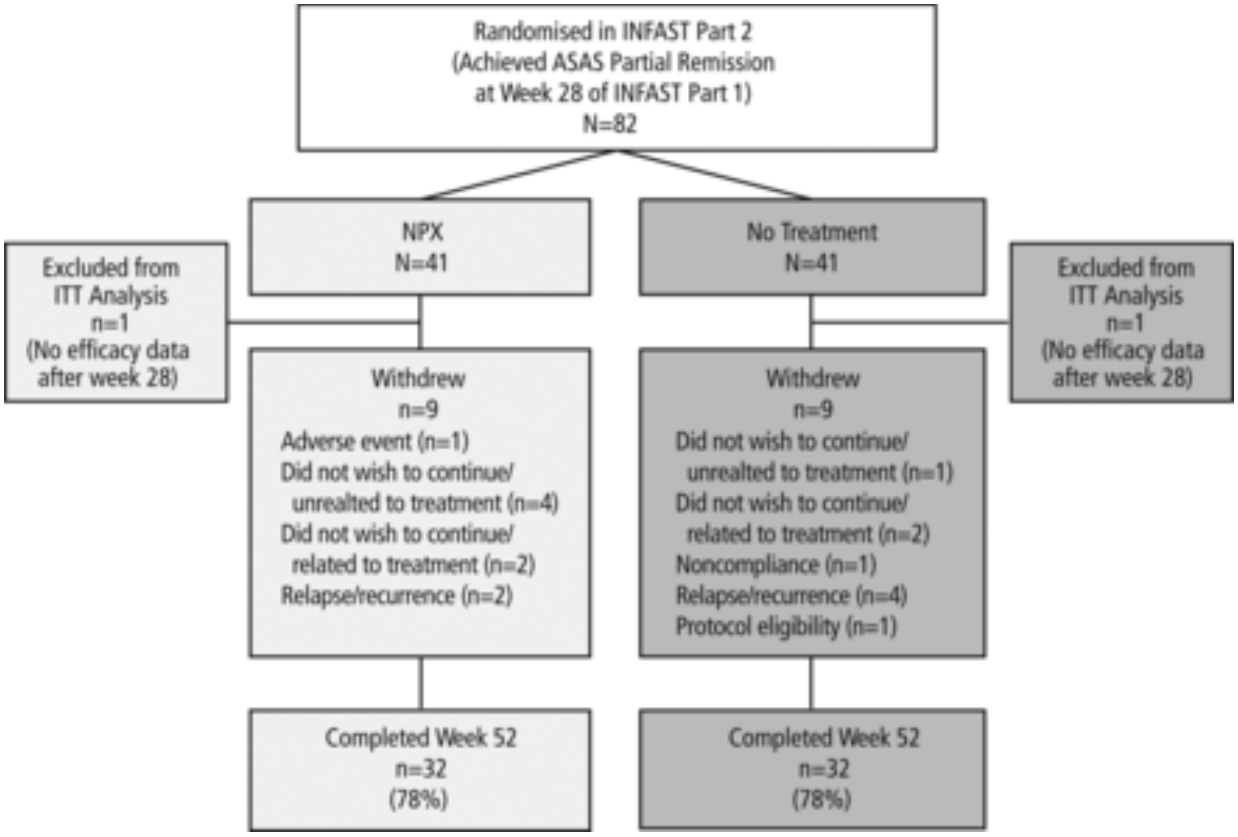

FIG. 33: *Patient disposition for INFAST Part 2.*

5.2.4.2. Baseline characteristics

For patients who entered INFAST Part 2, the treatment groups were similar in demographic and clinical characteristics at baseline of INFAST Part 1 (week 0) and clinical characteristics at baseline of INFAST Part 2 (week 28) (Table 42). Patients were selected for INFAST Part 2 only if they had reached partial remission in INFAST Part 1, and therefore, disease activity at the beginning of the follow-up phase was low. For example, mean BASDAI scores were 0.7 and 0.6 in the NPX and no-treatment groups, respectively, at week 28, an improvement from a mean of approximately 6.0 at baseline of INFAST Part 1 (week 0).

Patient characteristics at baseline of INFAST Part 1 (week 0)	NPX	No treatment
Baseline demographic characteristics	N=41	N=41
Gender (male), n (%)	34 (82.9)	30 (73.2)
Age (years), mean (SD)	29.3 (7.02)	29.5 (7.82)
Race, n (%)		
White	31 (75.6)	38 (92.7)
Asian	10 (24.4)	3 (7.3)
Body mass index (kg/m^2), mean (SD)	23.6 (3.52)	23.3 (4.19)
Clinical characteristics at baseline of INFAST Part 2 (week 28)	N=41	N=41
TJC68, mean (SD)	0.2 (0.95)	0.1 (0.40)
SJC66, mean (SD)	0.0 (0.00)	0.0 (0.16)
Patient Global Assessment of Disease Activity (0–100 mm), mean (SD)	5.7 (5.82)	5.7 (6.63)
Back pain (0–100 mm), mean (SD)	6.1 (5.64)	6.5 (6.69)
Physician Global Assessment of Disease Activity (0–100 mm)	8.9 (8.61)	8.7 (8.72)
Chest expansion (cm)	5.5 (1.64)	5.4 (1.97)
BASDAI (10 cm VAS), mean (SD)	0.7 (0.66)	0.6 (0.70)
BASMI, (10 cm VAS), mean (SD)	1.5 (1.05)	1.7 (1.13)
BASFI (10 cm VAS), mean (SD)	0.6 (0.60)	0.7 (1.00)
CRP (mg/dl), mean (SD)	0.39 (0.786)	0.58 (0.747)
ESR (mm/h), mean (SD)	7.2 (8.25)	9.1 (8.27)

TABLE 42: *Demographic and baseline characteristics for patients in INFAST Part 2 (all randomised patients).*

5.2.4.3. Exposure and adherence

In the NPX group, the average daily dose of NPX was 936.6 mg, with 99.4% adherence to the number of doses, regardless of dose amount.

5.2.4.4. Efficacy

At week 52, similar percentages of patients in the NPX group (47.5%, 19/40) and the no-treatment group (40.0%, 16/40) met the ASAS partial remission criteria, p=0.65 (Figure 34A). Overall, the percentage of patients in partial remission decreased steadily during the 6-month follow-up period. At each assessment point, similar percentages of patients in the NPX group and the no-treatment group maintained ASAS partial remission (p>0.05 at each time point). The median duration of partial remission was 23 weeks (95% CI 14.43 to 25.14) in the NPX treatment arm and 12.6 weeks (95% CI 10.71, upper bound not estimable) in the no-treatment group, a difference that was not statistically significant (p=0.38).

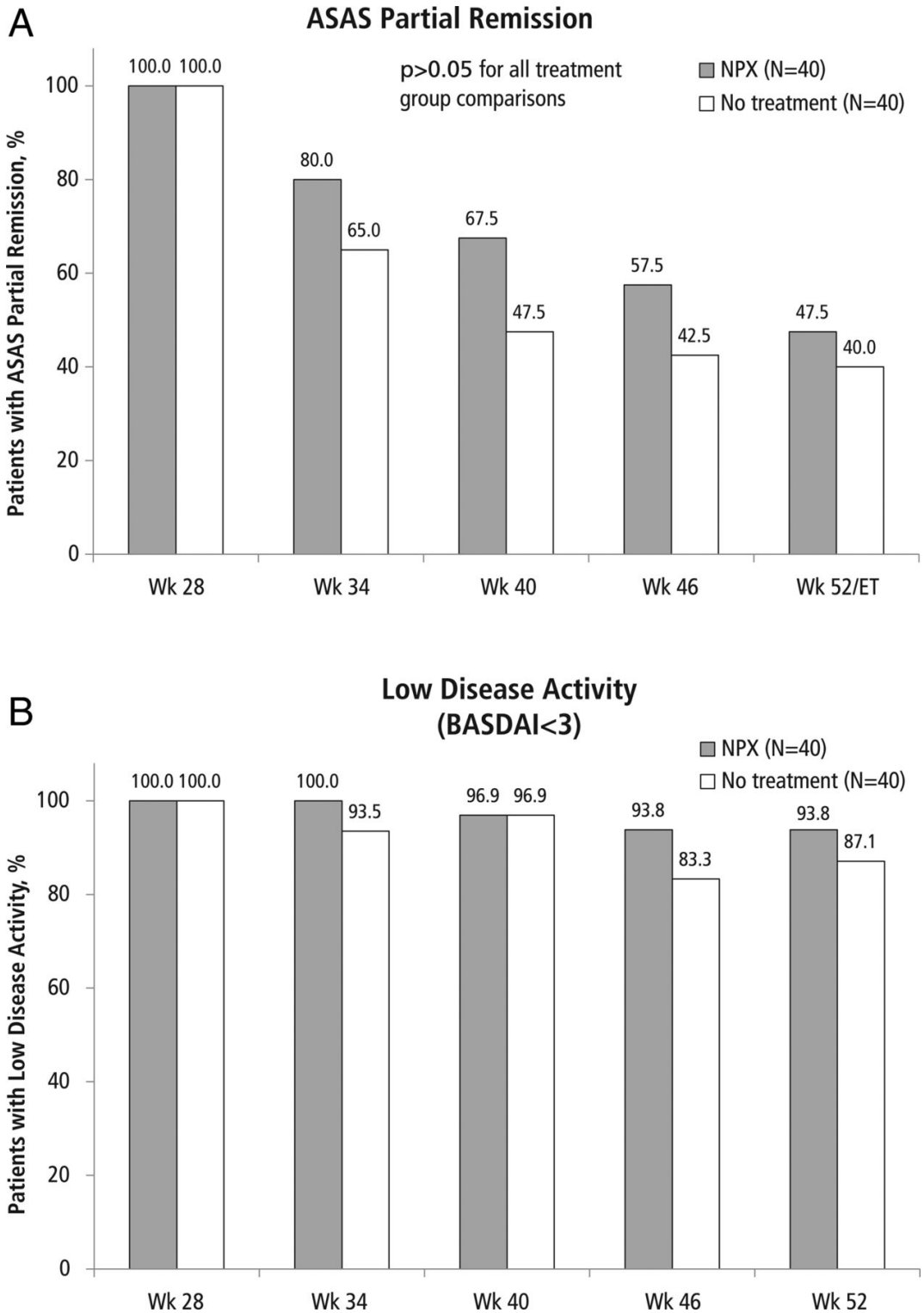

FIG. 34: *Percentage of patients in INFAST Part 2 who had ASAS partial remission (A) and low disease activity (BASDAI<3 in patients with non-missing data) (B) at each visit.*

Although the percentage of patients in partial remission decreased steadily over the 6-month follow-up period, few patients in either treatment group met the criteria for disease flare (NPX, 1/40, 2.5% and no

treatment, 3/40, 7.5%; p=0.62) and the vast majority of patients (83% to 94%) in both groups maintained a state of low disease activity (BASDAI<3) at all visits (Figure 34B).

All efficacy measures indicated some worsening from week 28 to week 52, but overall disease activity, as measured by BASDAI and ASDAS, remained very low in both the NPX and no-treatment groups (Table 43). BASMI, BASFI, ESR, CRP and EQ-5D showed similar patterns (Table 43), with no statistically significant differences between the treatment groups.

Efficacy measures	NPX N=40				No treatment N=40				p Value for treatment group difference
	Week 28, mean	Week 52, mean	Change, mean (SD)	% Change	Week 28, mean	Week 52, mean	Change, mean (SD)	% change	
ASDAS	0.9	1.5	0.6 (0.71)	145.8	1.0	1.6	0.6 (0.63)	95.5	0.84
BASDAI (10 cm VAS)	0.7	1.2	0.6 (1.06)	71.3	0.5	1.7	1.1 (1.37)	214.5	0.11
BASMI (10 cm VAS)	1.5	1.8	0.3 (0.47)	30.2	1.6	1.7	0.3 (0.63)	19.6	0.89
BASFI (10 cm VAS)	0.6	1.0	0.5 (0.79)	73.5	0.6	1.5	0.9 (1.41)	144.1	0.30
CRP (mg/dl)	0.37	0.69	0.29 (0.924)	85.0	0.53	0.72	0.26 (0.707)	34.3	0.99
ESR (mm/h)	7.1	14.7	7.6 (11.63)	209.8	9.4	13.6	5.1 (10.10)	134.0	0.46
EQ-5D index score*	0.85	0.73	−0.12 (0.228)	−13.9	0.84	0.74	−0.12 (0.232)	−12.0	0.95

TABLE 43: *Efficacy outcomes by treatment group. *An increase in this score indicates improvement. For all other measures, a decrease in score indicates improvement.*

Figure 35 illustrates the gains that were made in the first 28 weeks and maintained over the 6-month follow-up period by showing the data over the full-year study period for the group of patients who participated in Part 2. For example, BASDAI scores decreased substantially for patients at the start of treatment in INFAST Part 1. In Part 2, after patients were randomised to NPX or no treatment, the NPX group appeared to have a slightly lower BASDAI at each visit. Patterns were similar for ASDAS based on CRP (ASDAS-C), CRP and BASFI.

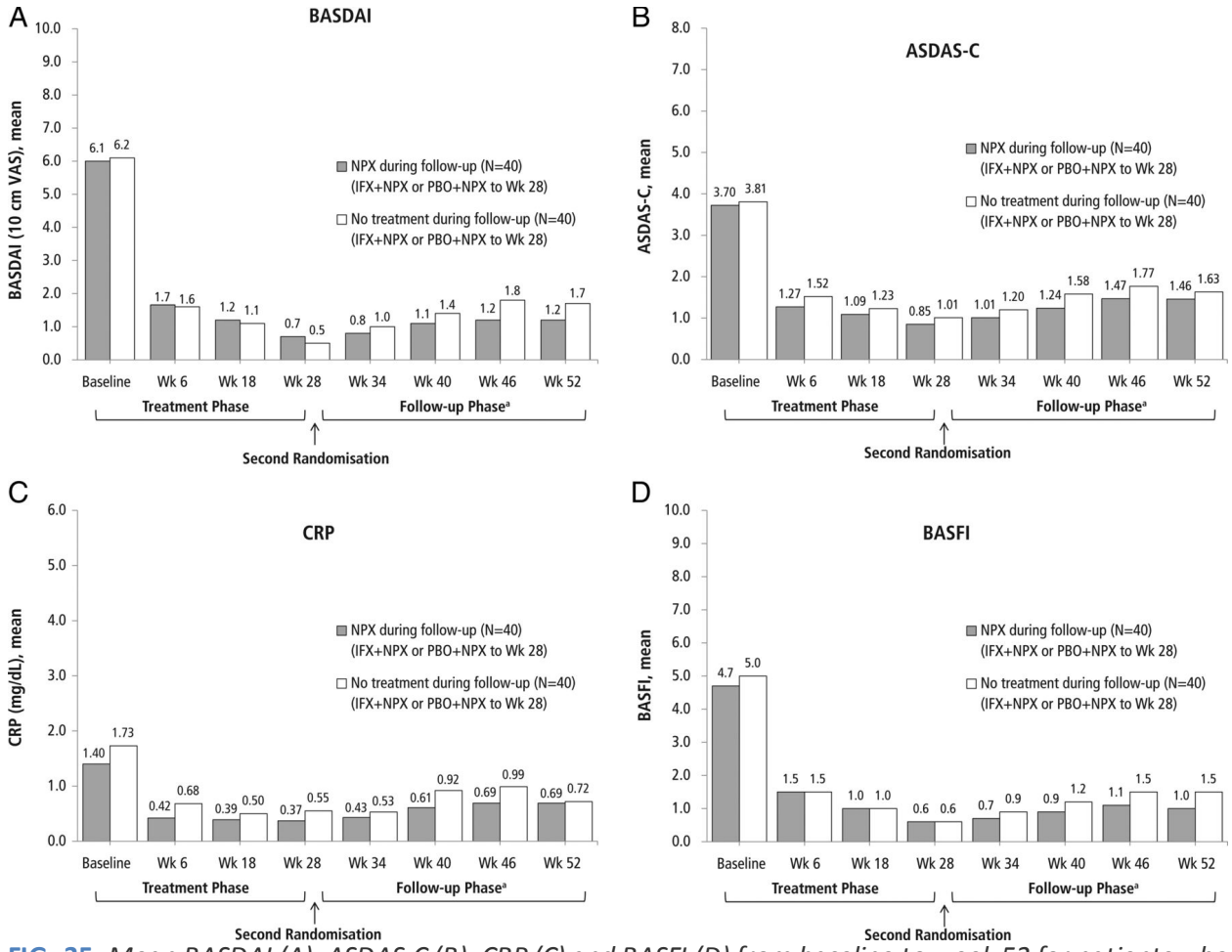

FIG. 35: *Mean BASDAI (A), ASDAS-C (B), CRP (C) and BASFI (D) from baseline to week 52 for patients who participated in INFAST Part 2. [a]During the follow-up period, patients with ASAS partial remission were assigned to either NPX or no treatment, with assignments stratified by initial treatment group.*

Figure 36 shows BASDAI and ASDAS-C scores for the Part 2 participants, grouped according to their randomised assignments in both Part 1 and Part 2. Patients receiving IFX+NPX in Part 1 showed greater improvement than patients receiving PBO through week 34. By week 52, differences were no longer evident between the groups. Although it is useful to see the overall patterns across groups in Part 2, it should be noted that the numbers of subjects in these four groups are small.

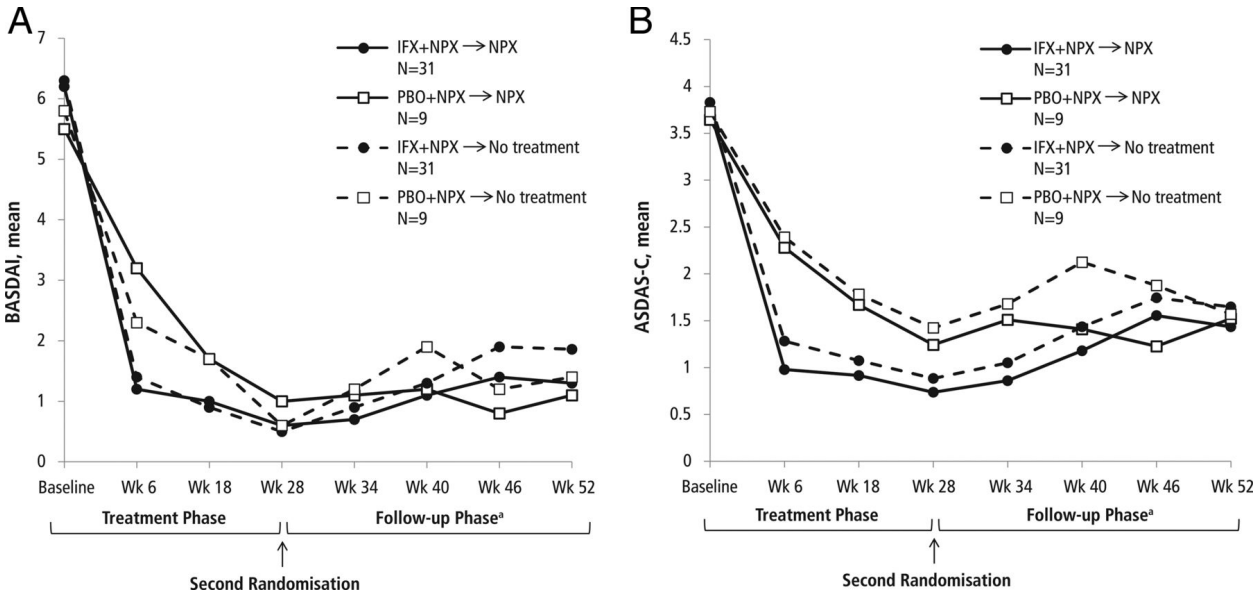

FIG. 36: *BASDAI (A) and ASDAS-C (B) by treatment sequence and visit for patients who participated in Part 2. [a]During the follow-up period, patients with ASAS partial remission were assigned to either NPX or no treatment, with assignments stratified by initial treatment group.*

Single and two-factor logistic regression analyses examined predictors of sustained remission at week 52. Regardless of treatment in Part 1 of INFAST, disease duration in years was the only characteristic that had a robust association with remission at week 52. In the single-variable analysis, the estimate was −1.673 (SE=0.572, p=0.03), indicating that patients with shorter disease duration were more likely to have sustained remission than patients with longer disease duration.

5.2.4.5. Safety

During the follow-up period, the percentage of patients with treatment-emergent adverse events (TEAEs) was higher in the no-treatment arm (41.5%; 17/41) than in the NPX arm (26.8%; 11/41). The most frequently reported TEAEs in the NPX group were rhinitis and intervertebral disc protrusion (each in two patients). The most frequently reported TEAEs in the no-treatment group were nasopharyngitis (three patients), bronchitis (two patients) and respiratory tract infection (two patients). During the follow-up period, one serious TEAE (carcinoma in situ) was reported in the no-treatment group (the patient had received IFX+NPX in INFAST Part I), and one TEAE leading to early withdrawal (fatigue) occurred in the NPX group. No deaths occurred.

5.2.5.Discussion

In this study of patients with early, active, moderate-to-severe axial SpA who had reached ASAS partial remission following 28 weeks of treatment with IFX+NPX or PBO+NPX, remission was maintained at week 52 by similar percentages of patients who either stayed on NPX therapy (47.5%) or in whom all treatments were stopped between weeks 28 and 52 (40.0%). Although the rate of partial remission, a stringent criterion for disease activity, decreased steadily over the follow-up period, other measures of disease activity indicated that most of the substantial improvement achieved over the first 28 weeks of treatment was well maintained during the follow-up period. For example, mean BASDAI across treatment groups was approximately 6 at baseline of INFAST Part 1, approximately 0.6 at baseline of INFAST Part 2 (week 28) and approximately 1.5 at week 52. Approximately 90% of patients had

BASDAI<3 at week 52. As assessed by several other measures of disease activity, inflammation and functioning (eg, ASDAS-C, CRP and BASFI) improvements achieved during the initial treatment phase of INFAST were generally maintained during the 6-month follow-up period, and very few flares were observed.

One issue of importance to patients, clinicians and payers is whether patients with axial SpA who are treated with TNF-α antagonists can stop therapy without experiencing disease flare. Although studies in AS populations have shown that patients continue to respond to TNF-antagonist treatment over periods of several years, available evidence indicates that nearly all patients will flare once treatment is stopped [10, 11] suggesting that the biologic-free remission rates found in INFAST would be unlikely in patients with established AS and longer disease duration. In the current study's population of patients with early disease, 78% of the patients in the follow-up study had received IFX+NPX in the initial treatment phase of INFAST. When all IFX treatment was stopped at week 28, almost half of the patients maintained partial remission to week 52. Overall, the data suggest that both combination treatments with IFX+NPX and NPX monotherapy in the first 6 months had long-lasting benefits in those patients who reached partial remission, with few patients in any treatment group experiencing disease flares.

The initial positive responses to treatment in INFAST Part 1 and the well-maintained response shown in INFAST Part 2 are among the highest rates of response for studies of TNF-α antagonist treatment in patients with axial SpA [5, 12-14]. The high response rates are possibly due to the very short disease duration of the population, patient selection for signs of inflammation on MRI and the intensified treatment during Part 1 (either a full dose of NPX or NPX+IFX) in a population of patients that had not yet failed NSAIDs or were naïve to NSAIDs at study entry. Patients in INFAST reported a mean of fewer than 2 years since the onset of symptoms, and previous studies [4, 12, 15] have shown that short disease duration is a predictor of better response to TNF-α antagonists in patients with axial SpA and AS. Shorter disease duration was associated with sustained remission in our study, which may indicate the existence of a window of opportunity for treatment of axial SpA early in the course of disease, as has been described in early RA [16]. This is the first trial in axial SpA demonstrating that a remission-induction strategy in patients with very early disease can actually keep these patients in a state of low disease activity, even without medication. One limitation of this study is that it is not known whether these results could be achieved after stopping medication in a population of patients who had already failed NSAIDs.

Although there was a tendency for slightly numerically better outcomes in patients who received NPX rather than no treatment during the follow-up period, none of these differences were statistically significant. It is difficult to draw any conclusions about the possible superiority of NPX because the follow-up phase of INFAST was an exploratory study that was underpowered to detect smaller differences between the NPX and no-treatment groups. Although significant clinically relevant differences could have been missed because of the small sample size, the small differences between the two groups detected here are likely to be too small to be of clinical significance even if a statistically significant difference had been shown in a study with greater power. The open-label nature of the study might be considered a weakness that could bias the results in favour of the NPX group, but the NPX group was not superior to the no-treatment group, suggesting that the open-label design should not influence the overall interpretation of the data.

The results of the INFAST follow-up study demonstrated that patients with early, active, moderate-to-severe axial SpA who achieved partial remission during 28 weeks of IFX+NPX or PBO+NPX treatment had

similar rates of partial remission whether they received NPX or no treatment during 6-months of follow-up. Overall, patients had low disease activity and very few flares during the follow-up period, whether they received NPX or no treatment at all. Whether such a low level of disease activity could be maintained beyond 6 months is an important question for future studies.

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5.3. Partial Remission in Ankylosing Spondylitis and Non-Radiographic Axial Spondyloarthritis and Associations Between Partial Remission and Baseline Disease Characteristics During Treatment With Infliximab Plus Naproxen or Naproxen Alone

5.3.1. Abstract

Objectives

To evaluate partial remission during treatment with infliximab (IFX [Remicade])+naproxen (NPX) vs NPX alone in patients from the 2 subgroups of axial spondyloarthritis (SpA) and explore baseline predictors of partial remission.

Methods

INFAST was a double-blind, randomized controlled trial of IFX in biologic-naïve patients with early, active axial SpA. Patients were randomized (2:1) to receive 28 weeks of treatment with IV IFX 5 mg/kg (weeks 0, 2, 6, 12, 18, and 24)+NPX 1000 mg/d or IV placebo (PBO)+NPX 1000 mg/d. The current post hoc analysis evaluated outcomes in patients who did or did not meet modified New York x-ray criteria for ankylosing spondylitis (AS).

Results

The analysis included 94 patients who met AS criteria and 56 with nonradiographic axial SpA (nr-axSpA). At week 28, Assessments in Ankylosing Spondylitis (ASAS) partial remission was greater with IFX+NPX than PBO+NPX for both the AS group (70.5% vs 33.3%, respectively) and the nr-axSpA group (50.0% vs 37.5%, respectively). A similar pattern occurred with several efficacy measures. Larger treatment effects occurred in the AS group than the nr-axSpA group, possibly due to baseline differences in disease characteristics. Multivariable analyses identified type of treatment, age, and HLA-B27 status as predictors of ASAS partial remission in the total study population. MRI SI scores were associated with partial remission during IFX+NPX treatment.

Conclusions

Patients with AS had greater partial remission to IFX+NSAID than NSAID therapy alone; patients with nr-axSpA had a smaller treatment effect. Baseline disease characteristics and age were associated with partial remission to IFX therapy.

5.3.2. Introduction

For patients with axial spondyloarthritis (SpA), only 2 types of treatments have proven efficacy: nonsteroidal anti-inflammatory drugs (NSAIDs) and tumor necrosis factor (TNF)-α–targeted therapies (1). NSAIDs are considered first-line treatment, and patients who fail 2 NSAIDs are considered candidates for TNF antagonist treatment (1). Clinical trial results have shown good response to TNF antagonists in both patients with ankylosing spondylitis (AS) and patients with nonradiographic axial SpA (nr-axSpA) (2-7). Recently, 3 TNF- blocking agents (adalimumab [8], certolizumab pegol [9], and etanercept [10]) have been approved for treatment of nr-axSpA in the European Union. Good outcomes of anti-TNF therapy have been associated with better function at baseline, human leukocyte antigen (HLA)-B27 genotype, elevated C-reactive protein (CRP), male gender, higher inflammation score on magnetic resonance imaging (MRI), and younger age in patients with AS (11-15). In patients with nr-axSpA, elevated CRP and MRI scores, shorter disease duration, and younger age also have been shown to predict better outcomes (3, 16).

In the Infliximab as First Line Therapy in Patients with Early Active Axial Spondyloarthritis Trial (INFAST) study, patients with early, active axial SpA who had been treated with suboptimal doses of NSAIDs were treated with naproxen (NPX) at the maximally recommended and/or tolerated dose with either infliximab (IFX [Remicade®, Janssen, Titusville, NJ]) or placebo (PBO) for 28 weeks (17). This study included both AS and nr-axSpA patients with moderate to severe disease with a disease duration of ≤3 years. The combination of NSAID and IFX treatment resulted in better rates of Assessment in Ankylosing Spondylitis (ASAS) partial remission than NSAID treatment alone (61.9% vs 35.3%, respectively) (17). In this post hoc analysis of INFAST, we describe the results for the subgroups of patients who had AS versus nr-axSpA, and we explore predictors of partial remission in this patient population that had early disease.

5.3.3. Patients and methods

5.3.3.1. Design and Patients.

INFAST was a randomized, double-blind, PBO-controlled study of IFX in adults with moderate to severe, active axial SpA who were not refractory to NSAIDs (Protocol P05336, NCT00844805). Details of the study methods have been previously reported (17). The study was conducted in accordance with the Declaration of Helsinki and standards of good clinical research practice. Written informed consent was required to participate, and the study protocol was reviewed by appropriate institutional review boards for each study site. Patients were enrolled in 9 countries (Austria, Belgium, Denmark, France, Germany, Hungary, Russia, South Korea, and Ukraine). Data collection occurred from 22 October 2009 to 20 September 2011. Patients who achieved partial remission criteria at week 28 were eligible to participate in a follow-up study of NPX vs no treatment up to week 52; data from this portion of the study are reported in Sieper et al. (18) and are not used in the analysis reported here.

Patients in INFAST were 18 to 48 years of age, had a diagnosis of axial SpA, and had disease duration of ≤3 years. All patients had inflammation of the sacroiliac (SI) joints (per ASAS criteria for axial SpA [19]) as determined by MRI read by local investigators. All patients had active disease, defined as a total back pain evaluation of ≥40 mm (visual analog scale [VAS] of 0–100 mm), and a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥4 cm (0–10 cm VAS). Patients were either NSAID-naïve or had been treated with not more than two thirds of the maximal recommended NSAID dose during the 2 weeks prior to screening.

For the current subgroup analysis, the patients were divided into 2 groups: those who met the New York modified radiographic criteria for AS (bilateral ≥ grade 2 or unilateral ≥ grade 3 lesions, as assessed by the local investigator) and those who had nr-axSpA.

5.3.3.2. Study Treatment.

During Part I (28 weeks) of INFAST, patients were randomized at a 2:1 ratio to receive either intravenous (IV) IFX 5 mg/kg or IV PBO at weeks 0, 2, 6, 12, 18, and 24. Both groups also received oral NPX at the maximum dose of 1000 mg daily, if tolerated. Randomization was not stratified by whether patients met AS radiographic criteria.

5.3.3.3. Outcome Measures.

The primary efficacy measure was the percentage of patients in each treatment group who met ASAS partial remission criteria at week 28. A number of secondary measures of disease activity, clinical signs and symptoms, and patient-reported outcomes were also assessed at each study visit. MRI lesions in spine and SI joints were assessed at baseline and week 28. Adverse events (AEs) and several other safety measures were also collected at each visit.

5.3.3.4. Statistical Analyses.

The originally targeted sample size for INFAST was 150 patients (100 receiving IFX+NPX and 50 receiving PBO+NPX) for 90% power to detect a 30% difference in ASAS partial remission between treatment groups, assuming a 15% withdrawal rate. The study was not powered for evaluation of treatment effects in the subgroups of patients analyzed here.

This post hoc analysis included patients who were randomized, received at least 1 dose of study medication, had at least 1 efficacy evaluation after baseline, and had baseline radiographs for determination of AS versus nr-axSpA status. For the main efficacy measure, ASAS partial remission, Fisher's exact tests were used to compare treatment arms within the AS and nr-axSpA groups. Other efficacy measures were analyzed descriptively.

To evaluate predictors of ASAS partial remission, a multivariable logistic regression model was used with stepwise selection of covariates with an entry criterion of P = 0.25 and a retention criterion of P = 0.15. Patients with AS and nr-axSpA were combined for this analysis. Variables of specific interest were explored further in the individual treatment groups using multivariable analyses.

5.3.4. Results

5.3.4.1. Patient Disposition

Of the 156 randomized patients in the INFAST intention-to-treat population, 93% of patients in the IFX+NPX group and 89.3% in the PBO+NPX group completed the study through week 28 (17). At baseline, 94 patients met the criteria for AS (IFX+NPX, 61; PBO+NPX, 33), 56 had nr-axSpA (IFX+NPX, 40; PBO+NPX, 16) according to local reading of the SI joint x-rays, and 6 patients were excluded from the analyses reported here because they were missing baseline radiographs and could not be classified accurately.

5.3.4.2. Baseline Characteristics

For each radiographic group, most baseline characteristics were similar in the IFX+NPX and PBO+NPX groups (Table 44). Compared with the nr-axSpA group, the AS group appeared to have greater concentrations of inflammatory markers, greater Berlin MRI scores, a greater percentage of patients with HLA-B27–positive status, and a greater percentage of males.

	Patients with AS		Patients with Nr-axSpA	
Baseline Characteristics	IFX+NPX (N = 61)	PBO+NPX (N = 33)	IFX+NPX (N = 40)	PBO+NPX (N = 16)
Gender (male), n (%)	51 (83.6)	28 (84.8)	19 (47.5)	10 (62.5)
Age (years), mean (SD)	31.2 (8.19)	31.0 (7.55)	31.8 (8.89)	30.9 (7.28)
Race, n (%)				
White	52 (85.2)	29 (87.9)	36 (90.0)	14 (87.5)
Asian	9 (14.8)	4 (12.1)	4 (10.0)	1 (6.3)
Multiracial	0	0	0	1 (6.3)
Body mass index (kg/m2), mean (SD)	23.8 (4.08)	24.0 (3.22)	24.7 (4.89)	24.1 (4.02)
Diagnosis duration years, mean (SD)	1.06 (0.891)	0.74 (0.701)	0.53 (0.587)	0.50 (0.417)
Symptom duration years, mean (SD)	2.01 (0.868)	1.84 (0.927)	1.44 (0.855)	1.54 (0.898)
BASDAI, mean (SD)	65.99 (15.17)	63.98 (16.28)	64.10 (16.34)	61.25 (13.90)
Nr of SpA manifestations, mean (SD)	4.1 (1.45)	4.1 (1.34)	3.4 (1.27)	3.9 (1.06)
Inflammatory back pain, n (%)	53 (86.9)	30 (90.9)	37 (92.5)	15 (93.8)
Arthritis, n (%)	34 (55.7)	10 (30.3)	13 (32.5)	4 (25.0)
Dactylitis, n (%)	3 (4.9)	1 (3.0)	0	0
Psoriasis, n (%)	1 (3.0)	2 (6.1)	2 (5.0)	0
Family history of SpA, n (%)	9 (14.8)	4 (12.1)	6 (15.0)	6 (37.5)
Uveitis, n (%)	4 (6.6)	4 (12.1)	2 (5.0)	2 (12.5)
History of CD/UC, n (%)	0	0	0	0
Enthesitis (heel), n (%)	9 (14.8)	5 (15.2)	4 (10.0)	5 (31.3)
HLA-B27–positive status, n (%)	54 (88.5)	32 (97.0)	31 (77.5)	12 (75.0)
CRP (mg/dL), mean (SD)	2.75 (7.335)	2.13 (1.514)	0.98 (1.221)	0.74 (0.698)
ESR (mm/h), mean (SD)	26.8 (17.56)	33.8 (17.65)	18.1 (16.06)	18.8 (11.57)
Overall MRI SI score at screening, median	4.0	6.5	3.3	6.5
Overall Berlin MRI spine score at screening, median	1.5	3.0	0.5	0.5
Previous good response to NSAIDs, n (%)*	43 (70.5)	21 (63.6)	26 (65.0)	12 (75.0)

TABLE 44: *Baseline Demographic and Disease Characteristics in Patients With AS or Nr-axSpA.*

5.3.4.3. Efficacy

ASAS partial remission. For both the AS and the nr-axSpA groups, ASAS partial remission rates at week 28 were greater in the IFX+NPX group than the PBO+NPX group (Table 45; Figure 37). The treatment effect favoring IFX+NPX in the AS group (70.5% for IFX+NPX vs 33.3% for NPX alone, P = 0.0009) was greater than the treatment effect favoring IFX+NPX in the nr-axSpA group (50.0% for IFX+NPX vs 37.5% for NPX alone, P = 0.55).

Secondary efficacy outcomes. For several other clinical and patient-reported outcomes at week 28, including BASDAI, ASDAS, BASFI, and EQ-5D, improvement was greater for patients who received IFX+NPX than NPX alone in the 2 subgroups (Table 45). The advantage of IFX+NPX over NPX alone was generally smaller in the nr-axSpA group than the AS group.

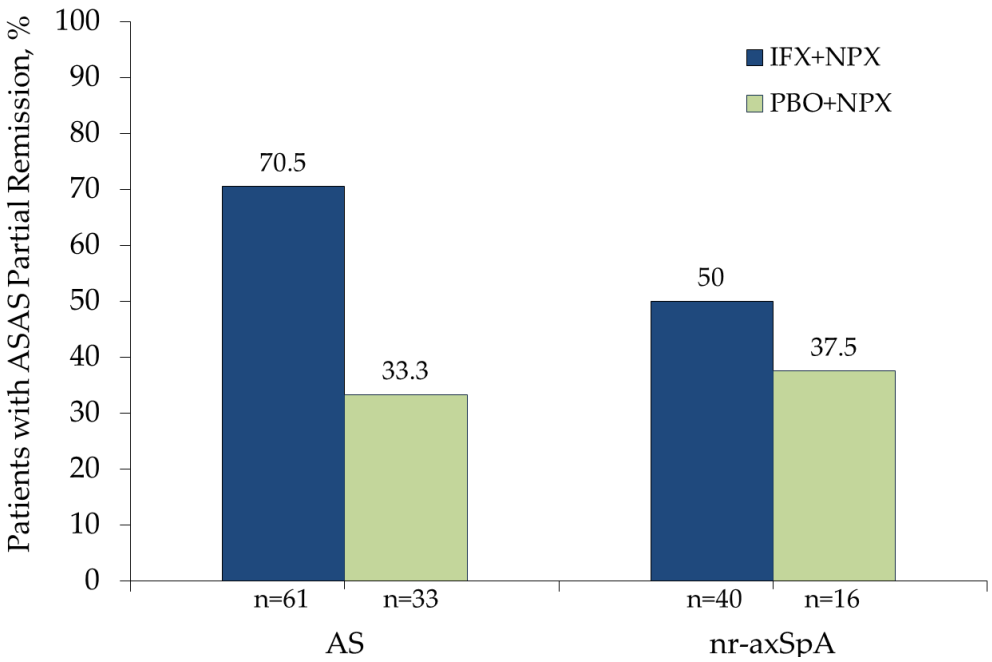


FIG.37: Percentage of patients who achieved ASAS partial remission at week 28 (observed data) by radiographic status and type of treatment.

	Patients with AS		Patients with nr-axSpA	
Efficacy Measure	IFX+NPX (N = 61)	PBO+NPX (N = 33)	IFX+NPX (N = 40)	PBO+NPX (N = 16)
ASAS partial remission at week 28, n (%)	43 (70.5)	11 (33.3)	20 (50.0)	6 (37.5)
ASAS40 at week 28, n (%)	53 (86.9)	18 (54.5)	24 (60.0)	9 (56.3)
ASAS20 at week 28, n (%)	53 (86.9)	24 (72.7)	29 (72.5)	11 (68.8)
BASDAI, mean (SD)				
Baseline	6.50 (1.517))	6.40 (1.628)	6.41 (1.634)	6.13 (1.389) 2.82
Week 28	1.38 (1.861)	3.54 (2.468)	2.50 (2.436)	(2.906)
BASDAI < 3 cm, n (%)				
Baseline	1 (1.6)	0	1 (2.5)	0
Week 28	50 (86.2)	15 (50.0)	22 (61.1)	7 (53.8)
BASFI , mean (SD)				
Baseline	51.7 (23.26)	59.2 (21.09)	55.4 (20.85)	45.2 (21.01) 16.1
Week 28	15.2 (19.61)	32.9 (23.98)	20.5 (23.12)	(17.77)
ASDAS-C, mean (SD)				
Baseline	3.950 (0.9231)	4.106 (0.7828)	3.607 (0.8842)	3.399 (0.7116)
Week 28	1.417 (1.1919)	2.549 (1.2115)	1.434 (1.0708)	2.023 (1.1072)

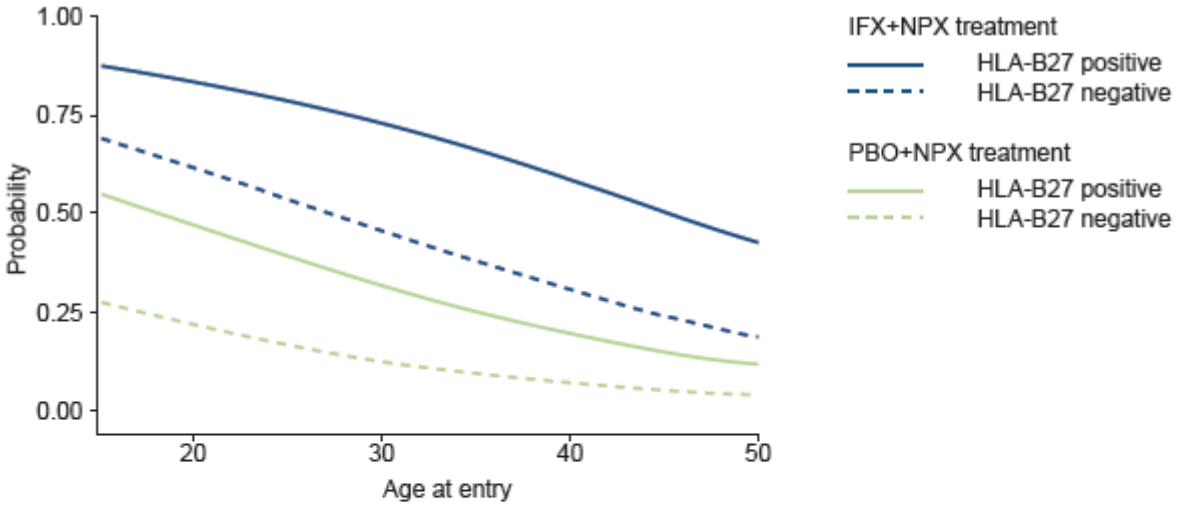
ASDAS-C < 1.3, n/N (%)				
Baseline	0	0	0	0
Week 28	33/57 (57.9)	5/30 (16.7)	19/36 (52.8)	4/13 (30.8)
EQ-5D Index score, mean				
Baseline	0.38	0.28	0.37	0.43
Week 28	0.76	0.55	0.71	0.69
Overall MRI SI score, median				
Screening	4.0	6.5	3.3	6.5
Week 28 (or ET)	1.0	2.0	0.5	2.5
Median change	–3.0	–3.0	–2.0	-3.5
IQR of change	(–7.5, –0.5)	(–6.5, –0.5)	(–5.0, 0.0)	(–4.5, –1.0)
Percent change	–75.0	–46.2	–61.5	–53.8
Overall Berlin MRI score, median				
Screening	1.5	3.0	0.5	0.5
Week 28 (or ET)	0.0	1.0	0.0	1.0
Median change	–1.0	–1.0	0	0
IQR of change	(–6.0, 0.0)	(–6.0, 0.0)	(–2.0, 0.0)	(–0.5, 0.5)
Percent change	–66.7	–33.3	0	0
CRP (mg/dL), median (Q1, Q3)				
Baseline	1.21 (0.53, 2.10)	1.87 (0.78, 3.05)	0.48 (0.10, 1.43)	0.62 (0.10, 1.02)
Week 28	0.36 (0.10, 0.60)	1.23 (0.35, 1.58)	0.10 (0.05, 0.34)	0.43 (0.29, 1.00)
ESR (mm/h), median (Q1, Q3)				
Baseline	26.0 (14.0, 39.0)	35.0 (29.0, 38.0)	13.0 (7.0, 25.0)	18.0 (9.0, 27.0)
Week 28	6.0 (4.0, 10.0)	18.5 (12.0, 28.0)	4.0 (2.0, 7.0)	17.5 (8.5, 27.0)

TABLE 45: *Secondary Efficacy Outcomes in Patients With AS or Nr-axSpA.*

Associations between baseline factors and ASAS partial remission. The multivariable logistic regression model used to explore factors associated with partial remission for the full group of axial SpA patients included the following factors: type of treatment (IFX+NPX vs PBO+NPX), age (continuous), gender (male vs female), HLA-B27 status (positive vs negative), baseline CRP (continuous and log-transformed), and MRI SI joint score (continuous and log-transformed). Factors significantly associated with greater likelihood of ASAS partial remission were IFX+NPX treatment (odds ratio [OR] = 5.786; confidence interval [CI] = 2.477, 13.516; P < 0.0001), positive HLA-B27 status (OR = 3.209; CI = 1.014, 10.150; P = 0.0472), and younger age (OR = 0.937; CI = 0.892, 0.985; P = 0.0100) (Figure 38).

CRP and MRI SI-joint score at baseline were not associated with ASAS partial remission in this logistic regression analysis that included the total population. However, in the group of patients who received IFX+NPX, patients with CRP ≥ ULN had a higher ASAS partial remission rate than those with CRP < ULN (88.1% vs 53.1%, respectively; P values for the difference were not calculated because of low statistical power). Within the group treated with NPX alone, remission rates were similar for those with and without elevated CRP (34.4% vs 35.3%, respectively). A similar pattern occurred in the relationship between MRI scores and partial remission; in patients treated with IFX+NPX, patients with an elevated MRI SI-joint score (≥3.9) had a higher remission rate than those without elevated MRI score (78.4% vs

46%, respectively). In patients treated with NPX alone, partial remission rates were similar whether or not MRI score was elevated (34.5% vs 35%, respectively).



Effect	Odds ratio estimate	95% wald Confidence limits		*P* Value from Chi square
Treatment group (IFX+NPX vs PBO + NPX)	5.786	2.477	13.516	<0.0001
HLA-B27 (Yes vs No)	3.209	1.014	10.150	0.0472
Age (continuous)	0.937	0.892	0.985	0.0100

FIG. 38: Predicted probabilities of achieving ASAS partial remission according to treatment group, HLA-B27 status, and age in logistic regression model. Note: Model includes both patients with AS and nr-axSpA.

The AS and nr-axSpA groups differed in some baseline characteristics; mean CRP concentration was greater in the AS group, and to a lesser extent, MRI scores were greater in the AS group (Table 45). Because CRP (3, 11, 12, 14-16, 20, 21) and MRI (3, 13, 21) have been shown to be predictive of outcomes during TNF antagonist treatment, 2 logistic regression models were performed in the IFX+NPX treatment group. The first explored the effects of baseline CRP and axial SpA diagnosis (AS vs nr-axSpA) on ASAS partial remission, and the second explored the effects of baseline MRI SI joint score and axial SpA diagnosis (AS vs nr-axSpA) on ASAS partial remission. The logistic regression analysis for the PBO+NPX treatment arm was not performed because of the small number of subjects.

CRP values were not predictive of clinical remission in patients treated with IFX+NPX, as evidenced by the shallow slopes in Figure 39A. Both the AS and nr-axSpA subgroups had high remission rates, but the odds of ASAS partial remission were 2.4 times higher in the AS group than the nr-axSpA group, controlling for baseline CRP. Thus, the lower CRP values in the nr-axSpA group were not a sufficient explanation for the difference in partial remission between the nr-axSpA and AS groups.

Figure 39B shows that baseline MRI scores were associated with increased likelihood of ASAS partial remission (P = 0.006). However, again similar levels of MRI inflammation resulted in a higher partial remission rate in patients with AS than nr-axSpA (P = 0.04). The odds of ASAS partial remission were 2.5 times higher in the AS group than the nr-axSpA group (P < 0.05).

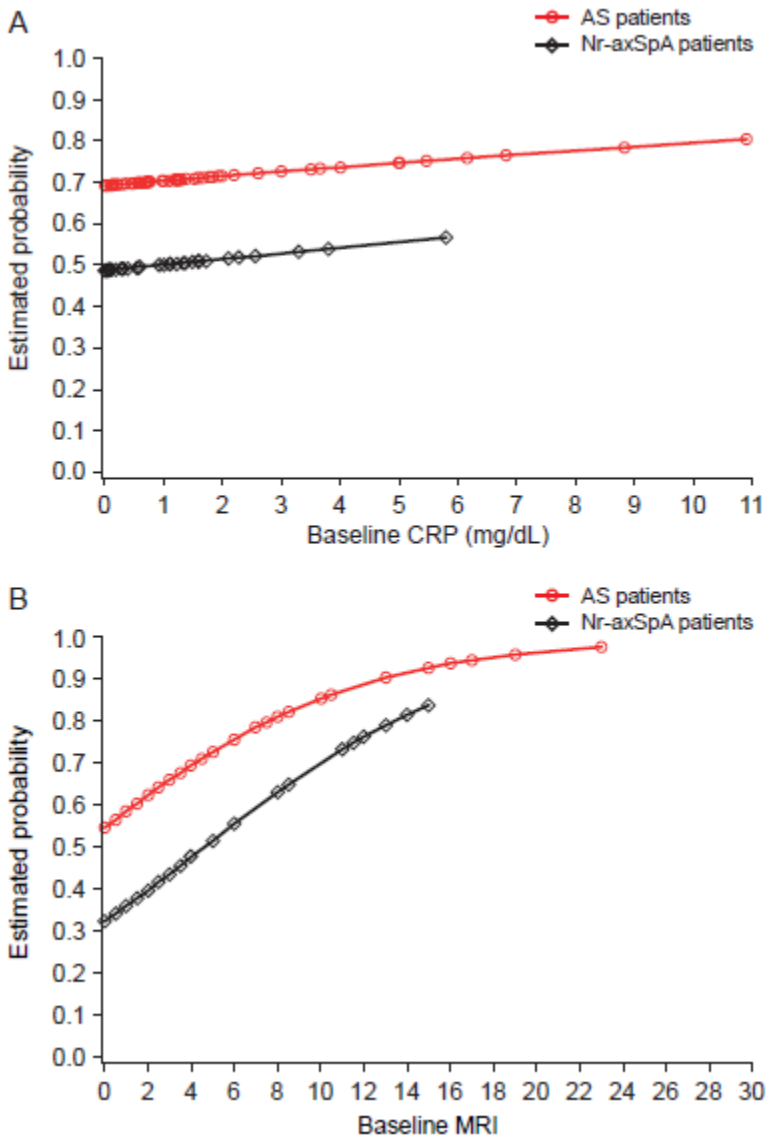


FIG. 39: Predicted probability of achieving ASAS partial remission from logistic regression models according to baseline CRP concentration (A) or baseline MRI SI joint score (B) in patients with AS or nr-axSpA who were treated with IFX+NPX.

5.3.5.Discussion

The strongest predictor of attaining remission in the INFAST trial was treatment with the TNF-antagonist, infliximab. HLA-B27 positivity and young age were also positive predictors, as has been reported before in patients with AS (11, 12, 14, 15, 20) and also in patients with nr-axSpA, although

often with a weaker association (3 ,16). Interestingly, CRP levels and active bony inflammation on MRI were not significantly associated with remission in this multivariable logistic regression analysis. Nonetheless, within the patient group treated with IFX+NPX, those with elevated CRP and those with elevated MRI SI-joint scores did have numerically higher partial remission rates than patients with lesser CRP and MRI scores. Both of these factors have been predictive of outcomes in other TNF-blocker trials in axial SpA (3, 20, 21).

The clinical outcome was clearly better in patients with AS than in patients with nr-axSpA. The INFAST population is unique from previous studies in that the patients had short disease duration and were selected if they were naïve to NSAIDs or were using a suboptimal dose of NSAIDs. This selection of patients may help explain why the 70.5% partial remission rate in the AS group was considerably greater than the 15% to 20% rates of partial remission typically reported in patients with longstanding, established AS (5 ,6, 22). In contrast, in a study of patients with axial SpA (both AS and nr-axSpA) who had symptom duration of less than 5 years and were treated with etanercept, partial remission rates were approximately 50% during unblinded treatment (23). In another study of patients with AS and nr-axSpA with symptom duration < 3 years who were treated with infliximab, partial remission rate was 56% (24).

Recent evidence suggests that patients with AS and patients with nr-axSpA respond similarly well to TNF antagonists (3, 4, 7, 23-25). In INFAST, however, the nr-axSpA group did not appear to benefit as much from IFX+NPX as the AS group. Major differences in the baseline characteristics of the AS versus nr-axSpA groups included higher CRP concentrations and MRI SI scores, a higher percentage of HLA-B27 positivity, and a higher proportion of male patients. In addition, CRP concentrations were lower in the PBO+NPX group than the IFX+NPX group, whereas MRI SI scores were comparable in the 2 treatment groups.

The relatively flat slopes in **Figure 39A** indicate that estimated probability of ASAS partial remission did not increase with increasing baseline CRP in this study population. Thus, higher CRP values at baseline in the AS patients could not explain the better partial remission rate in this group. The steeper slope in **Figure 39B** indicates that higher baseline MRI SI scores were associated with greater probability of ASAS partial remission in the IFX+NPX group, but that at similar levels of MRI inflammation, partial remission was better in AS patients than nr-axSpA patients. The most important baseline differences that might explain the difference in the clinical response rate between the AS and nr-axSpA groups are the higher HLA-B27-positivity in the AS group at baseline (**Table 44**). HLA-B27-positivity was indeed predictive of a better partial remission rate in the multivariable logistic regression analysis while gender, CRP, and MRI were not.

As noted earlier, the population in INFAST was unique in that patients had not failed NSAIDs before starting biologic treatment and patients had a short mean disease duration (≤2 years). Some of the results presented here probably can be generalized, such as the very good clinical response to NSAIDs when treatment begins early for patients with either AS or nr-axSpA. In INFAST, ASAS partial remission was achieved with NPX treatment by 33.3% of patients with AS and 37.5% of patients with nr-axSpA. However, the high partial remission rate to IFX+NPX in this population that is not refractory to NSAIDs cannot automatically be generalized to all axial SpA patients who are refractory to NSAIDs.

A limitation of this study is that the analysis of the AS population was not planned, and the study was not powered for analysis of subgroups of patients; therefore, inferences about the differences between the 2 subsets of the populations should be made with caution. Another limitation is that the

classification of patients in the AS group was based on x-ray readings performed by the local investigator, and they were not independently confirmed by a central reading.

5.3.6.Conclusions

Patients with early axial SpA had better outcomes when treated with IFX+NPX than NPX alone, but also showed good outcomes when receiving NPX alone. Other predictors of partial remission were HLA-B27 positivity and young age. Objective signs of inflammation, such as CRP and MRI-inflammation, were less predictive in this early axial SpA cohort. Thus, early diagnosis seems to be important to achieve a good treatment effect, including in patients who already fulfil the modified New York criteria for AS. Patients with nr-axSpA had lesser response to IFX than patients with AS, which may partly be explained by differences in baseline disease characteristics.

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Chapter 6: Outcome-based Treatment Decisions in RA and Axial SpA Treatment recommendations
- Discussion -

A critical review of the RA and Axial SpA management recommendations is done and specific proposals on how the clinical tools and data presented in **Chapter 4** and **Chapter 5** may help refine guidelines are formulated.

Response to 'Feasibility of tailored treatment based on risk stratification in patients with early rheumatoid arthritis'.

Vastesaeger N, Fautrel B, Smolen J.
Arthritis Res Ther. 2015 Jun 20;17:166.

Models to select Rheumatoid Arthritis and Axial Spondyloarthritis patients for Anti-TNFα treatment: is it time to introduce personalized medicine into clinical practice?

Vastesaeger N, Van den Bosch F, Sieper J, Elewaut D
Submitted manuscript.

6.1. Relevance of outcome-based patient selection in RA

Combination therapy with more than one synthetic disease modifying agent (DMARD) or with DMARDs and biologics or corticosteroids has better disease activity suppressing effects and slows progression more than a single DMARD [1-5]. The use of combination therapy comes with increased complexity and toxicity and in the case of biological agents increased cost. Fact is also that DMARDs show response in a significant proportion of patients even if used as single agent [6] and they slow down the progression of the disease [7-12]. Intensive treatment regimens are thus not needed for all patients and should be reserved for those in whom single agents do not allow to achieve treatment goals. In practice this often means that clinicians will try less intensive treatment first, will see that disease activity is not sufficiently controlled and will only then proceed with the next, more intensive/expensive treatment step. Inadequate treatment during the early 'window of opportunity' however, may mean that an opportunity to change the course of the disease on the long run is missed [13-15].

Tools that provide insight on patients or sub-populations at risk of developing significant morbidity under specific treatments such as MTX mono-therapy allow selecting the more appropriate treatment regimen for such patient or sub-population without going through a trial and error phase first. Each unnecessary step allows continued uncontrolled disease activity to lead to disability and progression of organ damage, which a better initial treatment choice would avoid. For use in daily clinic, such tools should be user-friendly, simple and based on demographic, diagnostic or disease related characteristics that are readily available in practice. It is equally important that the outcome parameter is important enough to counterbalance potential incremental toxicity or risk for side-effects that can be anticipated from combining multiple agents in a more intensive treatment regimen. Finally these tools should be reliable in predicting the outcome.

6.1.1. Predicting and preventing poor prognosis in RA

Models for risk of bad outcome of cardiovascular disease (CVD) and osteoporosis (OP) are well known and the build-up of these models was the inspiration for the RA poor prognosis model [16, 17]. These models use readily-available characteristics to predict an unambiguous event that is important from a health perspective and a socio-economical perspective. Risk is quantified as the proportion of patients within a sub-population that dies or incurs a major osteoporotic fracture. The result does not highlight 'black and white' who will certainly die or have a fracture vs. who will live or not have a fracture. Instead, the tools present an increasing gradient of probability of an event which implicitly provides insights where treatment should be envisioned and where not (e.g. bisphosphonate use for OP, lipid-lowering drugs for CVD). They do not show however the potential of that treatment to reduce an event.

The model we introduced for RA in **Section 4.1.** directly compares the ability of different therapies to reduce the risk of poor prognosis [18]. The advantage is that it allows going beyond the question whether to treat but it quantifies the likelihood of a treatment to avoid poor prognosis. Directly comparing 2 treatments facilitates physicians' choice as he selects a preferred treatment for a specific patient. We also introduced numbers needed to treat (NNT) to avoid rapid radiographic progression (RRP) in RA sub-populations which facilitates treatment choice from a societal and health-economical perspective.

6.1.1.1. Outcome predictors

The factors that were retained in the poor prognosis model for RA are well established in the rheumatology literature and are valued and recognized as predictors of radiographic progression in RA [19-23]. It is however interesting to see different datasets bring forth different predictors and models (**Section 4.2.**) [18, 24-26]. The summary provided in Table 46 shows this and raises the question which 'final' model a physician should use.

Source data	SJC28	Rheuma Factor	Anti-CCP	CRP	ESR	Gender	Smoking	Erosions
ASPIRE CRP model	3 categories	3 categories by units/L		3 categories by mg/L				
ASPIRE ESR model	3 categories	3 categories by units/L			3 categories by mm/hr			
BeSt study model		pos/neg	pos/neg	3 categories by mg/L				erosion score
SWEFOT model 1		pos/neg	pos/neg		3categories by mm/hr	male/female		
SWEFOT model 2				3 categories by mg/L			yes/no	present/not
ESPOIR model	3 categories		pos/neg	3 categories by mg/L				present/not

TABLE 46: *Summary of characteristics identified as predictor of poor prognosis in models.*

Some differences are caused by whether a predictor-characteristic was measured in the study or not. Anti-CCP and smoking for example were not collected in ASPIRE and their use as predictor could thus not be investigated. A characteristic like SJC was measured and predictive in ASPIRE but not BeSt. One can further wonder whether associations established in a population have any relevance for an individual; e.g. a patient with high CRP may not develop erosions. These situations may mimic clinical practice where treatment decisions are made even if not all information is available (e.g. anti-CCP not reimbursed and therefore not done). Since literature heavily supports the association of factors such as RF, Anti-CCP, ESR and CRP with radiographic progression they have high face-validity for use in poor-prognosis prediction models in RA [19-23].

Categorization of variables such as SJC, CRP and ESR in these publications was done pragmatically based on the tertiles in the individual database, allowing an even distribution over the dataset of a study. Other and/or more cut offs could have been chosen and could have led to slight differences in the reported RRP rates. As an example, if a different cut-off for SJC would results in a slight change of the percentages in the grid (e.g. risk of RRP of 46% goes down to 42%). This will likely not have an impact on clinical decision making for an individual RA patient.

If used for policy and reimbursement decisions, a slight change in percentage may mean that society will or will not pay for the treatment of a patient with RA (e.g. treatment reimbursed if risk of RRP is >45%). This explains why rheumatologists have expressed concern with our model. Decisions ruling some patient sub-populations out of benefitting from treatment are however already made by authorities. The Guideline Development Group of the National Institute for Clinical Excellence (NICE) in the UK for example, developed RA treatment recommendations in which TNF alpha inhibitors should only be used in adults who have high disease activity (DAS28>5.1) and who have undergone trials of two DMARDs,

including MTX [27]. As the goal for this recommendation is preventing joint damage, one can argue why a patient who has failed 2 DMARDs and has high RF, high anti-CCP levels, erosions within 6 months after diagnosis and a DAS28 = 4.8 would not be recommended, whereas a patient who has a DAS28 of 5.2 who is anti-CCP and RF negative and has no erosions would be eligible for treatment with a biologic after failing 2 DMARDs.

6.1.1.2. Poor prognosis as outcome parameter

The outcome parameter chosen to reflect prognosis of the disease must be relevant enough to weigh on treatment choice. Is rapid radiographic progression in RA an unambiguous event that is important from a health perspective and a socio-economical perspective? Clinicians, patients and payers may think differently about this.

For the RA model the annual progression rate of at least 5 SHS was a pragmatic definition for RRP. Radiographic progression stratified for risk of RRP at baseline in the BeSt study in **Figure 40** nicely shows that about half of patients with risk of RRP >=50% progressed with 20 or more SHS units during 5 years in spite of intensive management targeting remission [24].

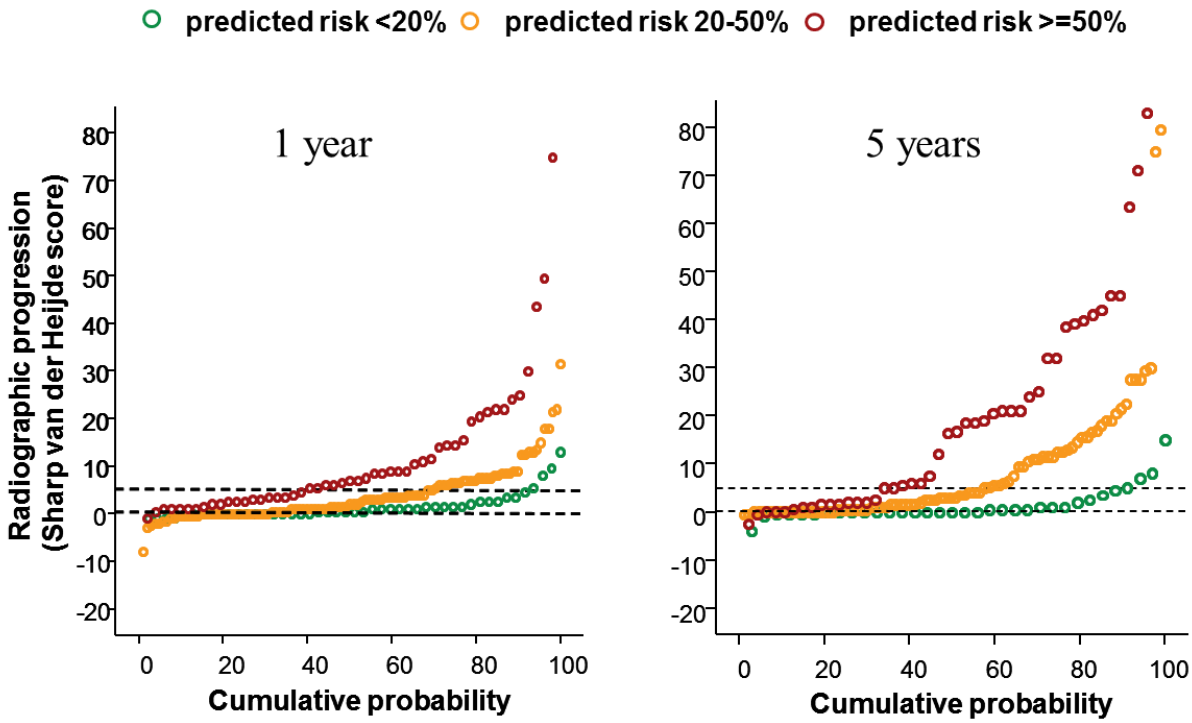

FIG.40: *Radiographic progression over 1 and 5 year based on predicted risk of progression. Modified from: Visser et al. Ann Rheum Dis;2010, 69(7):1333-7 [24].*

None of the patient-subgroups randomized to initial therapy with corticosteroids or infliximab had a risk >=50% (see **Section 4.1**) and nearly all the patients highlighted in red are patients who started with mono-therapy. Progression with 20 or more on the SHS score is deterioration equivalent to at least 4 completely destructed joints over 5 years which could have been avoided with intensive treatment based on predicted risk.

It is well established that radiographic damage has an important effect on long-term functionality [28-31]. In the BeSt study patients with RRP had worse functional ability over a course of 8 years compared to those who did not have RRP; **Figure 41** [32]. The tables of **Section 1.5** highlight the financial impact of these HAQ score findings.

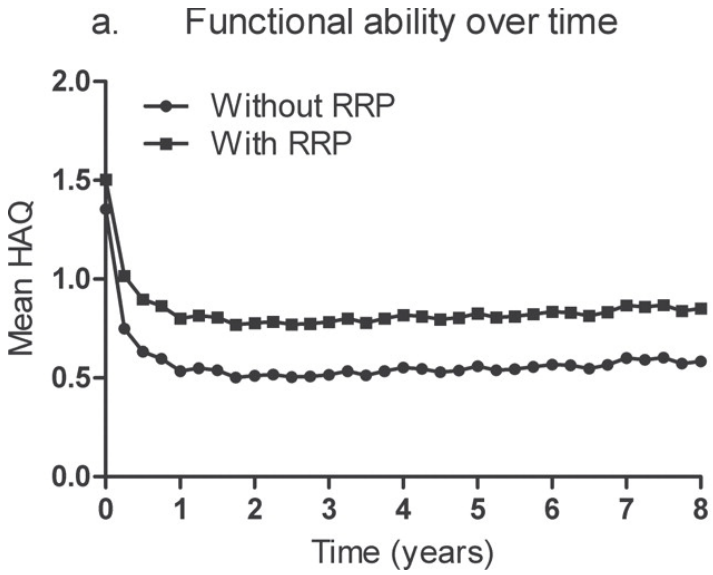

FIG.41: *Mean HAQ in patients stratified by the occurrence of RRP from baseline to year 1. From: van den Broek et al. Ann Rheum Dis 2012; 71:1530–1533 [31].*

These data confirm that joint damage over a 1-year time-frame as predicted outcome is a good surrogate of the consequences of disease activity as the driver of destruction and long-term disability.

6.1.1.3. Predictive capacity, NPV, PPV and NNT

The predictive capacity of the poor prognosis models developed from RCTs (**Section 4.1** and **4.2**) in clinical practice has been investigated in nice work from Belgium, France and the US [34-36]. Disease duration, disease activity, treatment, X-ray readers, proportion of RRP in the overall cohort and the number of patients between the RCTs and clinical practice cohorts might have contributed to the somewhat disappointing findings in 2 reports [32-34] even if adequate performance and good validity is shown in 1 report [35].

Risk of RRP remains at the lower end of the potential range between 0% and 100% (4% to 47% in the ASPIRE study, 1% to 78% in the BeSt study, 12% to 63% in the SWEFOT study) [18, 24, 26]. As such the negative predictive value (NPV) is better than the positive predictive value (PPV). Cut-offs for NPV and PPV can be used to define thresholds for treatment decisions. Risk of RRP <20% in the BeSt study has high NPV and can be used as guidance in the clinic as threshold below which combination therapy should not be used to prevent damage to joints. The NNT to prevent one case of RRP using intensive compared with less intensive therapy can also help determine a threshold below which a patient should not receive intensive therapy. The negative predictive value of the NNT to prevent RRP from occurring of 9.17 was 100% in the report from Belgium (sensitivity 100%, specificity 53.3%) [33].

The more difficult argument to make is at which point the risk of RRP is high enough to start intensive therapy early. Only patient sub-groups who were treated with initial MTX in the ASPIRE study or initial

monotherapy in the Best study had a risk of RRP of 30% or more and 50% or more respectively (**Section 4.1** and **Section 4.2**) [18, 24]. The risk of RRP of patient sub-populations initially treated with combination therapy with either anti-TNFα or corticosteroids and DMARDs always remained below these percentages which can thus be envisioned as thresholds at which moment initial treatment with combination therapy would be recommended.

Figure 42 could be an example of a model to guide treatment recommendations based on NNT of the ASPIRE model. The area in red corresponds with patient-subgroups in ASPIRE that have a predicted risk higher than 30% when treated with MTX alone and for which combination therapy may be considered [18]. The green area has patients in whom the NNT to prevent one case of RRP with monotherapy is lower than 9.17 at which time MTX can be recommended. The choice for the sub-populations represented in white is not clear and a trial and error strategy could here be default.

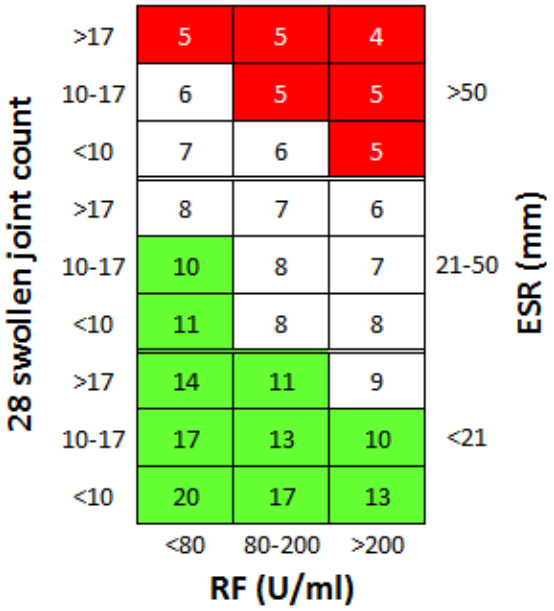

FIG.42: *hypothetical model based on the ASPIRE data. Area in red is where initial intensive therapy is recommended, area in green is where initial monotherapy with MTX is advisable.*

Even if the predicted capacity is modest at best, the important question is whether such models are an improvement over what is done in practice and whether advocating their use would have an incremental benefit over current treatment recommendations to help reduce progression of radiographic damage in the long run.

A collaborative group has been set up with the aim of creating one 'final' poor prognosis model. And this resulting model will, without a doubt, still have its weaknesses as also the models for CVD and OP have their shortcomings even if they are more widely used than the one for RRP. Clinicians should be aware of the strengths and weakness of the information they use for decisions.

6.1.2. Response to 'Feasibility of tailored treatment based on risk stratification in patients with early rheumatoid arthritis'.

Markusse et al. recently investigated whether RA patient-subgroups formed according to the presence of poor prognostic factors respond differently to initial monotherapy or combination therapy [36]. Since both subgroups experienced a better response to initial combination therapy, the authors concluded that patient tailored treatment based on prognosis as suggested by the EULAR recommendations [37] is currently not feasible.

As a general remark, the authors should be reminded that the EULAR recommendations primarily suggest combination of MTX with low dose glucocorticoids as its efficacy is not surpassed by biologicals and it prevents overtreatment in 20-25% of patients [60]; delaying TNF-inhibitor initiation by 6 months does not affect outcomes [61]. Moreover, the definitions of poor prognosis (PP) used by Markusse contrast with the stratification suggested by EULAR which, as this paper's supplementary files highlight, influences outcomes [37]. We therefore recommend that its readers look at the supplementary information before drawing conclusions.

Markusse proposes presence of 3 of 4 characteristics as definition of PP (erosions, RF/ACPA combination, SJC, elevated DAS). In contrast, the definition of PP established by Visser in the same trial population (sic!) uses a different approach, namely CRP, erosion-score and RF/ACPA-combination to determine who had >50% chance of rapid radiographic progression (RRP; ≥5 SHS units/year) [24]. Median SHS progression between initial combination and initial monotherapy in PP patients differed only 1.5 SHS units in Markusse's model, but 3.5 units in Visser's. Of initial monotherapy patients, 64% and 26%, respectively, had RRP whereas this was only 12% and 10% for initial combination therapy by these models. This highlights that the definition of PP used by Visser (provided only as supplement) in line with other work [18] is much better at identifying a PP population.

In line, the odds of response to initial combination versus initial monotherapy in the PP versus non-PP populations were much higher when using Visser's versus Markusse's approach (OR of ACR20/50/70: 10.0, 9.74, 9.33 versus 2.72, 5.39, 4.22, respectively). Separation of the HAQ score between PP and non-PP patients treated with initial combination therapy is only seen with Visser's definition. This highlights that definition of poor prognosis influences the effect of clinical outcomes.

In accordance with the EULAR research agenda [37], we also believe it is important to study what effect patient stratification based on poor prognosis parameters has on clinical outcomes. Alas, we feel that Markusse's study did not address the question appropriately and therefore does not provide a good answer.

6.1.3. Predicting achievement of remission & low disease activity in RA

Radiographic progression seen in practice is much less extensive than what it was a decade ago due to earlier diagnosis, earlier treatment and better use of DMARDs and biologics. Even if studies have suggested that there may be an uncoupling of persistence of elevated disease activity and progression of radiographic damage of the joints, a lag time between disease activity state and X-ray damage may be an explanation and the risk of major radiographic progression in the absence of measurable synovitis is very slim [39, 40]. Treatment of RA should be aimed at reaching a target of remission or low disease activity (LDA) in every patient [37]. As such, in addition to identifying who will have radiographic

damage, an equally relevant question is to identify who will achieve remission or LDA and what treatment would get a patient there. Assuming that this disease state will prevent radiographic progression as well, one could argue that identifying patients who achieve controlled disease state may be more relevant than identifying who will have joint damage.

Work presented in **Section 4.3** highlights how several characteristics that are associated with improvement are inversely associated with achievement of a controlled disease state. This observation makes the use of predictors for solid decision making (i.e. who to treat and who not) difficult.

6.1.3.1. Predictors of remission

Katchamart et al. nicely summarized the literature on predictors of remission in rheumatoid arthritis therapy with DMARDs and biologics [41]. They report that the following characteristics predict remission with biologics: gender, age, smoking, comorbidities, disease activity at baseline, HAQ score at baseline, concomitant treatment, previous treatment, RF, serum RANKL, CRP and radiographic damage at baseline. Several of these characteristics were also predicting remission with DMARDs and the following predictors were retained only in DMARD studies: age at onset of disease, pain, time to treatment, ACPA, shared epitope and other genetic markers and serum IL-2. There was heterogeneity in the nature of the predictors, the effect size of the characteristics to predict, the moment at which remission was measured and the assessment instrument for measuring predictors and remission which affects the interpretation. Most predictors represent the disease severity of RA at baseline (e.g., disease activity, functional status, history of failed DMARDs, the presence of RF and anti-CCP, acute-phase reactant, or evidence of radiographic damage) and it can be concluded that these factors should be associated with RA outcome. Smoking as predictor seems to be associated with the presence and titer of ACPA and the authors note that these results need further confirmation [41]. Since this publication which appeared in 2010, a number of additional studies report on these characteristics but also imaging with MRI, ultrasound and additional genetic markers are identified as predictors of remission [42-47].

The same caveats that were noted for selection of predictors and categorization into a poor prediction model apply here. The described literature again indicates face-validity of the selected characteristics and supports use in our model. We report reasonable predictive capacity of a combination of these characteristics to predict remission and LDA within the GO-MORE dataset (**Section 4.3**). Even if the study was large and the clinical characteristics are similar to those of RA patients in clinical practice, validation in other datasets will be important to understand its reliability and relevance to clinical practice.

The remission prediction model was created from an uncontrolled dataset and this did not allow us to introduce therapy as predictor of outcome. As such, NNT to achieve remission or LDA for different treatment options could not be compared. **Figure 43** indicates that differences in patient selection lead to different outcome rates of both biologicals and comparator agents in clinical trials. It seems however that the outcomes of both the biologic treatment group and the comparator group (in this case MTX monotherapy) evolve in the same way so that the delta between biologic and MTX remains quite similar [48]. In patients who have had inadequate response to MTX, biological + MTX combination therapy had NNT to achieve ACR20, 50 and 70 that were 3.2, 4.2 and 7.7 respectively compared to MTX alone. The NNT to achieve DAS28 remission at 6 months was 9.1 [49]. It is not clear whether introduction of an alternative treatment possibility in the prediction model would help identify patient sub-populations in which a biologic would result in a greater proportion of patients in remission vs comparator than in another sub-population (resulting in NNT that increase from the top right to the left bottom of a model). Such information would help to better understand the context of a treatment choice especially from a societal and payer's perspective.

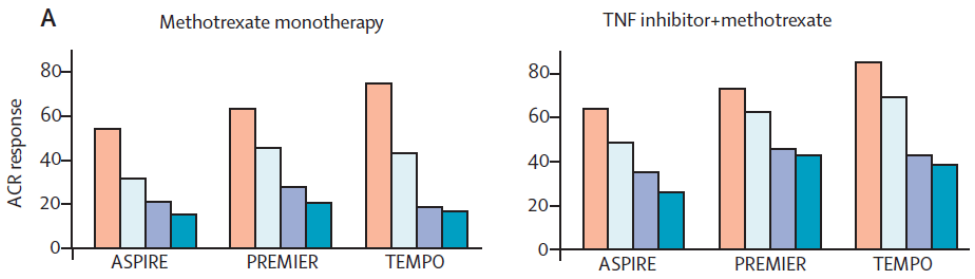

FIG.43: *ACR 20, 50 and 70 response rates in clinical trials which compare TNF inhibitors versus MTX monotherapy in DMARD naïve early RA patients. From: Smolen et al. Lancet 2007; 370: 1861–74 [48].*

The below **Figures 44A-D** highlight how selected characteristics that predict remission also relate to sick leave and disability [50].

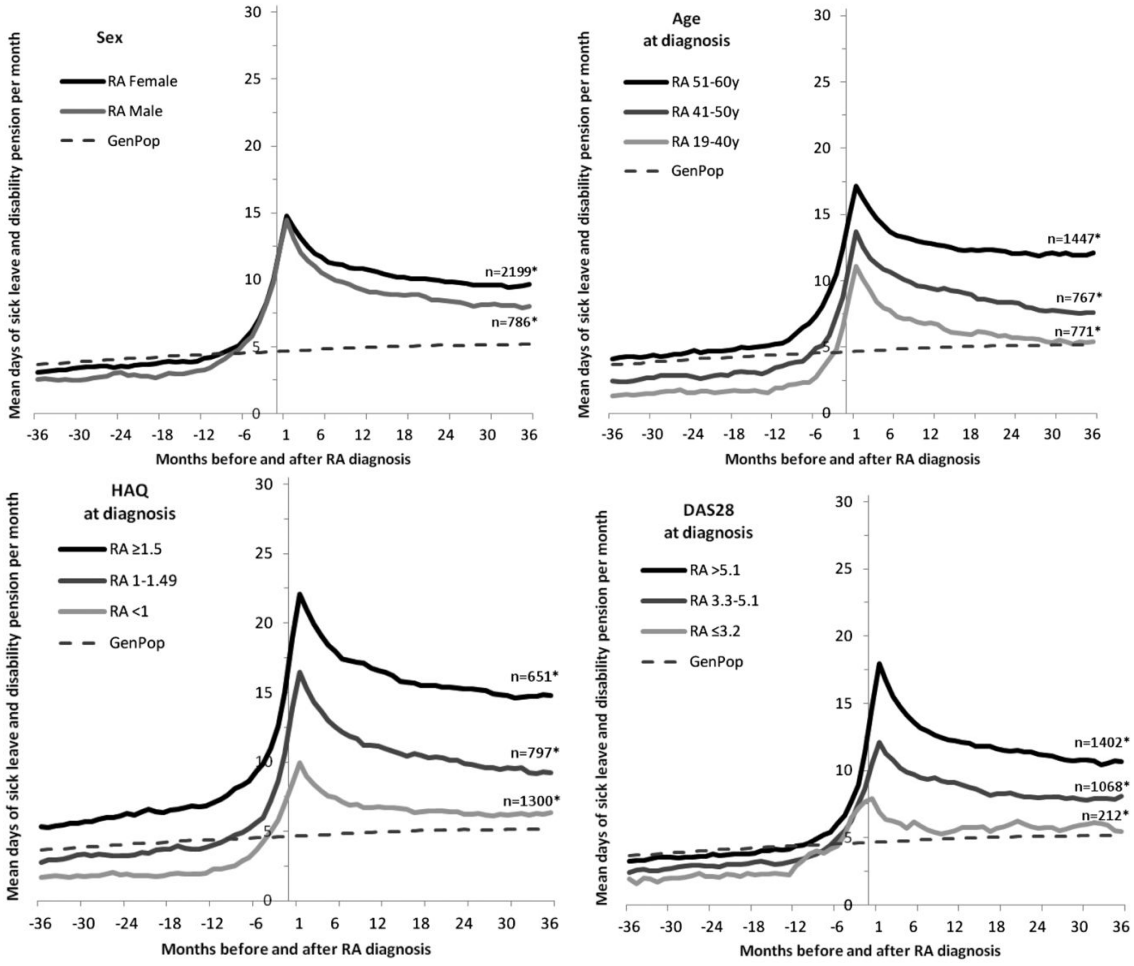

FIG.44A-D: *association of gender, age, HAQ and DAS28 with sick leave in Sweden. From: Olofsson et al. Ann Rheum Dis. 2014; 73(5):845-53 [50].*

This adds to the information already presented in **Section 1.5** on the relationship of disease activity state with cost and supports the relevance of our model for health economical decision making.

6.1.3.2. Is disease activity state the relevant outcome to predict in RA?

In **Section 3.2** it is shown that disease activity state as measured by DAS28 best reflects the decision of a rheumatologist. Prevention of poor prognosis and of function deterioration can be assumed as long as disease activity is suppressed well enough [51-57]. Moderate disease activity is tolerated in clinical practice for patients with long-standing DMARD refractory disease [57]. LDA however leads to much better functional and structural outcomes than moderate or high disease activity and is a good alternative goal for most patients in clinical practice with long-standing disease that cannot attain remission [37, 54-55]. More stringent criteria than DAS28 remission allow achieving even better functional improvement and radiographic results [37, 51]. The definition of the disease activity state is also affecting the identified predictors [58].

Our data show that the same set of well-selected predictors of outcomes of disease state predicts both LDA (not stringent) and remission (more stringent) as assessed with different outcome instruments (DAS28-ESR, SDAI, DAS28-CRP) (**Section 4.3**). It can be expected that a higher probability of achieving a disease state like DAS28 remission will increase the likelihood of achieving an even more stringent disease state like the Boolean ACR/EULAR remission definition (**Figure 45**).

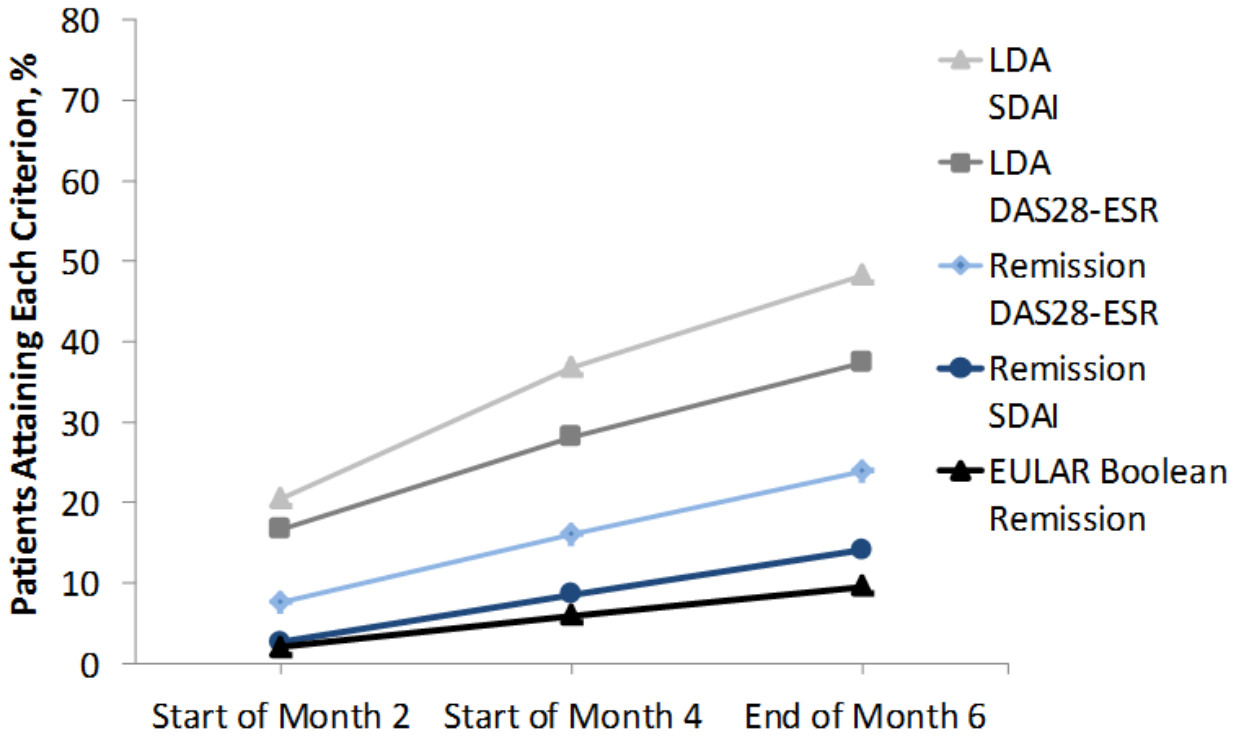

FIG.45: *Proportion of patients meeting different criteria for disease state in the GO-MORE study. From Combe et al. Submitted manuscript.*

If the goal is to make value based decisions, it is important to repeat that especially health assessment and the disease activity state to a lesser extent are correlated with the mean annual cost of care in RA (see also table 5 of **Section 1.5**). When the information of the GO-MORE remission prediction model is directly linked to the data from recently published Canadian analyses on the cost of treatment for patients on biologics, it becomes clear that the disease state achieved will continue determine the cost of patients maintained on a biologic agent; see **Figures 46 and 47**.

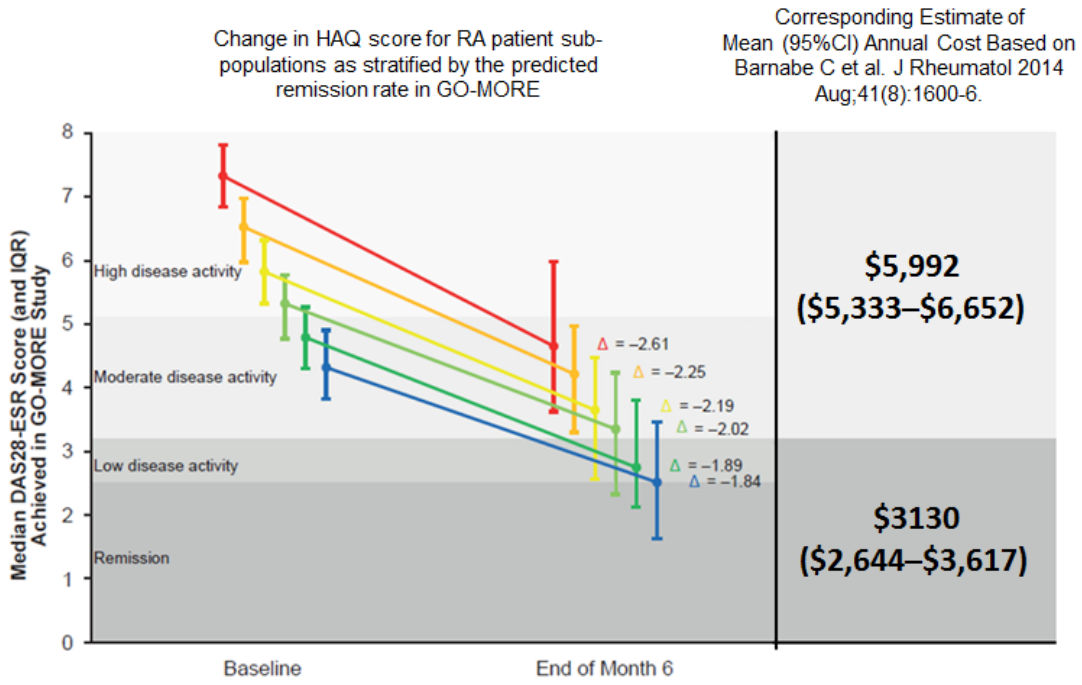

FIG.46: *Change in DAS28 score and corresponding estimate of the mean annual cost.*

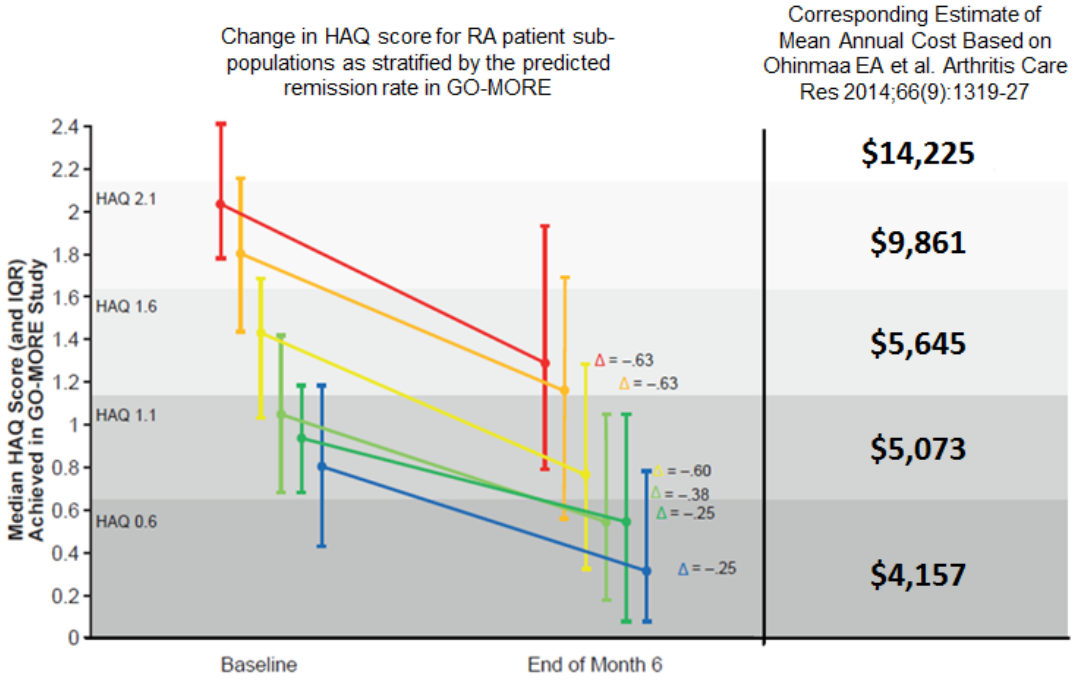

FIG.47: *Change in HAQ score and corresponding estimate of mean annual cost.*

The Canadian reports in which the vast majority of patients were treated with anti-TNF, show that the cost of care was highest in patients who switch from one to another biological agent due to absence of or insufficient response. This was followed nonbiologic DMARD control patients and nonbiologic DMARD patients going on to anti-TNF therapy. Patients on a biologic who are in sustained response had the

lowest total annual health care costs. The magnitude of the healthcare cost savings varied according to the remission definition but was significantly lower for patients in sustained remission versus those who were not in sustained remission The in-hospital and outpatient clinic costs were the drivers of the differences observed [58, 59].

As **Figure 48** highlights, good disease activity state is not a guarantee for good health nor is good health always coinciding with control of the disease activity. One could thus argue that if HAQ has a better association with cost, HAQ rather than DAS28 remission should be the outcome to predict.

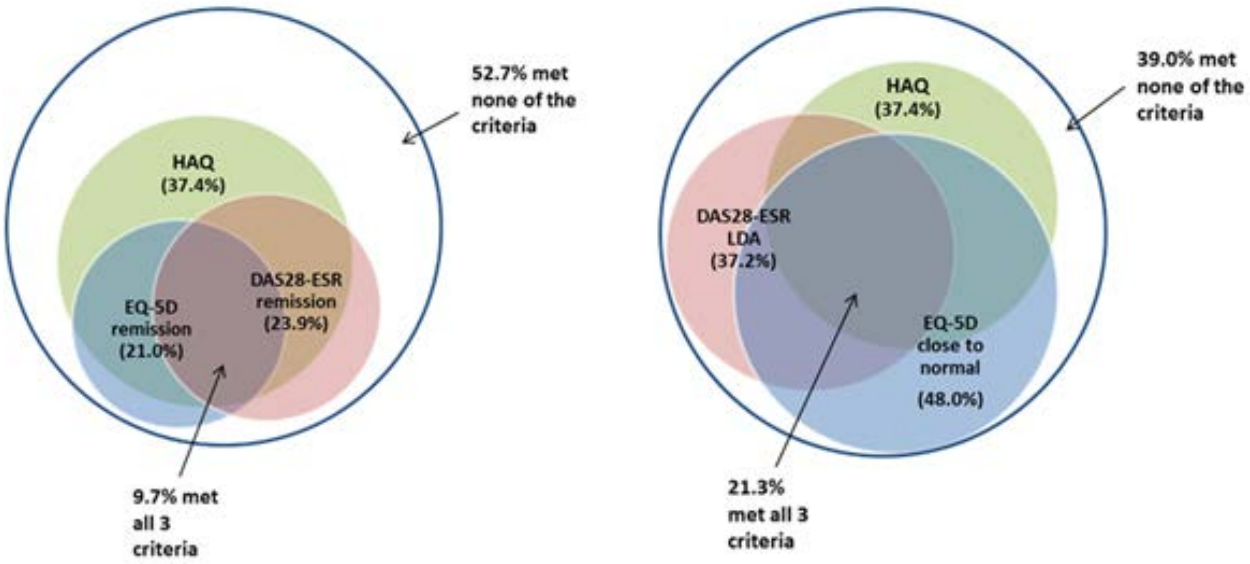

FIG.48: *Proportion of patients achieving different health states as measured by HAQ<0.5, DAS28 remission (left figure) or LDA (right figure) or EQ-5D≥0.8 (left figure) or EQ-5D≥078 (right figure) in the GO-MORE study. From Combe B et al. Submitted manuscript.*

In **Section 4.3** we highlighted that selected predictors of remission were also associated with HAQ state (i.e. age, gender, HAQ score at baseline and comorbidity). It has been described as well that disease state as measured by DAS28 is directly related to radiographic progression and that remission prevents progress of joint damage in nearly all patients. Remission or LDA is finally still the goal of therapy according to international guidelines which makes it the outcome of choice for a prediction model aimed to help making choices in practice.

6.1.4. Conclusion: Improving treatment recommendations of RA

6.1.4.1. Better define poor prognosis and risk

Risk stratification using high disease activity state and/or autoantibody positivity (rheumatoid factor and/or antibodies to citrullinated proteins) and/or the early presence of joint damage is advocated for the therapeutic approach to RA. The EULAR recommendations are very clear on which DMARD strategy is to be considered in case of 'low risk of poor RA outcome' or 'patients with a high risk'. Yet 'low risk', 'high risk' and 'poor prognosis' have not been defined nor is it very clear how the risk characteristics should be interpreted. Since the use of poor prognosis for therapeutic choice is highly valued by the EULAR Task Force, more specifics on the definition of risk (e.g. rapid radiographic progression) and a better definition of high and low risk based on the proportion that is at risk of developing may need to be provided to help clinicians. Even if the predictive capacity of the currently available models is moderate at best they may still be an improvement over what is currently recommended.

6.1.4.2. Avoid conflict between characteristics of poor prognosis and good outcomes

Predictors associated with achievement of a good disease state may be inversely associated with good improvements of disease activity and high disease activity as predictor of poor prognosis is inversely associated with achieving a good disease state. This highlights that patient stratification for treatment choices in RA is complex. To avoid such conflicts, it seems essential to establish consensus on a goal of treatment which reflects superior value for patients, physicians and payers and use patient stratification to maximize the likelihood of achieving that goal. Clinical disease state determined with a disease activity instrument like DAS28 can be considered to directly affect both health state (measured with an instrument like HAQ or EQ-5D) and prognosis based on radiography even if there is no complete overlap. This which makes it an appropriate goal and recommendations should maximize the likelihood that it is achieved. Risk stratification for poor prognosis using high disease activity may preclude patients from attaining LDA or remission. If the goal for RA management continues to be disease state, one may wonder whether a characteristic like high disease activity for stratification for poor prognosis should thus not be omitted in future recommendations.

6.1.4.3. Move towards a stratification that is aimed at achieving remission or LDA

Radiographic progression seen in practice is much less than what it was a decade ago due to earlier diagnosis and intervention and better use of DMARDs and biologics. As the cause of radiographic progression is synovitis, it can be questioned whether poor prognosis should still be considered when making a treatment choice. As '*Treatment [of RA] should be aimed at reaching a target of remission or low disease activity in every patient.'*, the more relevant question may be what this patient who will achieve remission looks like and what treatment would be needed to get that patient into remission (thus preventing radiographic progression as well). The data that is introduced through our work highlights how patients can be selected for treatment based on a predicted likelihood of achieving the treatment goal. The relevance of treatment choices from the economical perspective are described and indicate how treating different patient sub-populations translates in different financial consequences for payers.

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6.2. Relevance of outcome-based patient selection in Axial SpA

In axial spondyloarthritis, the treatment options for axial disease are limited to NSAIDs and anti-TNFα agents [1]. Ankylosis progresses very slowly and there are a few reports that identify characteristics of progression [2-5]. One such report used the poor prognosis prediction methodology we used in RA to highlight the association of baseline syndesmophytes, acute-phase reactants, and smoking status with spinal radiographic progression over 2 years in patients with axial spondyloarthritis (**Figure 49**) [5]. The percentages in the figure represent patients with any spinal radiographic progression according to the modified Stoke Ankylosing Spondylitis Spine Score units over 2 years.

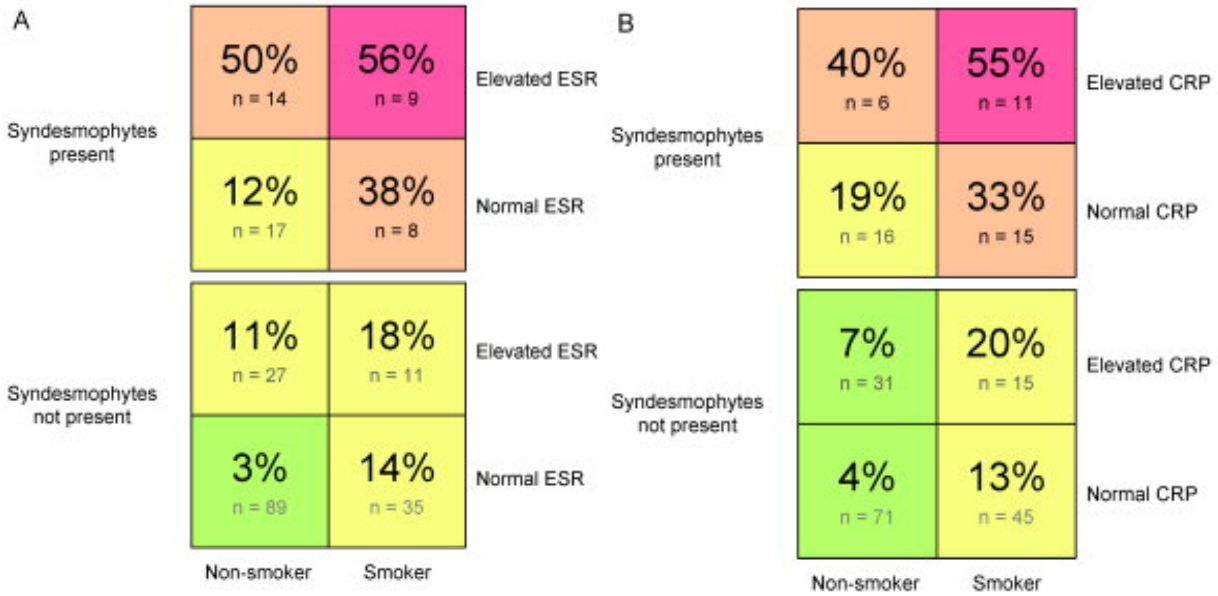

FIG. 49: *Poor prognosis model for ankylosis as stratified by predictors of ankylosis progression. From Poddubnyy D et al. Arthritis Rheum. 2012; 64(5):1388-98* [5].

At present there is no definite evidence that anti-TNFα treatment can halt progression of ankylosis in AS or Axial SpA [6-8]. Such evidence for NSAIDs exists but is limited to one report [9]. Unlike RA, treatment recommendations in this disease are therefore not guided by the use of characteristics that indicate poor prognosis [1, 10, 11]. As such, not progression of ankylosis (or poor prognosis) but good outcomes of therapy can be assumed to be the treatment goal. Stratification for poor prognosis is still important for patient selection in clinical studies that are aimed at proving the effect of therapy on progression of ankylosis. For use in clinical practice and for guidelines however, prediction of good outcomes to therapy is more relevant, particularly for selecting candidates for treatment with a biologic.

6.2.1. Predicting response and disease state in AS and Axial SpA

When the ASAS/EULAR recommendations for management of AS were issued, there were no good predictors for treatment response. Anti-TNFα was recommended for patients who fail NSAIDs and who have an elevated disease activity since most such patients were thought to benefit from it [10-13]. Experts who treat axial SpA patients with an anti-TNFα agent should consider clinical features (history

and examination) as well as either serum acute phase reactant levels or imaging results, such as radiographs demonstrating rapid progression or MRI scans indicating inflammation [12]. It is however not specified how these characteristics need to be considered by the clinicians.

6.2.1.1. Outcome predictors

Several reports on predictors of good clinical outcomes of AS have been published in the past years [13-16]. Acute phase reactants, disease activity measured with BASDAI, functional status measured with BASFI, age, and HLA-B27 were identified as independent baseline predictors of clinical response. Some of these characteristics were repeatedly identified as independent baseline predictors of anti-TNFα treatment continuation as well. Single predictors have only moderate capacity to predict treatment response in the individual patient whereas models that allow to combine these predictors may lead to more robust prediction instruments to support physicians in decision making on TNFα blocking therapy in AS in daily clinical practice [16].

In **Section 4.3** we present a model that combines these clinical characteristics with enthesitis score to predict response to and disease state following either continued use of NSAIDs or anti-TNF alpha treatment as measured with different AS outcome instruments. The advantage of this way of representing the data is that it allows clinicians in practice to easily understand how they should '*consider clinical features (history and examination) as well as either serum acute phase reactant levels*' as is indicated in the ASAS/EULAR recommendations [12] when they make a decision to treat. The absence or low value of one of the characteristics does not mean that response will not occur since the presence or value of another characteristic also has an influence on outcome.

Some of the same practical issues related to the selection of predictors that were described for the RA models apply in this AS prediction model as well. As an example, the predictors identified are not always retained in all studies; HLA-B27 highlighted in the supplementary table 8 of **Section 4.3**, was a predictor in 2 studies but was not retained as a predictor even though studied in 2 other studies. Enthesitis score was only investigated in our ASSERT/GO-RAISE analysis and this is thus the only study that could retain that variable. This may affect the confidence in these prediction models and may influence the extent with which they are used for decision making. As with RA however, also for Axial SpA we would argue that our model is more straightforward for clinicians to interpret than the advice currently provided by ASAS/EULAR and that its use in practice may help clinicians move from an intuitive choice towards an empirical, individualized selection of individuals for treatment based on more precise knowledge about therapeutic outcome.

MRI results were not investigated as predictor for inclusion in the ASSERT/GO-RAISE model and MRI imaging may be particularly useful to evaluate whether patients who have low values for CRP need treatment. The presented model however indicates that MRI imaging, which is costly, time-consuming and rather cumbersome for patients may not be necessary for all AS patients which are evaluated for treatment. If the clinical characteristics indicate that the probability of response is really high, MRI information may not alter the likelihood of response to that extent that anti-TNFα treatment would suddenly no longer be started. Similarly, if the likelihood of response is very low based on clinical characteristics, it would be useful to know whether inflammation visible on MRI would significantly increase the likelihood that a patient would respond to therapy. As such, similar to the approach in osteoporosis where DEXA scanning to assess the bone mineral content is only recommended when the extra information it will provide is relevant for the decision to treat a patient – see **Figure 50** [17], the color coding of future models predicting response to therapy may indicate when an MRI would not be

needed and when it would be helpful to determine whether anti TNF alpha therapy would be indicated in Axial SpA.

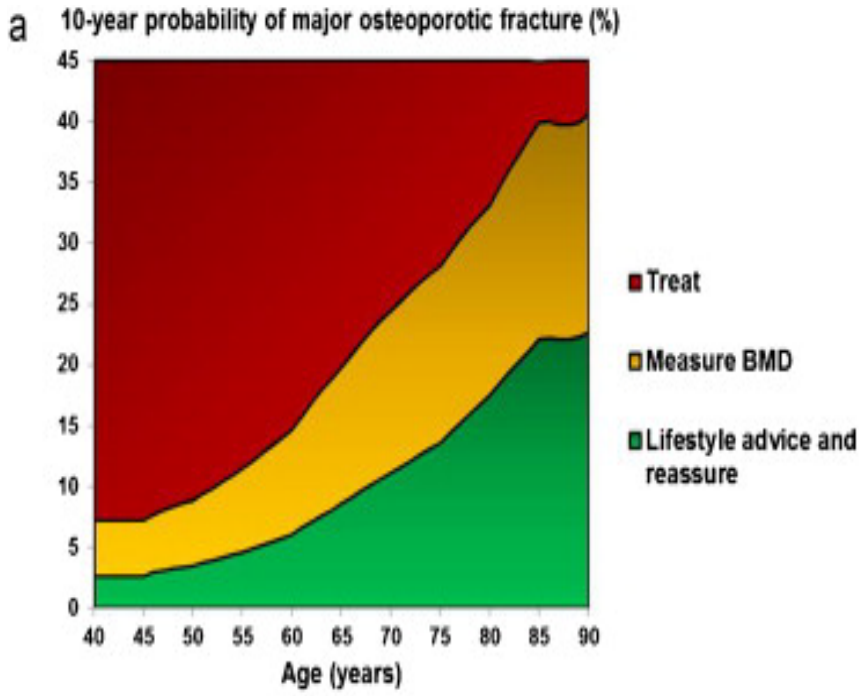

FIG. 50: *Prediction model in osteoporosis uses color coding relevant for treatment decisions. From: Compston J et al. Maturitas. 2013 Aug; 75(4):392-6 [12].*

6.2.1.2. Response and disease state as outcome

When comparing the response / remission prediction model in AS to the remission / LDA model in RA the advantage is that the selected predictors have the same direction of association with improvement as with disease state. AS patients who have a low likelihood of achieving a good disease state following anti-TNFα therapy will also have a low likelihood to improve whereas in RA, patients who had high likelihood to achieve remission had less improvement and vice-versa. Since the AS model thus clearly highlights patient sub-populations who will not benefit from treatment this may make this model more straightforward to include in treatment recommendations than the RA model.

6.2.1.3. Selection of AS patients for treatment

The BASDAI score has been used for patient selection in clinical studies and the ASAS/EULAR treatment recommendations reflect this [1, 12]. **Section 4.5** shows that patient selection using elevated disease activity measured with BASDAI, makes approximately 50% of AS patients followed in rheumatology practice in 2005 eligible for treatment independent of the likelihood that this is the proportion of patients who will do well with therapy. The ASDAS instrument contains CRP which the BASDAI does not and this disease activity instrument thus allows selecting different profiles of Axial SpA patients. If the ASDAS would be used for patient selection in treatment recommendations, more patients would be eligible for treatment with anti-TNFα alpha which could have budget consequences in countries where such treatment is fully reimbursed. Should restrictions on patient eligibility be needed for budget reasons, the prediction analyses using NNT combined with elevated disease activity measured with ASDAS rather than BASDAI can help establish treatment eligibility based on good treatment outcome.

From a health care provider or payer perspective, currently an 'all or nothing' methodology is usually applied: either you get full reimbursement or no reimbursement at all. An alternative choice of selection criteria could result in a setting where 'the payer' reimburses in an equal total number of AS patients but with a better return due to better overall outcomes in the population treated. If patients would be selected based on ASDAS>=2.1 rather than BASDAI>=4, this would mean an increase of about 16% on the treatment eligible population (**Section 4.5**). If at the same time only patients who have a NNT to have BASDAI50 response <=5 would be selected (**Section 4.4**), about 16% of patients who have a relatively low likelihood of response compared to NSAIDs would not remain eligible. The return for society would be better with the same proportion of patients treated. Using the NNT also alternative approaches can be conceived. If resources are limited and payers would want to limit the budget spent on the treatment of AS, the expected outcome could determine the extent of co-pay for a patient; e.g. a patient who has a NNT to achieve ASDAS clinically important improvement <3 does not co-pay, a patient who has NNT of 3-5 has a 10% co-pay, a patient with NNT >5 has 50% co-pay. Indeed, if more than 5 patients need to be treated with an anti-TNFα agent to have one more patient achieving a clinically important improvement than when they are treated with NSAIDs, one can consider this to be too limited return of value for money.

It is probably also important to emphasize that not being eligible for anti-TNFα does not mean that patients will not be cared for. Our modeling highlights that the likelihood of good treatment outcomes (meeting response criteria as well as achieving good disease state) with anti-TNFα is low for certain patient subgroups. The NNTs indicate that in that case the difference in outcomes between anti-TNFα and continued NSAID treatment is not large which highlights that continuing NSAIDs may be the preferred management option at that moment. The results of the INFAST study presented in **Section 5.1** are highlighting the effect of increasing NSAID to the maximally recommended dose. Maximizing the potential of NSAIDs in this disease will always remain a valid patient management option [18, 19].

6.2.1.4. Selection of Axial SpA patients for treatment

The prediction model originates from patient populations with established AS and it is not certain that it is useful for patients in whom ankylosis is not visible on conventional X-rays. Even if there seems to be similarity in the characteristics that predict outcomes of AS and non-radiographic Axial SpA [20, 21, **Section 5.3**], research to establish the value of the model in a non-radiographic population is needed. The objective of the new ASAS classification for Axial SpA described in **Section 1.1** has as a goal to increase the sensitivity and specificity to diagnose the condition in an early phase of disease so that it can be treated early. In this context of early intervention, appropriate patient selection for therapy may be even more important than in the setting of more established disease when a key irreversible disease feature like ankylosis is present.

Conclusion: Improving treatment recommendations of Axial SpA

6.2.1.5. Change the selection instrument for elevated disease activity

The disease activity instrument currently recommended for patient selection in treatment recommendations is the BASDAI. The BASDAI score is however inversely correlated with good outcome of therapy. Since CRP is a component of the ASDAS and a predictor of anti-TNFα therapy outcome it better allows selecting patients who are likely to respond. In addition, ASDAS has a greater sensitivity than BASDAI to distinct response to placebo (or continued treatment with NSAIDs) from response to anti-TNFα treatment. This is another reason why ASDAS would be a better patient selection instrument than BASDAI to use in clinical practice.

6.2.1.6. Include information on predictors of outcome as foundation for treatment

Experts who treat axial SpA patients with an anti-TNFα agent should consider clinical features (history and examination) as well as either serum acute phase reactant levels or imaging results, such as radiographs demonstrating rapid progression or MRI scans indicating inflammation [12]. An expert should be a doctor, usually a rheumatologist, with expertise in inflammatory back pain and the use of biological agents. Experts should be locally defined.

The literature support of the selected predictors indicates that there now is a large enough basis to use predictors to guide the choice of treatment with an anti-TNFα agent. The AS prediction model helps to establish how these characteristics can be used by clinicians and provides an evidence-based foundation for patient selection. The current recommendation which is based largely on how an expert intuitively uses a number of clinical features can thus be restated as a more empiric recommendation which could read something like 'The threshold of response-rate or remission-rate at which treatment should be initiated should be locally defined' rather than that 'Expert should be locally defined'. The local definition could be established based on AS outcome prediction.

It is also clear that MRI has a much more prominent role in establishing a diagnosis than it previously did. Data highlights that inflammation identified by this imaging technique is associated with clinical outcomes and MRI thus has a role in Axial SpA patient selection for treatment as well. Further refinement of the prediction model may help establish when an MRI would be needed for anti-TNF alpha treatment initiation.

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6.3. Anti-TNF Treatment discontinuation as treatment goal

6.3.1. Rheumatoid Arthritis

If a patient is in persistent remission after having tapered glucocorticoids, one can consider tapering a biological, especially if this treatment is combined with a DMARD. This is how recommendation 12 of the EULAR guidelines reads [1]. Tapering the anti-TNFα inhibitor dose in case of remission (i.e. DAS28<2.6) shows good results in early [2] and established RA [3, 4]. More profound and persistent responses increase the likelihood of successful discontinuation of a biological [7]. However, most established RA patients will flare upon withdrawal of a TNFα inhibitor [5-8] and when needed, reinstitution of a biological can be done without safety concerns and with an expectation that a good outcome can be achieved again [7, 9, 10]. RA has a fluctuating disease course in some patients and these findings indicate that treatment may be used during episodes when disease activity is present in such cases.

Data from registries in the Nordic countries is highlighting that the population receiving a first anti-TNFα inhibitor has changed over time [11-13]. The disease activity of the population treated has gradually gone down from high activity at baseline early 2000 to moderate activity 10 years later. This coincides with a more than twofold increase in the proportion of patients achieving remission. In the patients most recently treated with a biologic, the treatment goal of LDA or remission is achieved in more than half of the population [11, 12]. The proportion of patients who achieve sustained remission however, remains lower than 20% [13]. Yet, several of the predictors of achievement of sustained remission (i.e. the calendar year of treatment start, low HAQ and DAS28 at the treatment start) indicate that the changing population characteristics should lead to an increase in the proportion of treated patients who will achieve sustained remission [13].

It thus only seems a matter of time before more patients will start asking their clinician about the possibility of treatment discontinuation upon sustained disease control. Rapid induction of remission (i.e. at approximately 4 months versus later in the disease course) increases the likelihood of successful tapering and discontinuation of anti-TNFα therapy in practice [14]. The tool that we established which identifies patients who will go into remission fast can help install remission off biologic as a future treatment goal (**Section 4.2**). One can imagine that a proactive approach aiming for remission in selected patients may lead to a revisited treatment recommendation 12 (see first sentence of the first paragraph in this section) that starts with the word 'When' instead of 'If'. Communicating this more ambitious treatment goal to patients may further increase the likelihood of achieving it. Since it is built on the premises of first establishing treatment success (i.e. remission as treatment goal is achieved) the financial consequences of treatment optimization through tapering and intermittent use may compete quite well with other cost containment efforts that the payers of these medicines introduce (e.g. mandatory price decreases, facilitating use of biosimilar agents).

6.3.2. Axial Spondyloarthritis

The ASAS/EULAR recommendations advise to assess patients with the measures included in the ASAS core set for daily practice and the BASDAI. A specific treatment goal for the treatment of Axial SpA is currently not established [15, 16]. Anti-TNFα treatment discontinuation in established AS has been tried without much success [17] and ASAS/EULAR has thus not included it either as a recommendation [16].

The INFLIXISPINE trial was the first study to show that patient selection for treatment with an anti-TNFα agent in early Axial SpA allowed achieving remission rates that were more than double than what could be achieved within AS [18, 19-22]. Whereas the data shown in **Section 4.3** shows that patient selection allows to come to much higher remission rates in selected AS populations, information presented in **Section 5.1** establishes that ASAS partial remission and ASDAS remission are attainable treatment goals for the early Axial SpA population and **Section 5.3** helps understand which patient characteristics can further refine the selection for biologic use aiming at remission in Axial SpA.

The lack of breadth in therapeutic options for Axial SpA and the absence of well-established thresholds for disease activity states may have been the reasons why treatment goals and treat-to-target approach is not established the way it is in RA. The ASDAS is a new instrument that allows to better distinct disease activity states in the Axial SpA population and provides a solid basis for a treatment goal. The still limited number of medicines that have proven effects on axial disease remains a reason why the appetite to run through the options fast in pursuit of remission may still not be there. Yet, as Axial SpA is known to have a more relapsing-remitting disease course [24], the possibility of discontinuation may be an argument to introduce therapy at an earlier stage. In addition, as several anti-TNFα agents are now approved in non-radiographic Axial SpA [23], the possibility to discontinue treatment in patients who have not had the disease for a long time and who go into remission rapidly will become a more common situation in clinical practices that may require guidance from groups like ASAS/EULAR.

With the approval of anti-TNF agents in non-radiographic Axial SpA [23], manufacturers of these agents made post-approval commitments to perform randomized studies evaluating the possibility to discontinue / interrupt treatment. The European Medicines Agency (EMA) states that there is very limited knowledge on how long treatment should be continued in subjects in whom there is no disease activity following treatment, or the efficacy (and safety) of retreatment after disease flare. The market authorization holders are thus commended to conduct blinded withdrawal trials that will provide information on how long treatment should be continued in responders; what proportion of patients treated early in their disease achieve remission and also provide data on the efficacy and safety of re-treatment in this setting. **Section 5.2** provides information of the first of such studies which highlights, similar to RA, that treatment discontinuation can be considered when remission is achieved in Axial SpA. The additional evidence that can be anticipated from the stop-studies in non-radiographic SpA with other anti-TNFα agents will likely allow for a significantly altered treatment strategy in which life-long treatment with anti-TNFα may be replaced by treatment episodes in case remission (as treatment goal) is not present.

6.3.3. Conclusion: Proactive approach towards biologic-free disease control

The approach towards use of biologics in both the EULAR recommendations for treatment of RA and the ASAS/EULAR recommendations for treatment of Axial SpA are currently founded on the principle that cheaper non-biological agents first need to fail. This has been a very successful approach that significantly changed the profile of patients currently seen in rheumatology practice versus roughly 15 years ago in Western countries. In order to continue to make progress in the coming decades, it is very likely that more patients will need to be treated with more expensive treatment options. Cost of therapy and health-care budget management of rheumatic diseases therefore becomes an even greater concern and challenge. Scientists continue to search for genetic and other markers that predict treatment response to further optimize treatment and avoid waste due to non-response. While this quest continues to go on, clinical models like the ones presented in this thesis should allow improving patient selection based on the anticipated outcomes.

Treatment recommendations that strive for a proactive disease management approach which maximizes the likelihood to achieve a disease state that allows successful treatment tapering and discontinuation is a way to continue to improve the treatment of RA and Axial SpA patients while optimizing the treatment costs.

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6.4. Models to select Rheumatoid Arthritis and Axial Spondyloarthritis patients for Anti-TNFα treatment: is it time to introduce personalized medicine into clinical practice?

6.4.1. Abstract

Objectives

Recommended use of biologic agents in clinical practice should be guided by presence of poor prognostic factors in Rheumatoid Arthritis (RA) but use of outcome-predictors is not yet recommended in Axial Spondyloarthritis (SpA). We review user-friendly models combining individual treatment outcome-predictors to increase the predictive capacity beyond that of single predictors and argument why their use can facilitate rational anti-TNF treatment decisions of RA and Axial SpA in clinical practice.

Methods

Published models that combine characteristics which are readily-available in the clinic and are associated with RA and Axial SpA outcomes are described. Literature-search was done with PubMed.Gov for RA and Axial SpA separately and outcomes of interest were radiographic deterioration (poor prognosis), response and low disease activity / remission (good outcomes).

Results

For RA, 8 models predicting poor prognosis and 4 predicting good treatment outcomes were identified. One model predicting poor prognosis and one predicting good outcomes were found for Axial SpA. Some heterogeneity in the retained predictors and differences in model build-up explain the nuances between the models. Models originating from randomized studies allow directly comparing outcomes of different therapeutic choices which increases its value and predictive capacity. Models containing characteristics that predict multiple outcomes and using characteristics that can be easily applied in practice may be preferred for clinical decision making.

Conclusions

We describe a number of practical models predicting outcomes of RA and Axial SpA and present arguments on how their use in RA and axial SpA treatment recommendations could result in better treatment outcomes.

6.4.2. Introduction

The Rheumatoid arthritis (RA) and Axial Spondyloarthritis (SpA) classification criteria help rheumatologists to diagnose and treat patients at an early stage (1-3).

According to the American treatment recommendations, use of an anti-TNF agent with or without MTX can be envisioned as first-line therapy in patients who have high disease activity and poor prognostic features (4). If Low Disease Activity (LDA) or remission is not achieved with Methotrexate (MTX) with or without corticosteroids, in the absence of poor prognostic factors, change to another Disease Modifying Anti-Rheumatic Drug (DMARD) strategy should be considered according to the European RA management-recommendations. When poor prognostic factors are present, biological agents can be added and biologicals should also be considered when alternative DMARD strategies fail (5).

Experts who treat Axial SpA are recommended to use clinical features, serum acute phase reactant levels and imaging results when starting an anti-TNF agent. Patient-stratification based on predicted outcome is however not part of the Axial SpA treatment-recommendations and anti-TNF-agents are recommended for patients who fail Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and have elevated disease activity (6).

Even if society has paid for the benefits of biologics in RA and Axial-SpA, increasing healthcare costs is an issue which better patient selection and personalized treatment may help solve. Efficient use of genetics and biomarkers identified with new technology as predictors may require redefining of the taxonomy of the diseases into distinct genetic, molecular and cellular groups. Additionally, since the associations of biomarkers with outcomes may differ with the outcomes they predict and a variety of outcome-instruments determine the result of therapy, finding 'universal' predictors that have good Positive and Negative Predictive Values for all relevant outcomes may be an illusion.

Several models that combine readily-available disease characteristics predicting treatment-outcomes have been published. In this report we review models predicting poor prognosis and good results of RA and Axial SpA treatment. We present arguments how these tools can help clinicians in daily clinical practice to move from intuitive patient selection, usually based on severity, to more rational selection based on the knowledge of the anticipated treatment-outcome.

6.4.3. Methods

Literature-searches were done with PubMed.Gov using medical subject headings and other relevant keywords. Searches were done separately for RA and Axial SpA / Ankylosing Spondylitis (AS) and included randomized controlled clinical studies (RCT) and prospective studies on populations treated with approved anti-TNF agents, without restriction on sample size. Worsening of radiographic outcomes measured with conventional X-rays and scored with validated methods and improvement in clinical outcomes assessed with validated methods to measure response and disease state were used as definitions of poor prognosis and good treatment outcomes respectively.

Most literature describe the process of identifying predictors and reports associations of genetic, biological, clinical and/or demographic characteristics with outcomes in terms of odds or risk ratios with 95% confidence intervals, regression analyses or means of an independent variable, broken out per dependent variable categories. Whereas such data supports the validity of one or more predictors, its representation is not useful in the clinic. Description of predictors of anti-TNF therapy outcome has been done and was not within the scope of this report. Manuscripts identified through the literature-search

were reviewed with the aim to look for reports in which individual predictors were combined in practical models or tools that increase the predictive capacity beyond that of single predictors and that facilitates management decisions in clinical practice without the need for technology that is not readily available to clinicians.

6.4.4. Results

6.4.4.1. Prediction tools in Rheumatoid Arthritis

6.4.4.1.1. Poor prognosis prediction in RA

A very large body of evidence supports the association of a variety of clinical characteristics, imaging findings, genetic and biomarkers with progression of radiographic damage of the joints as measured by validated scoring methods. This is nicely summarized by Smolen et al (7).

Eight models originating from randomized controlled trials (RCTs) or non-interventional cohort studies were identified and are summarized in **Table 47** (8-13). They predict the probability of poor prognosis using a combination of usually 3 to 4 of the following characteristics: Swollen Joint Count (SJC), C-reactive protein (CRP), Erythrocyte Sedimentation Rate (ESR), Erosions on X-rays, Rheumatoid Factor (RF) with or without Anti-Citrullinated Protein Antigen (ACPA), smoking status and the disease activity score (DAS). In all models except 2, poor prognosis defined as deterioration with ≥5 units per year on the Modified van der Heijde Sharp X-ray scoring method was used as definition of rapid radiographic progression (RRP) or poor prognosis. All models identified patient sub-populations with worse radiographic prognosis than that observed in the total study-population. Models in which categorical (Models 1-3, 6, 7) rather than dichotomous variables (Model 4, 8) were used, allowed identifying patient-subpopulations with higher likelihood of poor prognosis. Models 1 to 7 have a similar 'Matrix-model' approach but use different predictors.

Model 1 and 2 are shown in **Figures 51A and 51D** and represent models predicting poor prognosis in (early) DMARD-naïve and DMARD refractory populations. Sub-populations with increasingly worse prognosis as defined by categorized predictors of radiographic progression are shown in green, yellow and red (9). Resulting from RCTs, **Figures 51B and 51C** illustrate how early combination therapy reduces the likelihood of progression in patient populations with different prognosis as stratified by their predictors compared to MTX alone.

In Model 8, dichotomized risk characteristics allow counting the predictors rather than categorizing them. C-statistics of described models validated in different datasets are shown in the bottom of **Table 47** (8-17).

Original Study Name		ASPIRE Study Rheumatology 2009;48(9):1114-21	BeSt Study Ann Rheum Dis 2010;69(7):1333-7; Arthritis Res Ther. 2014 Sep	SWEFOT Study Ann Rheum Dis 2014 Early Online	ESPOIR cohort Arthritis Res Ther. 2012; 14(6): R249	Nijmegen cohort J Rheumatol. 2015 Mar;42(3):391-7
Study Type		Double blind RCT	Double blind RCT	Double blind RCT	Prospective non-interventional	Prospective non-interventional cohort
RA Disease duration		>=3 months, <= 3 years	<=2 years	<1 year	<3 months	<1 year
Study Selection Criteria (for all reports X-ray availability was required)		SJC>=10, TJC>=12 and at least 1 of 3 characteristics: RF positive, presence of erosions in hands/feet, CRP>=2.0mg/dL	SJC>=6, TJC>=6 and either ESR>=28mm/hr or patient global health >=20mm	DAS28>3.2 and available X-rays	Initiation of MTX or LEF and available X-rays	Available X-rays and no anti-TNF used during study-period
Treatment		IFX + MTX versus placebo + MTX. MTX rapidly increased to 20 mg/week, IFX stable dose.	Initial MTX plus either CS or IFX vs. initial MTX monotherapy. 3-monthly treatment adjustment aiming at LDA.	Initial MTXI than addition of either IFX or 2 DMARDs if no LDA at 3 months	At rheumatologist discretion incl. anti-TNF	At rheumatologist discretion
SHS progression during 1 year; mean (SD)	CS+MTX	NA	2.0 (3.6) units	NA	NA	ND
	MTX	3.7 (9.6) units	7.1 (15.4) and 4.3 (6.5) units	5.04 (10.61) units	5.4 (7.0) units	
	anti-TNF + MTX	0.5 (5.6) units	1.3 (4.0) units	2.95 (6.07) units	NA	
Proportion progressing with >=5 SHS units in 1 year	CS+MTX	NA	13%	NA	NA	41.2% during 3 years [2]
	MTX	22.8%	33%		11.1% [1]	
	anti-TNF + MTX	8.3%	9%	25.4%	NA	NA
Poor prognosis models		**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**	**Model 6**	**Model 7**	**Model 8**
Selected predictors of radiographic progression		SJC, RF level, CRP level in matrix model	SJC, RF level, ESR level in matrix model	CRP level, RF/ACPA status, erosion score in matrix model	>=3 of 4 characteristics: DAS>=3.7, SJC>=10, erosion score>=4, both RF & ACPA positive	Smoking status, presence of erosions, CRP level in matrix model	SJC, CRP level, ACPA status, presence of erosions in matrix model	Prediction score 0 to 5.6 using ESR level, quantity of erosions, RF/ACPA status	Prediction score 0 to 3 using ACPA status, ESR >25 mm/h, and Ratingen score at baseline ≥ 1
% progressing with >=5 SHS units in 1 year	CS+MTX	NA	NA	1% - 32%	10%	NA	NA	approximately 10% to 90% [3]	9% [2], 25% [2], 49% [2], 57% [2] for 0, 1, 2, 3 risk factors present respectively
	anti-TNF+MTX	4% - 14%	2% - 17%	1% - 42%		12% - 63%	NA		
	MTX	7% - 47%	7% - 41%	5% - 78%	26%		2% - 64%		
ROC AUC (95% CI) in original dataset		ND	ND	0.81 (0.77 - 0.86)	ND	ND	0.75	0.77 (0.72–0.81)	0.75 (0.70–0.80)
ROC AUC in Leuven data		0.675	0.675	0.599	ND	0.344	0.351	ND	ND
ROC AUC (95% CI) in BRASS		0.59 (0.50–0.67)	ND	0.65 (0.58–0.73)	ND	0.57 (0.49–0.64)	ND	ND	ND
ROC AUC in Neimegen data		ND	ND	range 076 - 0.79	ND	ND	range 076 - 0.79	0.77 (0.72–0.81)	0.75 (0.70–0.80)

[1] patients in ESPOIR started either MTX (90.5%)or LEF (9.5%)

[2] In the Neimegen cohort the Ratingen score rather than the SHS score was used and progression was defined as increase with 5 points on the Ratingen score within 3 years rather than within 1 year

[3] exacte percentages not available - approximation derived from available figure plotting prediction score vs probability of progression of 5 per 3 years on Ratingen score

TABLE 47: *Prediction models combining disease characteristics to predict radiographic progression in RA. The table gives information on the dataset that the model originates from, a brief description of the model and the range of predicted progression rates. The bottom of the table describes the performance of the model to predict radiographic progression in the original dataset and other datasets.*

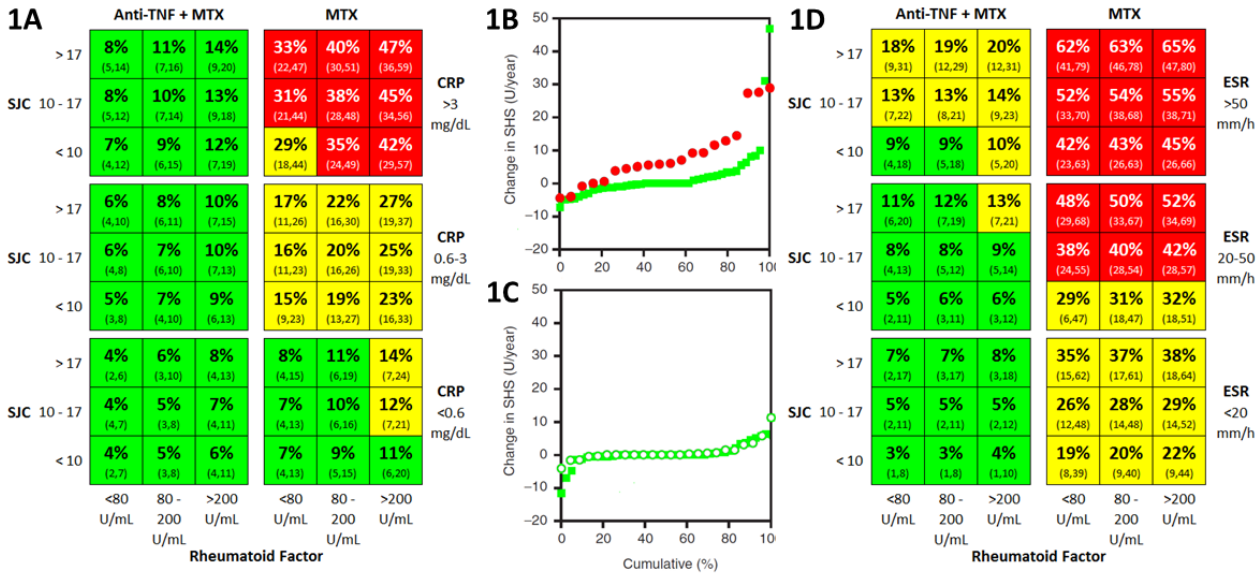

FIG.51: *Prediction of Poor Prognosis in RA. The model presents 27 RA patient sub-populations characterized by the combination of 4 predictors of rapid radiographic progression: Rheumatoid Factor (RF) level, Swollen Joint Count (SJC) and C-Reactive Protein (CRP, Fig 51A) or Erythrocyte Sedimentation Rate (ESR, Fig. 1D). Figure 51A compares methotrexate (MTX)-naïve patients who either receive initial MTX or initial combination of MTX plus infliximab in the ASPIRE study. Figure 51D compares MTX-refractory patients who either continue MTX or who receive infliximab in addition to MTX in the ATTRACT study. The percentages in Figure 51A and D represent the proportion and 95% Confidence Interval (95% CI) of patients within the sub-population that will progress with at least 5 Units of the Sharp van der Heijde Score (SHS) in one year (defined as rapid radiographic progression, RPP). Figures 51B and C represent cumulative probability plots of progression from baseline to 1 year in 3 patient-subpopulations representative for a high, medium or low risk population treated with MTX alone or infliximab + MTX. Figures 51A-C are modified from Ann Rheum Dis. 2010 Jul;69(7):1333-7).*

6.4.4.1.2. Prediction of Good Outcomes in RA

As for radiographic progression, quite some evidence on predictors of response and remission exists and this is summarized by Katchamart et al (18). We found 4 models that present the information in a practical way (Table 2) (19-21). Variations of predictor-associations with the investigated outcomes is the main reason why predictors like DAS28 or its subcomponents, age, smoking habits and comorbidity were retained in the final model or not. Stratification using predictors of response or remission leads to a magnitude of 9 times the probability of favorable outcomes between sub-populations. C-statistics were only reported for one model and validation in independent datasets was not done for any study.

Original Study Name	BSRBR registry Rheumatology 2006;45:1558–1565		SWEFOT study Ann Rheum Dis. 2011;70(3):469-75	GO-MORE study Arthritis Rheum. 2014;66(10):S1089
Study Type	Anti-TNF registry		Double blind RCT	Open label cohort study
Population	Multiple DMARDs failed, mean disease duration 14 y		MARD Naïve, disease duration <=2	>=1 DMARD failed, mean disease duration 7.6y
Study Selection Criteria	DAS28>5.1 (in accordance with NICE recommendations)		SJC>=6, TJC>=6 and either ESR>=28mm/hr or patient global health >=20mm	DAS28>=3.2, biologic naïve
Treatment	Etanercept or Infliximab during 6 months		MTX during 3 to 4 months	Golimumab during 6 months
Good EULAR response	18.1%		34%	36.0%
Moderate EULAR response	49.7%		41%	46.1%
DAS28 Remission / LDA	8.6% / NA		18% / NA	23.9% / 13.5%
Good outcome models	**Model 9**	**Model 10**	**Model 11**	**Model 12**
Selected predictors	Score 0 to 4: 1 point for either NSAID use or MTX use, 1 point for smoker; 1 point for medium and 2 points for high HAQ score	Score 0 to 8: 1 point for either NSAID use or MTX use, male 1 point, up to 2 points for HAQ score, number of previous DMARDs and DAS28 score	Gender, age, HAQ score, smoking status	Gender, age, HAQ score, presence of comorbidity, ESR or CRP, TJC or SJC
Good EULAR response	0 points: 8-10%; 1 point: 13-15%; 2 points 20-25%; 3 points:31-40%; 4 points:40-41%	ND	0% to 71% depending on combinations of the predictors	Patients stratified per 10% incresed of predicted likelihood of remission all had EULAR response rates within a range of 80% to 84%
Moderate EULAR response	0 points: 55-60%; 1 point: 56-60%; 2 points 54-58%; 3 points:48-52%; 4 points:40-41%	ND	ND	
DAS28 Remission / LDA	ND	DAS28 remission: 0-2 points: 3-4%; 3-4 points: 3-7%; 5-6 points: 14-20%; >6 points: 33-36%	DAS28 remission: 0% to 50% depending on combinations of the predictors	DAS28 remission: 4% to 77%; DAS28 LDA: 10% - 87%
ROC AUC (95% CI) in original dataset	ND	ND	ND	Ranging between 0.65 to 0.81

Table 48: *Prediction models combining disease characteristics to predict response or remission in RA. The table gives information on the dataset that the model originates from, a brief description of the model and the range of predicted outcome rates.*

6.4.4.2. Prediction of poor prognosis and good outcomes in Axial SpA

When recommendations were issued in 2010, there were no good predictors for treatment response and anti-TNFα was recommended for patients failing NSAIDs with elevated disease activity measured with the BASDAI instrument (5, 22-23). Several reports have since highlighted that acute phase reactants, disease activity, functional status, age and HLA-B27 have moderate capacity to predict outcomes of Axial SpA (24-28). Also enthesitis-score and MRI are recognized as response-predictor (28-30). A regression-model combining elevated CRP, short disease duration and MRI-inflammation in the spine predicted BASDAI50 response better than the individual characteristics (29). The clinical characteristics were combined in prediction Model 13 shown in **Table 49**. The same set of predictors allows accurately predicting a variety of clinical response and disease states at 3 and 6 months. One of those outcomes, ASDAS major improvement is shown in **Figure 52** (28). The predictive capacity of these Axial SpA prediction models has not been validated in other datasets.

We identified one report in which imaging results, inflammatory markers and smoking status were combined to predict ankylosis-progression (Model 14, **Table 49**) (31).

Original Study Name	**ASSERT & GO-RAISE studies** Rheumatology 2006;45:1558–1565	**GESPIC Cohort** Arthritis Rheum 2012;64(5):1388–1398
Study Type	Anti-TNF registry	Inception Cohort
Population	AS failing NSAIDs disease duration	Axial SpA incl. 115 with AS, 95 with non-radiographical Axial SpA
Study Selection Criteria	BASDAI>=4,	Available X-rays for spine & sacroiliac joints
Treatment	Infliximab or Golimumab during 6 months	Rheumatologist discretion incl Anti-TNF
Treatment outcomes	BASDAI50 response: 49%-51% ASAS20 response: 60%-61% ASAS partial remission: 21%-23%	Mean (SD) change in mSASSS score: 0.73 (2.34) units over 2 years. Definite X-ray progression (increase >=2 mSASSS units per 2 years): 14.3%
Prediction models	**Model 13 - good outcomes**	**Model 14 - poor prognosis**
Selected predictors	BASFI score, CRP level, age, HLA-B27 status, enthesitis score	Presence of syndesmophytes at baseline, smoking status, time-averaged ESR or CRP
Treatment outcomes	ASDAS clinically important imrovement: 1%-93% ASDAS major improvement: 0%-81% BASDAI50 response: 1%-81% ASAS20 response: 6%-81% ASDAS inactive disease: 0%-53% ASAS partial remission: 0%-55%	3% to 56% definite X-ray progression
ROC AUC in original datasets	0.75 to 0.84	ND

Table 49: *Prediction models combining disease characteristics to predict response/remission and progression of Axial SpA. The table gives information on the dataset that the model originates from, a brief description of the model and the range of predicted outcome rates.*

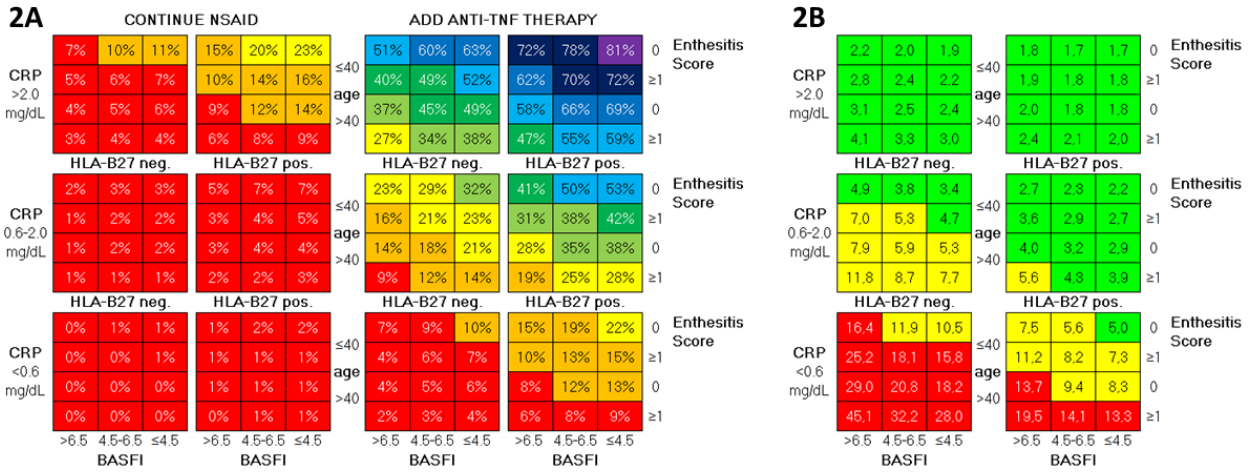

Figure 52: *Prediction of Good Treatment Outcome in Axial SpA. The model presents 72 AS patient sub-populations characterized by predictors of response and remission (C-Reactive Protein, Bath Ankylosing Spondylitis Functional Index, enthesitis score, age and Human Leucocyte Antigen-B27 Status) for biologic-naïve patients who either continue Non-Steroidal Anti-Inflammatory Drugs or who receive anti-Tumor Necrosis Factor in the ASSERT and GO-RAISE studies. The percentages represent the proportion within each the sub-population that achieves the outcome of interest. Figure 2A shows the Ankylosing Spondylitis Disease Activity Score major improvement rates after 3 months per treatment group; color coding applies standard fill colors in Microsoft Excel from red to purple with each increase of 10% probability of response. Figure 2B shows the Numbers Needed to Treat (NNT) with anti-TNF to achieve ASDAS major improvement after 3 months when compared to patients receiving placebo. Color codes are*

arbitrary: GREEN = NNT less than 5; YELLOW = NNT 5-12; RED = NNT>12. Figures are modified from Ann Rheum Dis. 2011 Jun;70(6):973-81.

6.4.5. Discussion

Disease characteristics associated with treatment outcomes can help individualize management of RA and Axial SpA, thereby optimizing treatment results, minimizing risks and maximizing cost-effectiveness. Whereas a large body of evidence supporting several predictors exists, there is only limited understanding and guidance on how they should be used in practice. This paper describes 14 published models that combine outcome-predictors to stratify the RA and Axial SpA population into sub-populations with different outcomes. We believe that the use of such models in treatment-recommendations, which currently do not go much farther than just listing predictors, may help introduce personalized medicine in daily rheumatology practice.

6.4.5.1. Outcome prediction models

Originating from RCTs, Models 1, 2, 3 and 13 allow directly comparing predicted prognosis of different therapeutic choices. In a situation where the clinician tries to identify the appropriate treatment option (i.e. choosing MTX or MTX+anti-TNF as first-line therapy for RA, adding anti-TNF to NSAIDs in AS), this helps establishing for which patient incremental value of anti-TNF versus comparator can be expected. This presents an important advantage of these models versus those that were established in databases that had no control group due to which treatment options cannot be compared.

Different datasets bring forth different predictors and models. The question thus becomes which model is the right one. Some differences exist because a variable was measured in the study or not. This mimics clinical practice where treatment decisions are made even if not all information is available (e.g. anti-CCP not reimbursed and therefore not done). In other occasions the characteristic was explored but did not contribute to the model. The wealth of data supporting the predictors retained in these models and their mentioning in existing treatment-recommendations, establishes a high face-validity for their use in prediction tools aimed to help make choices in clinical practice. Initiatives to better understand the validity of these models for practice are ongoing for both diseases and are needed.

Categorization of variables was done pragmatically allowing an even distribution of the study-dataset over the predictor-grids. Other and/or more cut-offs could have been chosen and would lead to slight differences in the reported outcome rates. Similarly, adding predictors to improve models would lead to altered percentages. As long as treatment-restrictions are not imposed based on these models, small changes in predicted outcome-rate would likely not have management consequences for an individual patient.

The contribution of predictors to the predicted probability of an outcome differs and depends on the nature of the outcome. When predicting good treatment outcome, models containing characteristics that predict multiple outcomes (e.g. Model 13) may increase its relevance in the clinic.

Finally, the nature of the predictor affects the usefulness of the model to clinical practice. Use of treatment history in Model 9 and 10 may be clinician-dependent and models that have only 'biologic' predictors may be preferred. Formal erosion scoring is not done in clinical practice which makes Model 3 and 4 difficult to use. 'Presence of erosions' on the contrary can be assessed in practice and is more easily implemented in the clinic.

6.4.5.2. Outcome prediction in Rheumatoid Arthritis

European and American RA management recommendations advise rheumatologists to use biologics in case of presence of one or more of 3 or one or more of 4 poor-prognostic factors respectively (4, 5). Patient-eligibility to studies like ASPIRE and BeSt was based on similar selection criteria (32, 33). Even if radiographic progression in the overall study population of these studies was substantial, prediction-modeling still allowed identifying patient populations with a risk of radiographic progression that exceeded that of the total study population. This highlights that how predictors are used, influences the extent to which they achieve their purpose; i.e. identifying poor prognosis patients.

The European recommendations use the terms 'low & high risk' and 'poor prognosis' which are however not defined (5). Most models presented in **Table 47** used progression with >=5 SHS units in a year or Rapid Radiographic Progression (RRP) as definition of poor prognosis. It has been shown that patients predicted to have RPP have much more progression over 5 years (10) and those who progress with 5 SHS units in a given year, have more functional limitations throughout 7 years following that year (14). It is furthermore a practical definition that can be explained to decision-makers and even patients (i.e. "Progression equivalent to one destructed joint per year"). A pragmatic definition for 'high risk' to recommend biologics could be based on the percentage above which prediction-models only predict occurrence of RRP in the monotherapy population but not the more intensive regimen. Models 1-3 are referenced in the European recommendations (5), but also Model 5-8 can be used to establish meaningful definitions for 'high risk'. Model 4 is inferior to the others as it yields lower probabilities of poor prognosis (34). In **Figure 51**, the color coding for 'high risk' (red) was chosen so that any level for the lower 95% CI of the proportion with RRP when treated with MTX did not overlap with any upper 95% CI of proportion with RRP occurring in MTX + anti-TNF treated patients. As such a risk of RRP of 20% with MTX can be considered 'high risk' and none of the patients treated with anti-TNF had a risk above this threshold. Epidemiological data used also to create Model 6 indicates that this would make about 13% of patients newly diagnosed with RA to have a high risk of poor prognosis (i.e. 13% had a predicted risk equal to or larger than 20% to progress with >=5 SHS units in one year).

The predictive capacity for these models in datasets that are not randomized is moderate only (15-17). It can thus be questioned whether it would be premature to introduce such models in recommendations. It should first be noted that therapy, which is one of the most important predictors, could not be studied as predictor due to the un-randomized nature of these validation studies. Omitting this predictor from a model will naturally result in reduced predictive power. It is also worth mentioning that, even though there is good evidence for the predictors of radiographic progression itself, the manner in which poor prognosis is introduced for treatment-choice in the most recent European and American treatment recommendations is also not backed by studies in which treatment choice stratified and directed by prognostic factors was compared to non-stratified and -directed treatment. **Table 47** highlights how the prediction tools are superior to using the '1 of 3 predictors' or '1 of 4 predictors' approach that the current treatment recommendations advise to use for establishing poor prognosis. We would thus argue that these models represent a more solid basis for patient-stratification than what supports the current RA recommendations even if the value of patient-tailored treatment choices still needs to be established.

Five-year X-ray results and health-state over 8 years stratified by RPP suggest that avoiding rapid progression matters (9, 14). One may still wonder whether it represents an unambiguous event that is important at the moment the treatment-decision is made. When patients expect pain-relief (35), clinicians aim for remission (4, 5) and payers want the most value at a minimum cost, it is not so obvious that prognosis is a decision-making element. Prevention of poor prognosis and of function-deterioration

can be assumed as long as disease activity is suppressed well enough (36-40). LDA leads to better functional and structural outcomes than moderate or high disease activity and is an alternative goal for patients with long-standing disease (38, 39). Arguably, identifying patients who achieve controlled disease state may thus be more relevant than identifying who will have joint damage.

There is a wealth of evidence as well supporting readily available predictors of response and remission (18). Remission-predictors frequently have an inverse association with disease activity improvement and with poor prognosis (41-43). Improvement of disease activity in patients with high disease activity is larger than improvement in patients with lower disease activity even if the likelihood of attaining LDA or remission is smaller in the former group. Rigorously applying selection-models using predictors of remission would thus exclude patients with high disease activity or poor prognosis from treatment. Selection of patients for Anti-TNF treatment using disease activity thresholds (e.g. DAS28>=5.1 in the United Kingdom) is at the same time predestined to lead to lower remission rates and also excludes patients from using therapy. To avoid this conflict, it seems essential to establish consensus on a goal of treatment which reflects superior value for patients, physicians and payers and use patient-stratification to maximize the likelihood of achieving that goal. Since patient-stratification in the RA recommendations aims for poor prognosis while the goal of treatment is remission (4, 5), this is currently not the case. Clinical disease state determined with a composite disease activity instrument directly affects both health state and radiographic prognosis. Rather than adjusting the treatment target based on the prognosis of a patient as has been proposed using model 8 (44), we believe that remission should remain the target and predicting who will achieve it (thus preventing radiographic progression as well) may be more important than prediction who will have poor prognosis. Tools that allow doing this in practice now exist (**Table 48**) but they were not created in RCTs and their value has not been validated in other cohorts. Validation of these tools will be important and further investigation to establish better RA treatment recommendations also needs a RCT that compares treatment choice stratified and directed by predictors of poor-prognosis versus treatment choice stratified and directed by predictors of achieving good disease state

6.4.5.3. Outcome prediction in Axial Spondyloarthritis

There is some evidence that NSAIDs suppress progression of ankylosis (45) but it is undecided whether anti-TNFα-treatment halts progression (46-49). The pathophysiological mechanism behind ankylosis is not well understood and we believe it is too early to use predictors of poor prognosis in treatment recommendations.

Recently, TNF-blockers received European Commission approval for the indication of non-radiographic axial SpA and their use should be guided by presence of objective signs of inflammation by elevated CRP and/or MRI, based on better response rates in analyses of the CRP- and/or MRI-positive subgroups (50). Most predictors identified in patients with established AS are also predicting outcomes in non-radiographic disease (50-54). Unlike RA, the direction of association of predictors with outcomes is the same for improvement and disease state in Axial SpA. This makes it more straightforward to include models predicting good outcomes in Axial SpA treatment recommendations.

As these models also identify patient-subgroups that have a low likelihood of response, a major concern is that they would lead to exclusion of patients from treatment. Personalized medicine is about making such choices but does not mean that a patient will not be cared for. If the likelihood of response is low for anti-TNFα and continued NSAID treatment (resulting in high NNT), rheumatologists should consider reevaluating a patient 3 months later and may postpone a decision to treat with an anti-TNF agent.

Model 13 also provides argumentation that patient-subgroups that are currently excluded for anti-TNF per treatment recommendation should be eligible. Epidemiological data indicates that selection with ASDAS>=2.1 rather than BASDAI>=4 would increase the anti-TNFα treatment eligible population with about 15% (**Figure 53A**) (28). **Figure 53B** shows how the profile of patients selected with ASDAS corresponds with a population that is more prone to have good outcomes (55, 56). Approximately 16% of patients have a NNT to achieve ASDAS major improvement >12 (corresponding with the darkened area in **Figure 3B** and the red area in **Figure 2B**). If inclusion of patients with ASDAS>=2.1 is combined with exclusion of patients predicted to have NNT>12 on ASDAS major improvement, the return on investment in anti-TNF therapy for society would be better with a similar proportion of patients treated.

	ASDAS <2.1	ASDAS ≥2.1	Total
BASDAI <4	358	**212** (18,3%)	570 (49.1%)
BASDAI ≥4	**32** (2.8%)	559	591 (50.9%)
Total	390 (33.6%)	771 (66.4%)	**1161 (100%)**

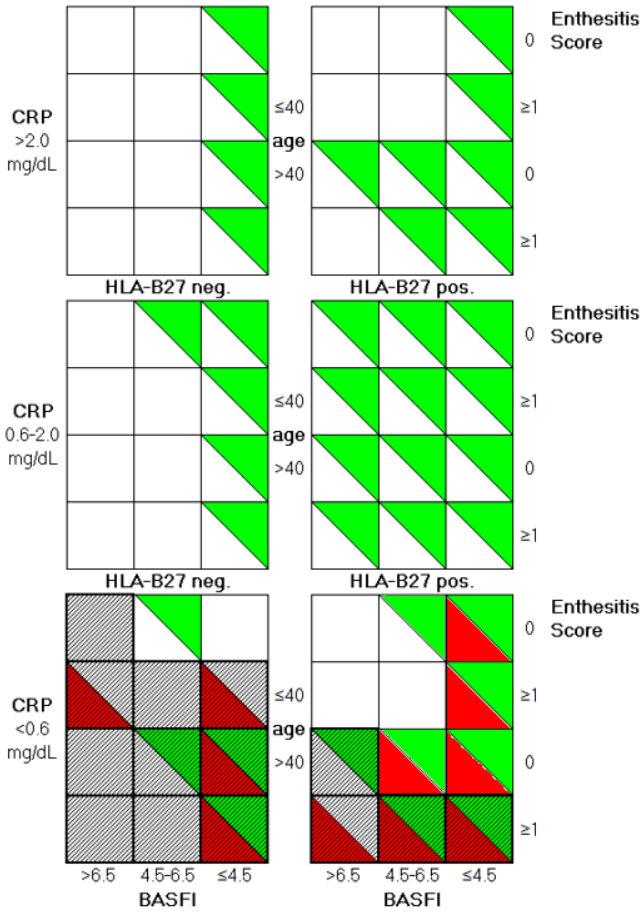

FIG.3: *Patient selection with ASDAS versus BASDAI: comparison of selected populations. The table highlights the proportion of patients with high disease activity that are selected with the ASDAS or BASDAI instrument from a representative sample of Axial SpA patients followed in rheumatology practice in Spain. The figure shows how the newly selected population that includes patients who have ASDAS>=2.1 rather than BASDAI>=4 is distributed over the predictor grid. Green triangles highlights sub-populations that include patients who have ASDAS>=2.1 but BASDAI<4 and who would be selected if the selection criterion changes as such. Red triangles highlights sub-populations that include patients with ASDAS<2.1 but BASDAI>=4 and who are no longer selected if the selection criterion changes. The shaded area represents the area that corresponds with sub-populations that based on the prediction model have a NNT to achieve ASDAS major improvement >12. Modified from Reumatol Clin. 2014 Jul-Aug;10(4):204-9.*

In addition to clinical examination and CRP, MRI results may be of use to help decide whether initiating anti-TNF-alpha therapy is warranted (30, 57). We believe that the clinical prediction models provide the context based on which the appropriate place for MRI imaging to help with treatment choice can be made. If clinical characteristics alone indicate that the likelihood of response is really high, MRI information may not alter the likelihood of response to that extent that anti-TNFα treatment would suddenly no longer be started. Similarly, if the likelihood of response is low based on clinical characteristics, MRI results may not dramatically alter this. In the intermediate situation however, MRI may help make better decisions. The color coding used in **Figure 2B** based on the NNTs for the ASDAS major improvement prediction model could hypothetically be associated with the following treatment recommendations for rheumatologists: RED = 'Expected benefit of anti-TNF is low, consider alternative analgesics'; YELLOW = 'Perform MRI. If positive consider anti-TNF, if negative consider alternative analgesics'; GREEN = 'Expected benefit from anti-TNF is high'. While researchers continue their search for predictors with new technologies, it should be avoided that this only leads to identifying expensive alternatives to what is measured already in practice. The research agenda should therefore continue to focus on how novel predictors are complementary to what is readily available.

6.4.5.4. Conclusions

Registry-data highlights that baseline disease activity of RA patients receiving an anti-TNF inhibitor has changed from high to moderate in the past 15 years (58-60). This coincides with a more than twofold increase in remission rates (58, 59) and rates of sustained remission (60) at which time *clinicians can consider tapering the biological agent* (5, 61). Remission rates in early Axial SpA are double of what is seen in AS (62-67). A first report of successful treatment-discontinuation in Axial SpA (68) and upcoming evidence from stop-studies commended by the European Medicines Agency (49) may help establish treatment tapering in this disease as well.

The RA and Axial SpA recommendations have likely contributed to the significantly changed profile of patients currently seen in rheumatology practice versus roughly 15 years ago in Western countries. In order to continue to make progress in the coming decades, it is likely that more patients need treatment with costly treatments. Scientists continue to search for outcome-predictors to further optimize treatment and avoid waste due to non-response. While this continues, the clinical evidence available today should already allow improving patient-selection based on anticipated outcomes.

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Summary

Prediction models to guide treatment choice in Rheumatoid Arthritis

Persistence of elevated disease activity and subsequent destruction of peripheral joints leads to functional impairment and disability in Rheumatoid Arthritis (RA), which may be irreversible. The therapeutic goal in RA is to bring a patient in remission or low disease activity. When that is not achieved with a first-line treatment strategy that includes non-biologic Disease Modifying Anti-Rheumatic Drugs (DMARDs), rheumatologists are recommended to use anti-TNF agents, which have an acceptable safety profile and reduce disease activity, improve function and slow radiographic progression in DMARD-naïve and DMARD-refractory patients.

In patients failing DMARDs, presence of poor prognostic factors like elevated serum level of Rheumatoid factor, joint-erosions visible on conventional X-rays and elevated disease activity should be weighed in when clinicians are considering to start anti-TNF therapy. In the EAP study presented in **Chapter 3** of this thesis, we investigated which of these characteristics was associated with the decision to increase the dose of an anti-TNF agent. This showed that the Disease Activity Score based on a 28 tender and swollen joint count (DAS28) best discriminates the decision of the rheumatologist to take anti-TNF related decisions. Other poor prognostic factors did not contribute too much. This nicely highlights the usefulness of the DAS28 score in clinical practice. The results also show that higher disease activity increases the likelihood that a physician will increase the dose of an anti-TNF agent. This is not a big surprise; it may even be obvious that a physician would use more intensive treatment options in patients who are more severely ill. However, in a situation where resources are scarce, one may wonder which patients should be treated so that the return on value for the investment (e.g. reimbursement of a treatment by health authorities) is maximized. Since the most severe patients are not necessarily the ones that benefit most from the envisioned treatment, the question becomes whether physicians should reserve more effective and frequently more expensive treatment options for severe patients (for example measured with DAS28) or for patients who will have the best outcomes from that medicine?

A number of studies were initiated with the aim to create user-friendly prediction models of treatment outcome that can be used in clinical practice to help rheumatologist understand for which patient initiation of anti-TNF therapy would be most valuable. These are included in **Chapter 4**. The data of 2 randomized clinical trials (the ASPIRE and ATTRACT studies) was used to create a model that predicts the risk of poor prognosis of a potential treatment choice (e.g. a single DMARD or a DMARD in combination with an anti-TNF agent) in a specific RA patient. Poor prognosis was defined as progression equivalent to destruction of one joint per year or 'rapid radiographic progression' and 3 disease characteristics of RA (i.e. number of swollen joints, rheumatoid factor level and level of C-reactive protein [CRP]) are used to inform a rheumatologist of the likelihood that rapid radiographic progression will occur in a patient treated with one DMARD or with combination therapy. For example, patient A with high CRP, high swollen joint count and high rheumatoid factor level has a risk of 14% to have rapid radiographic progression when treated with combination therapy and 47% if treated with one DMARD; patient B with low values for the 3 characteristics has a risk of 4% to have rapid progression when treated with combination therapy but 7% risk when treated with one DMARD. For patient A, the incremental value of combining DMARD with an anti-TNF to avoid rapid progression (or poor prognosis) is much larger than for patient B. The rheumatologist may use this information as support to initiate combination therapy in

patient A but may decide not to use anti-TNF (yet) for the initial treatment strategy of patient B, as the relative added benefit may not outweigh the increased costs and/or potential risks.

Remission is the ultimate goal of treatment in RA, and since it can be assumed that achievement of this disease state will also prevent rapid progression from occurring, a second model using data from the GO-MORE study was created to predict remission. In this research, 6 characteristics were predicting remission: low age, male gender, low number of tender or swollen joints, elevated markers of inflammation (CRP or ESR), low disability score and absence of comorbid diseases. Patients who have presence of all these characteristics have a chance of 77% to achieve remission, whereas elderly, disabled females with comorbid disease, and high disease activity (i.e. high joint counts combined with high level of inflammatory markers) have only 4% chance to go in remission with an anti-TNF agent.

Comparing the results of the poor prognosis model for rapid progression with the model predicting remission highlights a conflict in the European treatment recommendations for management of RA. Namely, that high disease activity predicts rapid radiographic progression or poor prognosis and that it is at the same time associated with a lower likelihood of achieving remission. Stratifying the RA population based on this characteristic of poor prognosis will thus reduce the likelihood of the selected population to achieve the treatment goal with anti-TNF. Suggestions are made in **Chapter 6** on how the RA treatment recommendations can be refined to avoid this conflict. One way could be to remove high disease activity as selection criterion for poor prognosis. Alternatively, it can be considered to remove the requirement to stratify the population based on the risk of poor prognosis overall, and move towards patient stratification that is aimed at maximizing the likelihood of achieving remission. The remission prediction model may come in useful if that would be considered.

Prediction models to guide treatment choice in Axial Spondyloarthritis

A treatment goal has not been adopted in the management recommendations for Axial SpA and use of outcome-predictors to guide treatment choice is not recommended at this time either. Biological agents should be used as second-line agents in this disease when elevated disease activity persists in spite of repeated trial with Non-Steroidal Anti-Inflammatory drugs (NSAIDs).

Rheumatologists who treat Axial SpA patients with anti-TNF agents are recommended to use clinical features, serum acute phase reactant levels and imaging results when making a decision to treat. The nature of the characteristics and how they should be used is however not specified. Presented in **Chapter 3**, the ASPECT study is one of the few studies that help understand what characteristics are really used in the clinic and highlights that disease severity characteristics such as high disease activity, worse functional capacity, elevated inflammatory markers, presence of extra-articular manifestations and advanced stage of damage visible on conventional X-rays are the main drivers behind initiation of an anti-TNF agent in Axial SpA.

Based on the premises that the most severe patients are not necessarily the ones that will do best on therapy, we wanted to create a tool that can be used in the clinic to help clinicians understand which Axial SpA patients will have the best outcomes with anti-TNF treatment. As presented in **Chapter 4**, data of the ASSERT and GO-RAISE studies was used to show that elevated CRP, HLA-B27 genotype, lower age, less functional impairment and lower enthesitis score was associated with higher likelihood of response after 3 months and remission after 6 months of treatment. Patients with these characteristics treated with anti-TNF had a chance of as high as 93% to have response at 3 months and up to 55% had remission

at month 6. Chance of response to NSAIDs in similar patients was never higher than 42% and to remission never higher than 7%. Likelihood of response in old, HLA-B27 negative patients with normal values for CRP who report very poor function and have a very high enthesitis was 28% when treated with an anti-TNF agent and 1% when treated with NSAIDs.

For the current recommendation to use clinical characteristics, acute phase reactants and imaging it is assumed that intuitively experts will use these characteristics in the appropriate way. Taking into account what a rheumatologist actually does in practice, we believe our model provides a better evidence basis allowing informed decision making in the clinic. Several published reports identified the same predictors we did which lends further support to make better use of anti-TNFα outcome-predictors in treatment guidelines. Also presented in **Chapter 4**, a study of the characteristics of the patient population identified with our prediction tool, allows us to also advocate for a change of the disease activity instrument used for selection of Axial SpA patients eligible for anti-TNF treatment. The instrument that is advocated for use according to current treatment recommendations excludes a number of patients in whom a high likelihood of response and remission can be expected. A recently described and validated disease activity instrument would select these patients that are currently not elegible for treatment and for which good outcome of therapy can be expected.

In RA, the practice of tapering or discontinuing an anti-TNF agent, once persistent disease activity control is achieved, is already part of treatment recommendations and helps control the cost of RA management. Early initiation of effective therapy is a key to success for this. For Axial SpA however, studies have shown that discontinuation of anti-TNF in long-standing disease leads to flaring of the disease activity. Patients who start an anti-TNF agent (very frequently at a young age) should thus continue this treatment for the rest of their life. Recently developed classification criteria of Axial SpA allow making an earlier diagnosis and treating the disease at an earlier stage. This new classification was used to select patients for treatment in the INFAST study presented in **Chapter 5**, which showed among the highest remission rates ever reported with anti-TNF; 62% patients treated with anti-TNF plus NSAID versus 35% treated with NSAID alone had remission after 6 months. When treatment with the anti-TNF agent was subsequently discontinued, the disease activity remained fairly controlled up to 6 months in the absence of anti-TNF therapy and nearly half of the patients remained in remission. Use of prediction models can help identify Axial SpA patients in which remission with anti-TNF and subsequent treatment discontinuation may be an attainable goal. In such patients, life-long treatment may not be needed.

Conclusion

In this thesis we show that rheumatologists will primarily select the most severe RA and Axial SpA patients for treatment with an anti-TNF agent. The prediction analyses we and other groups have done however, highlight that the most severe patients do not necessarily have the best anti-TNF treatment outcomes. User-friendly prediction models of RA and Axial SpA can assist rheumatologists to select patients for treatment with an anti-TNF agent in daily clinical practice based on good outcome of therapy. This may improve the outcomes of the treated population. Careful selection will also increase the proportion of patients that will achieve remission which allows to tape or discontinue the anti-TNF agent without flare of the disease. Aside from avoiding wastage of resources due to treatment of patients that turn out to be non-responders, these tools can thus also open the doors to tapering and/or discontinuing the anti-TNF agent and thus further reduce the cost of treatment for these diseases.

Samenvatting

Predictiemodellen ter ondersteuning van de therapie-keuze in Reumatoide Atritis

Aanhoudende verhoogde ziekteactiviteit en geassociëerde destructie van de perifere gewrichten leidt tot functionele beperkingen en handicap bij reumatoïde artritis (RA), die onomkeerbaar kunnen zijn. Het therapeutische doel is om RA patiënten in remissie of lage ziekteactiviteit te brengen. Als dit niet wordt bereikt met een eerste-lijnsbehandeling die niet-biologische disease-modifiërende anti-reumatische drugs (DMARDs) omvat, wordt reumatologen aangeraden om anti-TNF-middelen te gebruiken. Deze medicijnen hebben een aanvaardbaar veiligheidsprofiel, verminderen ziekte-activiteit, verbeteren de functie en verhinderen radiografische progressie bij DMARD-naïeve en DMARD-refractaire patiënten.

Volgens de therapeutische richtlijnen dient voor patiënten bij wie DMARDs falen, de aanwezigheid van slechte prognostische factoren zoals aanwezigheid van reumafactor, gewrichtserosies zichtbaar op röntgenfoto's en een verhoogde ziekteactiviteit door de rheumatoloog nagegaan te worden vooraleer anti-TNF-therapie wordt gestart. In het EAP studie gepresenteerd in **Hoofdstuk 3** van dit proefschrift onderzochten we welke van deze kenmerken werd geassociëerd met de beslissing om de dosis van een ati-TNF middel te verhogen. Dit toonde aan dat de Disease Activity Score waarbij 28 gewrichten worden geëvalueerd voor zwelling en pijn (DAS28) het best correleerde me de beslissing van de reumatoloog om een anti-TNF-gerelateerde beslissingen te nemen. Andere slechte prognostische factoren bleken minder belangrijk. Dit benadrukt enerzijds het nut van de DAS28 score in de klinische praktijk. De resultaten tonen anderzijds dat een hogere ziekteactiviteit de kans vergroot dat een arts de dosis van een anti-TNF-middel zal verhogen. Dit is geen grote verrassing; het lijkt zelfs evident dat een arts intensievere behandelingsopties kiest voor patiënten met meer ernstig ziekte. In een situatie waarin middelen schaars zijn echter, kan men zich afvragen welke patiënten moeten worden behandeld om de waarde van de investeringen (bijvoorbeeld de terugbetaling van een behandeling door de gezondheidsautoriteiten) te maximaliseren. Aangezien de meest ernstige patiënten niet noodzakelijkerwijs degenen zijn die de beste resultaten hebben van de beoogde behandeling, wordt de vraag of artsen doeltreffendere en vaak duurdere behandelingsopties best gebruiken in de meest ernstige patiënten (bijvoorbeeld gemeten met DAS28) of in patiënten voor wie de beste resultaten kunnen worden verwacht?

Een aantal studies werden gestart met het doel gebruiksvriendelijke voorspellingsmodellen van therapieresultaat te maken die door reumatologen kunnen worden gebruikt om in te schatten voor welke patiënt start van anti-TNF therapie het meest waardevol is. Deze werden geincludeerd in **Hoofdstuk 4**. De data van 2 gerandomiseerde klinische trials (de ASPIRE en ATTRACT studies) werd gebruikt om een model te creëren dat de kans op een slechte prognose van de potentiële behandeling (bijvoorbeeld een DMARD of DMARD in combinatie met een anti-TNF-middel) voorspelt voor een specifieke RA patiënt. Slechte prognose werd gedefiniëerd als progressie gelijkwaardig aan vernietiging van één gewricht per jaar of ‘snelle radiografische progressie’. Drie ziektekenmerken van RA (het aantal gezwollen gewrichten, reumafactor niveau en het niveau van C-reactieve proteïne [CRP]) worden gebruikt om een reumatoloog te informeren over de kans op snelle radiografische progressie bij een patiënt behandeld met één DMARD versus combinatietherapie. Bijvoorbeeld, een patiënt met hoge CRP, veel gezwollen gewricht en hoge waarde voor reumafactor heeft een kans van 14% op snelle

radiografische progressie wanneer zij wordt behandeld met combinatietherapie en 47% wanneer zij wordt behandeld DMARD; patiënt B met lage waarden voor de drie kenmerken heeft een kans van 4% op snelle progressie wanneer behandeld met de combinatietherapie en 7% wanneer behandeld met één DMARD. De meerwaarde van combinatietherapie met DMARD én anti-TNF om snelle progressie (of slechte prognose) te vermijden is veel groter bij patiënt A. De reumatoloog kan deze informatie gebruiken als ondersteuning om combinatietherapie te initiëren bij patiënt A. Hij kan beslissen (nog) geen anti-TNF te gebruiken voor de eerstelijns-behandeling van patiënt B, vermits het relatieve voordeel mogelijks niet opweegt tegen de hogere kosten.

Remissie is het uiteindelijke doel van de behandeling in RA, en het kan worden aangenomen dat het bereiken van remissie ook zal voorkomen dat er snelle radografische progressie optreedt. Met behulp van gegevens uit de GO-MORE studie werd daarom een tweede model gemaakt voor predictie van remissie. In dit onderzoek werden zes kenmerken weerhouden die remissie voorspellen: lage leeftijd, mannelijk geslacht, een laag aantal pijnlijke of gezwollen gewrichten, verhoogde acute fase reagentia (CRP of sedimentatie), betere score voor functie en de afwezigheid van comorbiede ziekten. Patiënten met deze eigenschappen hebben een kans van 77% om remissie te bereiken. Oudere vrouwen met comorbiede ziekten, een hoge ziekteactiviteit (dwz hoge gewrichten in combinatie met het hoge niveau van acute fase reagentia) en die minder goede scores voor functie hebben hebben slechts 4% kans om in remissie te gaan met een anti-TNF-middel.

Vergelijking tussen de resultaten van het predictie model voor slechte prognose of snelle radiografische progressie met het model ter voorspelling van remissie wijst op een conflict in de Europese behandelingsaanbevelingen voor de behandeling van RA. Een hoge ziekteactiviteit voorspelt namelijk snelle radiografische progressie en is tevens geassocieerd met een lagere kans op het bereiken van een remissie. Stratificatie van de RA populatie op basis van deze eigenschap van slechte prognose zal dus de waarschijnlijkheid verminderen om in de geselecteerde populatie met anti-TNF behandeling remissie te bereiken. Dit proefschrift bevat in **Hoofdstuk 6** suggesties om de aanbevelingen te verfijnen en dit conflict te vermijden. Eén manier zou kunnen zijn om een hoge ziekteactiviteit te verwijderen als selectiecriterium voor slechte prognose. Als alternatief kan het worden overwogen om de RA populatie niet langer op basis van het risico voor slechte prognose te stratifiëren maar de stratificatie te richten op het maximaliseren van de kans om remissie te bereiken. Het model voor voorspelling van remissie zou handig kunnen zijn om dit in de kliniek te implementeren.

Predictiemodellen ter ondersteuning van de therapie-keuze in Axiale Spondyloartritis

Een behandelingsdoel is nog niet gespecifieerd in de aanbevelingen voor management van axiale SpA en het gebruik van de therapieuitkomst-voorspellers ter ondersteuning van de behandelingskeuze wordt momenteel ook niet aangeraden. De richtlijn is aldus om biologische middelen voor deze aandoening te gebruiken in de tweede lijn, wanneer verhoogde ziekteactiviteit blijft bestaan ondanks herhaalde proef met niet-steroïdale anti-inflammatoire geneesmiddelen (NSAID's).

Reumatologen die overwegen om anti-TNF-middelen bij axial SpA patiënten te starten wordt aanbevolen om klinische kenmerken, niveaus van acute fase reagentia en beeldvormingsresultaten in acht te nemen bij het nemen van een beslissing. De aard van de eigenschappen en hoe ze dienen te worden gebruikt wordt echter niet vermeld. De ASPECT studie gepresenteerd in **Hoofdstuk 3** is een van de weinige studies die helpt begrijpen hoe deze kenmerken werkelijk worden gebruikt in de praktijk en

toont aan dat de ziekte-ernst (hoge ziekteactiviteit, erger functionele capaciteit, verhoogde inflammatoire markers), de aanwezigheid van extra-articulaire manifestaties en een gevorderd stadium van ankylose (aantoonbaar met conventioneel röntgenonderzoek) de belangrijkste drijfveren zijn tot het starten van een anti-TNF middel in axiale SpA.

Op basis van de veronderstelling dat in de meest ernstige patiënten niet noodzakelijkerwijs de beste resultaten worden bereikt, wilden we een instrument maken dat reumatologen in de kliniek duiding geeft over welke axiale SpA patiënten de beste resultaten met anti-TNF behandeling hebben. Gegevens van de ATTRACT en GO-RAISE studies werden in **Hoofdstuk 4** gebruikt en toonden dat verhoogde CRP, HLA-B27 genotype, lagere leeftijd, minder functionele beperkingen en lagere enthesitis score geassocieerd waren met een hogere kans op respons na 3 maanden en remissie na 6 maanden behandeling. In patiënten met deze kenmerken behandeld met anti-TNF was de kans op response tot 93% en remissie werd gezien bij 55% van dergelijke patiënten. Kans op respons bij vergelijkbare patiënten behandeld met NSAID's was nooit hoger dan 42% en remissie nooit hoger dan 7%. De waarschijnlijkheid van respons in oudere, HLA-B27 negatieve patiënten met normale waarden voor CRP die zeer slecht functioneren en met zeer hoge enthesitisscores was 28% wanneer behandeld met een anti-TNF middel en 1% behandeld met NSAIDs.

De huidige aanbeveling om klinische kenmerken, acute fase reagentia en beeldvorming te gebruiken gaat ervan uit dat deze karakteristieken intuitief op de juiste manier door de expert wordt gebruikt. We geloven dat ons voorspellingsmodel een beter basis (‘evidence basis’) is om een geïnformeerde beslissing te maken in de kliniek. Verschillende gepubliceerde rapporten hebben gelijkaardige associaties aangetoond van predictors met therapieuitkomst. Dit levert ondersteuning voor een gefundeerd gebruik van voorspellers van anti-TNF resultaat in behandelrichtlijnen. Een in deze thesis beschreven studie die de kenmerken van de patiëntenpopulatie vergelijkt op basis van voorpellers van goede therapie-uitkomst, laat ook toe te pleiten om het instrument ter bepaling van de ziekte-activiteit voor de selectie van Axial SpA-patiënten voor anti-TNF behandeling te veranderen. Het instrument dat volgens de huidige richtlijnen wordt aanbevolen sluit namelijk een aantal patiënten uit bij wie wel een hoge waarschijnlijkheid van de respons en remissie kan worden verwacht. Een meer recent beschreven en gevalideerd instrument voor meting van ziekteaktiviteit zou deze populatie die momenteel uitgesloten wordt wel selecteren en een goede therapie-uitkomst kan worden verwacht. Dit werk is ook ingesloten in **Hoofstuk 4**.

In RA is de praktijk om anti-TNF therapie af te bouwen of te stoppen wanneer de ziekteactiviteit langdurig is gecontrolleerd al een deel van de aanbevelingen die helpt om de kosten van RA management onder controle te houden. Vroegtijdige behandeling is hierbij een van de sleutels tot success. Bij axiale SpA patienten met lange ziektegeschiedenis leidde stopzetten van anti-TNF behandeling tot nog toe altijd tot het opnieuw opflakkeren van de ziekte-activiteit. Axiale SpA patiënten bij wie (heel vaak op jonge leeftijd) een anti-TNF middel wordt opgestart, dienen dit dus voor de rest van hun leven te blijven nemen. Recent ontwikkelde classificatie-scriteria van axial SpA maken het mogelijk de behandeling van de ziekte in een eerder stadium aan te vatten. Deze nieuwe axiale SpA classificatie werd gebruikt voor de selectie van patiënten in de INFAST studie, beschreven in **Hoofstuk 5**. Hierin bereikten na 6 maanden 62% van de patiënten behandeld met anti-TNF remissie versus 35% van deze behandeld met NSAID. Wanneer de behandeling met het anti-TNF middel vervolgens werd beëindigd bij patiënten die in remissie waren, bleef ziekteactiviteit gecontroleerd gedurende 6 maanden en bijna de helft van de patiënten bleef in remissie zonder gebruik van anti-TNF. Het gebruik van voorspellingsmodellen kan helpen om axial SpA patiënten te indentificeren die in remissie zullen gaan.

Dit zijn tevens de patiënten bij wie therapie-afbouw kan overwogen worden. Betere selectie van patiënten kan aldus levenslange behandeling onnodig maken.

Conclusie

In dit proefschrift tonen we dat de reumatoloog hoofdzakelijk de meest ernstige RA en axial SpA patiënten selecteert voor behandeling met een anti-TNF-middel. De analyses die wij en andere groepen hebben gedaan, benadrukken echter dat de meest ernstige patiënten niet per se de beste anti-TNF behandelingsresultaten zullen hebben. Gebruiksvriendelijke voorspellings-modellen van RA en axial SpA laten reumatologen in de dagelijkse klinische praktijk toe om patiënten voor behandeling met een anti-TNF-middel te selecteren op basis van goede therapie-uitkomst. Dit zou de behandelingsuitkomsten van RA en axiale SpA verder kunnen doen verbeteren. Meer zorgvuldige selectie zal ook het aandeel van de patiënten die remissie bereiken doen toenemen, welke op zich anti-TNF therapie-afbouw en -stop zonder ziekteopflakkering mogelijk maakt in een aantal patiënten. Naast het verminderen van verspilling ten gevolge van non-respons, kan dit helpen om de behandelingskosten te drukken.

Curriculum Vitae

Nathan Vastesaeger graduated as Medical Doctor with distinction at the Catholic University of Leuven, Belgium in 2002 and joined Schering-Plough Belgium as Medical Science Liaison for Oncology and Allergy. He obtained a master degree in Pharmacology and Pharmaceutical Medicine at the University of Brussels in 2004 was promoted to medical advisor and in that same year immunology was added to his scope of responsibilities. In 2006 he joined Centocor, Johnson & Johnson as Clinical Scientist Rheumatology for Spain and Portugal operating from Madrid, Spain. In 2007 he became Research Physician Immunology for Centocor Europe Operating from Leiden, The Netherlands and he returned to Schering-Plough at the end of 2008 as Medical Director for Rheumatology in Global Medical Affairs. Upon the merger of Schering-Plough with Merck, Nathan became responsible for Rheumatology in Europe and Canada. He was promoted to Executive Director in the Global Medical Affairs Strategy Team in 2011 and led a team of Regional Directors of Medical Affairs who coordinate the medical activities in Immunology, Respiratory, Women's Health, Osteoporosis and Pain in the different regions Merck operates in worldwide. In his current role, since March 2014, Nathan is Executive Director Medical Affairs leading a team of 40 medically trained Professionals who execute the Medical Affairs activities across Scandinavia and the Baltic States. He currently operates from Copenhagen, Denmark.

After conducting some research projects in Dermatology and the Ear Nose & Throat domain, Nathan became involved as researcher in an intense collaboration between the Belgian Academic Rheumatology Departments related to the EAP study; University of Ghent, Catholic University of Leuven, Catholic University of Brussels. The EAP study helped to establish the value of the DAS28 score for selection of rheumatoid arthritis (RA) patients for anti-TNF treatment according to the Belgian reimbursement criteria. In 2005 Nathan set up the ASPECT study investigating the epidemiology of ankylosing spondylitis (AS) and the start of anti-TNF use for AS in Belgium. When Nathan was working in Madrid he engaged in research collaboration between the collaborators of the ASPECT study and the University of Cordoba and Madrid (Regisponder study) which lead to insight in the importance of hip disease in the prognosis of ankylosing spondylitis. During his time in Madrid, he became interested in outcome prediction, which over the course of several years, resulted in a number of publications which are the core of this thesis.
Between 2008 and 20014, Nathan was research physician of several multi-center, multi-country randomized controlled studies. The design, conduct analysis and publication of these initiatives were done in collaboration with well-known rheumatology departments across Europe and included large projects such as the REMARK, RE-CUBE and GO-MORE studies investigating dose optimization of anti-TNF in RA, the RESPOND study investigating the value of anti-TNF in methotrexate naive Psoriatic Arthritis (PsA) and the INFAST study investigating the value of anti-TNF combined with naproxen versus naproxen alone and the possibility to discontinue anti-TNF for patients with Axial Spondyloarthritis (SpA) and the RADAR study on referral strategies for axial spondyloarthritis.

Nathan has presented different parts of this research during oral presentations at the ACR meeting in 2008 and 2010 and the EULAR meeting in 2011 and 2013 and has had numerous poster presentations at different meetings including the Belgian Society of Rheumatology meeting, APLAR, ACR and EULAR since 2007.

Publications included in this thesis

The epidemiology of ankylosing spondylitis and the commencement of anti-TNF therapy in daily rheumatology practice.

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Nathan Vastesaeger designed the study, coordinated the implementation and acted as study physician during the execution of this study, he supervised data analyses and participated in the interpretation of the results. He assisted with the writing of publications resulting from the study.

All authors are responsible for the work described in this paper. All authors were involved in drafting the manuscript and/or reviewing the manuscript for important intellectual content. All authors provided final approval of the version to be published.

DAS28 best reflects the physician's clinical judgment of response to infliximab therapy in rheumatoid arthritis patients: validation of the DAS28 score in patients under infliximab treatment.

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Nathan Vastesaeger helped coordinate the data collection and contributed to the analysis plan of this research. He participated in the study design and approved the final version of the manuscript.
BVC and SVL performed the statistical analysis, constructed the datasets and drafted the manuscript under the direct supervision of LB and FDK. RW, PD, FVdB, EV, HM, LDC, AP, MM, LV and FDK recruited and followed-up the arthritis patients. BVC, SVL, BW, NV, AG, LB, RW, PD and FDK participated in the study design. RW and PD were the initial investigators of the Belgian infliximab expanded-access program, in which the patients were enrolled. All authors have read and approved the final manuscript.

A pilot risk model for the prediction of rapid radiographic progression in rheumatoid arthritis.

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Nathan Vastesaeger was inventor of this method do predict efficacy which on May 5th, 2008 applied for patent as MATRIX MARKER MODEL AND METHODS FOR ASSESSING AND TREATING ARTHRITIS AND RELATED DISORDERS; Patent application number: 20100145901 and was issued on June 10th, 2010. He initiated and coordinated the analyses and interpreted the results. He was the principal writer of the manuscript.

All authors contributed to the study design, the analysis and interpretation of the data, and the preparation of and decision to submit the manuscript for publication.

Prediction of Remission and Low Disease Activity in DMARD-refractory Patients with RA Treated with Golimumab.

Vastesaeger N, Garcia Kutzbach A, Amital H, Pavelka K, Lazaro A, Moots RJ, Wollenhaupt J, Zerbini CAF, Louw I, Combe B, Beaulieu A, Schulze-Koops H, Dasgupta B, Fu B, Huyck S, Weng HH, Govoni M, Durez P.
Submitted manuscript.

Nathan Vastesaeger designed the GO-MORE study, was responsible to coordinate the implementation and acted as study physician during the execution of this multi-country study. He supervised data analyses and interpreted the data. He was the principal writer of this manuscript.
All authors are responsible for the work described in this paper. All authors were involved in drafting the manuscript and/or reviewing the manuscript for important intellectual content. All authors provided final approval of the version to be published.

Predicting the outcome of ankylosing spondylitis therapy.

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Nathan Vastesaeger initiated the analysis and interpreted the data and coordinated the proceeding of the statistical analysis of this post-hoc research initiative. He was the principal writer of the manuscript.
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ASDAS high disease activity versus BASDAI elevation in patients with ankylosing spondylitis as selection criterion for anti-TNF therapy.

Vastesaeger N, Cruyssen BV, Mulero J, Gratacós Masmitjá J, Zarco P, Almodovar R, Font P, Juanola X, Collantes-Estevez E; REGISPONSER Working Group.
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Nathan Vastesaeger set up the research collaboration between the researchers in Spain and Belgium. He initiated and supervised the analyses, interpreted the data and was the principle writer to this manuscript.
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Efficacy and safety of infliximab plus naproxen versus naproxen alone in patients with early, active axial spondyloarthritis: results from the double-blind, placebo-controlled INFAST study, Part 1.

Sieper J, Lenaerts J, Wollenhaupt J, Rudwaleit M, Mazurov VI, Myasoutova L, Park S, Song Y, Yao R, Chitkara D, Vastesaeger N; All INFAST Investigators.
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Nathan Vastesaeger helped design this study, was responsible to coordinate the implementation and acted as study physician during the execution of this study. He supervised data analyses, interpreted the data and helped with the writing of the study report and manuscripts of the study.

All authors are responsible for the work described in this paper. All authors were involved in drafting the manuscript and/or reviewing the manuscript for important intellectual content. All authors provided final approval of the version to be published.

Maintenance of biologic-free remission with naproxen or no treatment in patients with early, active axial spondyloarthritis: results from a 6-month, randomised, open-label follow-up study, INFAST Part 2.

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Nathan Vastesaeger helped design this study, was responsible to coordinate the implementation and acted as study physician during the execution of this study. He supervised data analyses, interpreted the data and helped with the writing of the study report and manuscripts of the study.

All authors are responsible for the work described in this paper. All authors were involved in drafting the manuscript and/or reviewing the manuscript for important intellectual content. All authors provided final approval of the version to be published.

Partial Remission in Ankylosing Spondylitis and Non-Radiographic Axial Spondyloarthritis and Associations Between Partial Remission and Baseline Disease Characteristics During Treatment With Infliximab Plus Naproxen or Naproxen Alone.

J Sieper, M Rudwaleit, J Lenaerts, J Wollenhaupt, L Myasoutova, S Park, Y Song, R Yao, S Huyck, M Govoni, D Chitkara, N Vastesaeger
Submitted

Nathan Vastesaeger helped design this study, was responsible to coordinate the implementation and acted as study physician during the execution of this study. He supervised data analyses, interpreted the data and helped with the writing of the study report and manuscripts of the study.

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Response to 'Feasibility of tailored treatment based on risk stratification in patients with early rheumatoid arthritis'.

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Nathan Vastesaeger took the initiative to write this letter to the editor and was the primary writer of the manuscript.

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Outcome-based anti-TNFα treatment decisions in Rheumatoid Arthritis and Axial Spondyloarthritis.
Nathan Vastesaeger, Filip Van den Bosch, Jochen Sieper, Dirk Elewaut
Submitted

Nathan Vastesaeger took the initiative to write this review and was the primary writer of the manuscript.
All authors are responsible for the work described in this paper. All authors were involved in drafting the manuscript and/or reviewing the manuscript for important intellectual content. All authors provided final approval of the version to be published.

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Submitted

List of Acronyms

ACPA	Anti-Citrillunated Protein Antigen
ACR	American College of Rheumatology
ACR20, ACR50, ACR70	20%, 50% or 70% improvement in the American College of Rheumatology criteria for response in rheumatoid arthritis
Act	Activity
AS	Ankylosing Spondylitis
ASAS	Assessment of Axial Sponyloarthritis International Society
ASAS20, ASAS40	20% or 50% improvement in the Assessment of Axial Sponyloarthritis score
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASDAS-C	Ankylosing Spondylitis Disease Activity Score using CRP instead of ESR
Anti-CCP	Anti-Citrulinated Citric Proteine
Anti-TNF	Anti-Tumor Necrosis Factor Alpha agent
ASPECT	Ankylosing Spondylitis in Practice Epidemiological Cross-sectional Trial: Cross-Sectional Epidemiological study of AS in rheumatologist practice in Belgium
ASPIRE	Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset: randomized controled study comparing IFX+MTX vs MTX+PBO in DMARD naïve early RA
ASSERT	Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy: randomized controlled study comparing IFX to PLB in AS patients failing NSAIDs
ATTRACT	Anti–Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy: randomized controlled study comparing IFX vs PLB in rheumatoid arthritis patients failing treatment with DMARDs
AUC	Area Under the Curve
Axial SpA	Axial Spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASDAI50	Improvement of 50% in the Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BeSt	The Behandeling Strategieen Study: randomized controlled study comparing different step-up and top-down treatment strategies aiming to achieve remission
CD	Crohn's Disease
CDAI	Clinical Disease Activity Index
CI	Confidence Interval
CRF	Case Report Form
CRP	C-Reactive Proteine
CS	Corticosteroids
CVD	Cardiovascular Disease
DIP	Distal Inter-Phalangeal joint
EAM	Extra-Articular Manifestation
EAP	Expanded Access Program: Prospective open label study with IFX in patients with severe RA refractory to DMARDs
EMA	European Medicines Agency

EQ-5D	EuroQoL = European Quality Of Life Assessment
ESPOIR	Prospective Epidemiological study of early Rheumatoid Arthritis in France
EULAR	European League Against Rheumatism
ESR	Erythrocyte Sedimentation Rate
ET	Early Termination
DAS28	Disease Activity Score using 28 joint count
DMARD	Disease Modifying Anti-Rheumatic Drug
FCA	Friction Cost Approach
GO-MORE	6-month prospective study of golimumab in RA patients failing DMARDs followed by a randomized controlled study of treatment optimization with IV golimumab vs standard golimumab
GO-RAISE	Randomized controlled study comparing golimumab to placebo in Ankylosing Spondylitis Patients failing NSAIDs
HAQ	Health Assessment Questionnaire
HCA	Human Capital Approach
HCQ	Hydroxychloroquine
HLA-B27	Human Leucocyte Antigen B27
HLA-DR	Human Leucocyte Antigen-DR
HCA	Human Capital Approach
IBD	Inflammatory Bowel Disease
IFX	Infliximab
IL	Interleukine
IMR	Inter-Malleolar Distance
INFAST	Infliximab as First Line Therapy in Patients with Early Active Axial Spondyloarthritis Trial: part 1 consists of a randomized comparison of IFX+NPX versus PBO+NPX in patients who have not failed NSAIDs; part 2 is a randomized withdrawal comparing NPX vs PLB in patients who went in remission by the end of part 1
INFLIXISPINE	Randomized contolled study comparing infliximab to placebo in HLA-B27 positive, MRI positive early Axial SpA patients who have failed NSAIDs
IQR	Inter Quartile Range
ITT	Intention To Treat
KBVR-SRBR	Koninklijke Belgische Vereniging voor Rheumatologie – Societe Royale Belge de Rhrumatologie
LDA	Low Disease Activity
ln	Variable normalized by taking the natural logarithm
MASES	Maastricht Ankylosing Spondylitis Enthesitis Score
MMP	Matrix Metallo Proteinase
mono	Monotherapy
MRI	Magnetic Resonance Imaging
mSASSS	Modified Stoke Ankylosing Spondylitis Spine Score
MTX	Methotrexate
NA	Not Available
NICE	National Institute of Clinical Excellence
NNT	Number Needed to Treat
NPV	Negative Predictive Value
NPX	Naproxen
NSAID	Non-Steroidal Anti-Inflammatory Drug

NYm_Def	Definite Ankylosing Spondylitis according to the New York Modified Criteria
OP	Osteoporosis
OR	Odds Ratio
PBO	Placebo
PGA	Patient Global Assessment
Phys	Physician
PhGADA	Physician Global Assessment of Disease Activity
PPV	Positive Predictive Value
PRO	Patient Reported Outcome
Pt	Patient
PtGADA	Patient Global Assessment of Disease Activity
QoL	Quality of Life
RA	Rheumatoid Arthritis
RANKL	Receptor activator of nuclear factor kappa-B ligand
REGISPONSOR	Prospective Epidemiological Cohort Study of Ankylosing Spondylitis in Rheumatologist Practice in Spain
RCT	Randomized Controlled Trial
ROC	Receiver Operating Characteristics Curve
ROC-AUC	Area Under the Receiver Operating Characteristics Curve
RRP	Rapid Radiographic Progression
SD	Standard Deviation
SDAI	Simplified Disease Activity Index
SE	Standard Error
SEM	Standard Error of the Mean
SF-36	Short Form 36 quality of life assessment
SHS	Sharp van Der Heijde Score
SQRT	Variable normalized by taking the squared root
SvH	Sharp van Der Heijde Score
SI	Sacroiliitis
SJC	Swollen Joint Count
SJC66	Swollen Joint Count based on the 66 joint count
SpA	Spondyloarthopathy
SPSS	Software package for statistical analysis
SSZ	Sulphasalzine
SWEFOT	Swedish Pharmacotherapy Study: Randomized Controlled Study comparing treatment with IFX + MTX versus DMARD triple therapy in patients who do not achieve low disease activity with MTX alone
TEAE	Treatment-Emergent Adverse Events
TJC	Tender Joint Count
TJC68	Tender Joint Count based on the 68 joint count
TNF	Tumor Necrosis Factor
UC	Ulcerative Colitis
UK	United Kingdom
ULN	Upper Limit of Normal
US	United States
USD	United States Dollars
VAS	Visual Analogue Scale
Wk / w	week

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