Measuring and monitoring outcomes in undifferentiated and rheumatoid arthritis

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Chapter 1

Introduction

ARTHRITIS: RHEUMATOID VERSUS UNDIFFERENTIATED ARTHRITIS

Rheumatoid arthritis (RA) is a prevalent (0.5-1/100 persons) auto-immune inflammatory disease which primarily affects the joints, but can also cause extra-articular manifestations.[1-3] Uncontrolled disease may lead to structural joint damage, disability, reduced quality of life, work productivity loss and premature mortality.[4-6] To date, the pathogenesis of RA is largely unknown, although some genetic risk factors and environmental factors have been suggested to contribute to the etiology.[7-9]

Until recently, RA has been classified according to the 1987 revised American College of Rheumatology (ACR) criteria[10] including: morning stiffness (for at least one hour); arthritis of at least three joints; arthritis of hand joints; symmetrical joint swelling; subcutaneous rheumatoid nodules; positive rheumatoid factor and typical radiographic changes on hand and wrist radiographs. Patients are classified as having RA, when at least four out of these seven criteria are present for at least six weeks. The 1987 ACR criteria were developed as classification rather than diagnostic criteria, to harmonize disease definitions used in clinical trials. However, the 1987 criteria lack sensitivity and specificity for early disease and reflect hallmarks of the chronic disease state.[11]

The 'window of opportunity' hypothesis states that treatment in an early phase of RA (e.g. when still in the phase of undifferentiated arthritis (UA)) can prevent progression or even establish reversal of the inflammatory process to a pre-disease state.[21] Therefore, it is preferable to diagnose and start treatment for RA in an early stage to maximize opportunity for steering the disease course towards a better outcome. This is why new criteria[12;13] have recently been developed, classifying RA in patients with recent onset arthritis in an earlier phase than was previously possible with the 1987 criteria.[14-16] As a consequence of classifying earlier, in some newly classified patients, their future disease course may not require medication or show persistence of symptoms and signs. As also the new criteria are developed to classify rather than identify RA, it remains a clinical process to diagnose RA.[17]

In patients presenting with recent onset arthritis it is often difficult to distinguish early RA from other types of inflammatory oligo- or polyarthritis. Undifferentiated arthritis is poorly defined as arthritis not fulfilling any of the classification criteria for a rheumatological disease.[18] Depending on baseline characteristics in various early arthritis cohorts, approximately one third of UA patients will eventually develop RA (according to 1987 criteria) and thus may be 'RA detected in an early phase', but the majority of UA patients has self-limiting disease.[18-20] Since the latest changes in classification criteria for RA, the characteristics of patients with 'UA' appear to also have changed. Literature in actual UA patients as oppose to early RA patients is scarce.

Despite the development of various prediction models [21-23], outcome prediction in patients with UA is difficult and early treatment is associated with the risk of overtreatment for patients with self-limiting disease.

Outcomes in arthritis and treat to target

To assess outcomes in (rheumatoid) arthritis patients numerous parameters are available. Properly defining outcomes and outcome thresholds ensures that results of interventions in clinical trials can be compared and uniformly interpreted. For UA, persistence of symptoms and signs can be considered an outcome, as well as a more clinically based 'physician's decision to start anti-rheumatic therapy'. Both in UA and RA, disease activity, structural damage as seen on radiographs of the most commonly affected joints, physical disability, health related quality of life (HRQoL) and mortality are amongst the most widely used outcomes.[24-27] The instruments used for the assessments of these outcomes have been further adapted during the past decades, yet limitations in their performance remain.

Outcomes are also important in light of the recent shift in the management of RA towards a treat to target approach.[28] It has been shown that not only regular assessments of disease activity in RA contribute to better disease control, but also therapy adjustments based on a pre-defined level result in improved outcomes.[29-31] International recommendations for the management of RA also emphasize a targeted approach aiming for remission or at least low disease activity by early introduction of disease modifying anti-rheumatic drugs (DMARDs), the use of methotrexate as an anchor drug and early introduction of combination therapy (which may include a biological agent in patients with poor prognostic factors).[28;32-34] Nevertheless, it is unknown which targets should be set, how and how strict should be monitored, and in what way this impacts on the outcome of RA.

Imaging

Inflammation in the joints leads to joint damage, of which both may result in physical disability, decreased health related quality of life and work productivity loss.[35;36] Inhibition or prevention of inflammation and subsequently joint damage, can prevent future disability and other unfavorable outcomes, and is therefore an important goal in anti-rheumatic treatment.[36;37] In clinical trials as well as in daily practice, different imaging modalities are used in arthritis patients to assess inflammation of the joints and the structural joint damage that is the measurable result after periods of active inflammation.[38;39] These imaging modalities include conventional radiographs, magnetic resonance imaging (MRI) and ultrasound (US).

Historically, radiographs of hand and feet are the most widely used and best manner of assessing joint damage. Radiographic damage is an objective measure, can be scored blinded,

randomized in time order, and damage progression can be measured over time.[40] Radiographs could display bony damage to joints, thinning of cartilage, and ligament or soft tissue abnormalities seen as malalignment in patients with arthritis.[40] Typical radiographic damage in RA includes erosions, joint space narrowing (JSN) and juxta-articular osteopenia.[41] Erosions are seen as cortex interruptions and reflect damage to the bone, whereas JSN is thought to reflect damage to the cartilage. Erosions are indicative for RA, yet single erosions may not be disease specific as erosions can also occur in for example psoriatic arthritis or gout, although the shape of the erosions in the respective disorders may differ. A recent EULAR initiative defined erosiveness typical for RA quantitatively when an erosion is seen on radiographs of both hands and feet in three or more separate joints at specific locations.[42]

Several scoring methods have been developed for the quantitative assessment of radiographic joint damage including different sets of joints, but in general hands and feet are included. Damage in these joints has been shown to associate with large joint damage, thereby implying that monitoring and prevention of joint damage in hands and feet is sufficient for the prevention of damage in the larger joints.[43]
Global scoring methods (per patient or joint) are available[37;44;45], but also methods scoring erosions and JSN separately.[46;47] Both factors were shown to carry independent information and thus assessment of both features is preferable.[41] Sharp was the first to develop a radiographic scoring system for erosions and JSN in hands and wrist, after formally testing which joints should be included in this system based on their involvement in RA and the reliability of scoring them.[48] The modification of the Sharp score by van der Heijde also included the feet in the scoring system, which are frequently displaying joint damage in an earlier phase of the disease and thus provides additional information.[49-51]. Also (sub)luxation was introduced as part of the JSN scoring in this modification.

Increased awareness of the potential treatment benefit in an early phase of the disease leads to earlier diagnosis and consequently more patients initiating treatment before radiographic damage is present.[52;53] Subsequently, other imaging modalities are progressively introduced as potentially more sensitive methods to detect joint damage or inflammation. US is more sensitive to detect synovitis than clinical examination[54-56] and could be used to rule out synovitis in case of uncertainty or absence of clinically inflamed joints. It has been shown that in patients in remission, abnormalities such as gray scale synovitis and power Doppler activity can be present[57;58], and that these abnormalities may be associated with joint damage on conventional radiographs.[59]

Likewise, MRI detects early changes in bone and cartilage and displays abnormalities such as erosions, bone marrow edema and synovitis, often without signs of damage on conventional radiographs.[60;61] MRI and US can predict future structural damage[53;62;63], although regression

of abnormalities may also occur, and the clinical relevance of these abnormalities on either US or MRI is not fully clarified to date.

Ongoing research is examining the additional value of these imaging techniques next to clinical and serological tests. Most studies on imaging techniques have concentrated on early RA patients. To assess the value of imaging techniques for patients with UA we have performed a systematic literature review to examine the diagnostic and prognostic value of radiographs, MRI and US (***Chapter 2 and 3***). These papers were used as the scientific base for the 3E recommendations on the management and follow-up of undifferentiated arthritis as displayed in ***Chapter 4***.

Physical functioning in relation to structural damage

Steinbrocker was the first to develop a classification method to measure functional disability on a four point scale[45], but the sensitivity to change of this measure was poor.[64] Nowadays, physical disability is nowadays usually assessed with the Health Assessment Questionnaire (HAQ), one of the most validated patient questionnaires in RA.[65] The original HAQ was developed in the 1980s and is an important outcome measure. It has shown to be associated with joint damage, quality of life, disease activity, work related measures and even mortality.[66-70] The initial HAQ comprised of five dimensions, which are undesirable for patients: death, disability, discomfort, iatrogenic effects and costs. Currently, a shorter version of the total HAQ, the HAQ disability index (HAQ-DI), is most frequently used and translated into more than over 60 languages or dialects including Dutch.[71;72] The HAQ consists of 24 questions regarding eight distinct categories ('dressing', 'arising', 'eating', 'walking', 'hygiene', 'reach', 'grip' and 'usual activities'). The total score (range 0-3) is calculated by summing the highest score per category and dividing the total by eight. If patients use any aids or devices for certain daily activities a minimum score of two per category is awarded. The HAQ is of immediate importance to patients and physicians as it reflects day-to-day physical abilities and is related to reversible components such joint pain and swelling due to inflammation, but also to more irreversible components such as damage to joints, deformations, or muscle weakness.[73]

The relationship of physical functioning with radiological damage has been extensively reviewed in literature.[35;74;75] Until now, the general paradigm states that radiological damage accumulates in time and causes limitations in physical functioning. A J-shaped curve has been described for physical functioning over time in which initially, when starting treatment, a marked improvement in HAQ is seen, whereas after 3-6 years of follow-up the HAQ score irreversibly starts to increase again due to accumulated joint damage.[36;37] Improved targeted treatment strategies, for example in the BeSt study, have been shown to prevent this deterioration after the initial improvement.[76] Yet, limitations in physical functioning due

to radiological damage remain important for certain subsets of patients. Recently, it has been suggested that in particular JSN on radiographs, rather than erosive damage, is associated with impaired physical functioning.[77] More JSN was associated with higher mean HAQ scores in patients in clinical remission. However, it remains unclear what the influence of damage in distinct joint groups on this relationship is, and also whether this relationship is still present in a longitudinally measured cohort. In ***Chapter 5*** we have addressed these issues.

Disease activity

Active disease in RA patients manifests through inflamed joints, usually in a symmetrical pattern and with frequent involvement of the small joints of hands and feet. Generalized morning stiffness may be a pronounced symptom. Other signs include rheumatoid nodules and swelling and tenderness of joints on examination. In laboratory tests elevated acute phase reactants (erythrocyte sedimentation rate, (ESR) and C-reactive peptide, (CRP)) can be found and patients may have inflammation related anemia. Evaluation of signs and symptoms over time as indicators of disease activity is advised to monitor patients' response to treatment.[34]

To harmonize and compare outcomes in clinical trials several core sets of disease activity indicators were defined. Moreover, different composite scores were developed by several groups, all based on the assumption that combinations of these indicators yield a more valid estimate of current disease activity.[78-80] EULAR/ACR recommendations on reporting disease activity in clinical trials advise the reporting of disease activity states and responses, both in composite measures and as individual measures. In addition, the course over time of these measurements should be reported.[81;82] Nowadays, it has been recognized that the composite scores are also useful to follow patients in daily clinical practice and to use a pre-specified level of disease activity as a treatment goal for therapy adjustments in individual patients in order to improve long-term outcomes, such as physical ability, HRQoL and radiographic damage progression.[29-31;83]

The Disease Activity Score (DAS)

The disease activity score (DAS) was the first score to be developed for the assessment of disease activity and included a swollen joint count (out of 44 joints scored), the Ritchie Articular Index (RAI) assessing tenderness in 53 joints (some scored per group), ESR and a visual analogue scale for patient's assessment of global health (VAS-GH).[84] The formula for the DAS is as follows: $0.54 * \sqrt{RAI} + 0.0065 * SJC + 0.33 * \ln(ESR) + 0.007 * VAS\text{-}GH$. The RAI includes a graded assessment for joint tenderness (0=no pain on examination; 1=pain on pressure, 2=pain and winced 3= winced and withdrew).[85] The DAS strongly relates to disability, joint damage and quality of life.[36;37;86]

Later, alternative versions of the original DAS using CRP rather than the ESR, as well as simplifications have been described, using only 28 joint counts for tenderness and swelling (DAS28).[87] Also, a composite score with a simplification in calculations (scoring 28 joints) has been described (simplified disease activity index (SDAI))[88;89] and further simplifications excluding the lab result of the acute phase reactants (clinical disease activity index (CDAI); modified DAS28)[90] are also available.[90] These composite scores could be used in case ESR or CRP are absent at time of the clinical consultation. All these adjusted measures excluded the feet for the assessment, mainly with the argumentation that examination of the feet is difficult and time consuming, although arthritis in the feet is a common problem in RA.[85]
A limitations of the DAS is the inclusion of the RAI which assesses joint tenderness on a grade scale (range 0-3), which can introduce additional interobserver error and complicates clinical assessments.[91] Whether this grading of joint tenderness is necessary for the assessment of disease activity or whether a simpler approach can be followed including pain as a yes/no variable in different amounts of assessed joints is discussed in ***Chapter 6***.

The Visual Analogue Scale (VAS)

For the assessment of disease activity both patient and physician can use a visual analogue scale (VAS), usually scored from 0-100 mm. Different VAS scores exist: a VAS score for pain, a VAS score for morning stiffness, a VAS score for assessment of general health (VAS-GH), but also a VAS for the assessment of disease activity. Within the DAS, the patient's VAS for general health is used, but sometimes this VAS-GH is replaced by the VAS for disease activity, although the latter is not formally validated as part of the DAS. In ***Chapter 6*** we validated the DAS including the VAS for disease activity.

In alternative versions of the DAS, such as the CDAI and SDAI, both a patient and a physician derived VAS for disease activity are used.[88;90] It is of interest to know how patients score their disease activity compared to physicians and which factors are influencing differences if present. This issue is of importance when considering patients satisfaction with our healthcare, as patients and health care providers have been shown to differ in their perspectives on health status. [92;93] Therefore, we investigated the difference between the patient and physician derived VAS for disease activity and its influencing factors in ***Chapter 7***.

Disease remission

Remission is the ultimate goal of RA treatment an can be defined as absence of disease (activity). It has been demonstrated that DAS remission is an attainable goal for many patients with the current treatment possibilities[94], and some patients even achieve drug free remission.[95;96] Many definitions of remission are available, often using cut-off points from composite scores of disease activity. It has been shown that these various remission definitions classify patients

with different levels of disease activity as being in remission.[94;97;98] Recently, new remission criteria have been developed by the ACR/EULAR[99;100], defining remission at certain absolute levels of a patient derived visual analogue scale for global health, swollen and tender joints counts and the CRP.

It has been argued that remission definitions should include a reference to time and a specification of the used medication to differentiate between long or short-term remission and drug free remission or remission while on anti-rheumatic drugs. Although not included in the current remission definition, other important factors to incorporate in a definition could include the absence of joint damage progression (by whichever method determined), absence of deterioration of disability, and absence of impaired quality of life. Furthermore, it is questionable whether the more strict remission definitions denote clinically significantly different states and whether they are relevant for the patient's outcome.

As treating to target is becoming the advocated strategy, it is necessary to investigate the impact of different definitions of remission on outcomes. In ***Chapter 8*** we compared nine composite scores and new ACR/EULAR remission criteria and determined the proportion of patients classified as in remission and other disease activity levels for each composite score, as well as the association with functional ability and structural joint damage.

Health Related Quality of Life

Health Related Quality of Life (HRQoL) can be assessed with generic or disease specific instruments. Although disease specific instruments could comprise more factors relevant to RA patients, generic instruments allow benchmarking against other conditions and can therefore be valuable for the development of health care management strategies.
HRQoL can be defined as the impact of (lack of) health on an individual's functional ability and perceived well-being in life, but also reflects patient's satisfaction and response to the disease.[25]

The Short-Form-36 is frequently used for the assessment of generic HRQoL and is based on three domains of health (functional status, well-being and overall evaluation of health) comprising eight scales: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health.[101] The total score of the SF-36 ranges between 0 and 100 with a higher score representing better HRQoL. Two summary measures, in which the relative contribution of the eight scales varies, can be calculated with the SF-36: a physical component scale (PCS) and mental component scale (MCS), and both can be compared with population-based norms.

HRQoL is an outcome measure reflecting a broad patient perspective on health, and it is therefore of interest to know how HRQoL relates to active disease. High disease activity has been related to impaired quality of life before[86;102;103] and disease activity steered treatment may thus lead to improved HRQoL outcomes. The magnitude into which achieving a certain disease activity *level*, and specifically remission in comparison to low disease activity, relates to better quality of life is less well known. This is especially interesting in the light of the treat to target paradigm.[28;34] In addition, the longitudinal relationship between HRQoL and disease activity levels has not been studied before. These relationships are investigated in ***Chapter 9***.

Implementation of regular monitoring in daily practice

Optimization of treatment resulting in improved outcomes in RA is a combined effort of physician and patient. To stimulate this collaboration, inclusion of the patient's perspective is becoming increasingly important and already frequently introduced in rheumatologic research, for example when determining a definition of a disease flare[104], treatment goals[105;106], or when defining benefits from treatment.[107] Patients are also more and more involved in the development of guidelines and recommendations, although in some more prominent than in others.[34;108;109] Core sets of health domains specifically for RA patients have been established and adjusted.[110-112]

Furthermore, patient reported outcomes (PROs), such as the patient VAS for disease activity or questionnaires assessing functional ability, are being recognized as important outcome measures[113;114], and these types of outcome measures have shown to be as sensitive to change as physician derived outcomes.[115-117] PROs can be derived from patients or actually measured by patients themselves for example by self-assessment of pain and swelling in their joints and subsequent calculating a patient derived composite score for disease activity. However, the assessment of swollen joints by patients is unreliable to date[118] as patients and physicians have shown a large disconcordance in their perceptions of swollen joints.[105;106;119;120]

Nonetheless, patients can be of great value recording other indicators of active disease, such as the VAS, their functional ability or HRQoL, for example by completing questionnaires. These questionnaires can then be incorporated into electronic medical records (EMRs), which have been proven to be reliable for quality assessment and allow for benchmarking between health care providers or hospitals.[121-123] Self-monitoring, through direct access to (parts of) such databases incorporated in electronic patients files can improve sense of ownership of disease monitoring. Since resources in health care are becoming scarce, electronic self-monitoring can be a tool to acquire useful clinical data without the requirement of face to face contact with health care providers. Patients and physicians attitude towards the use of EMRs in general is positive.[124;125] Even so, there may be practical problems that need to be addressed before all patients will use these tools. A first necessary step for the implementation

of systematic monitoring including patient perspective is acceptability and feasibility in daily practice by patients. We used the METEOR program[126] to assess feasibility and acceptability of regular monitoring of physical functioning in daily clinical practice, either home based or at the outpatient department before the visit to the rheumatologist. *(**Chapter 10**)*

Thesis outline

The first part of this thesis describes the work of the 3E initiative, an initiative in the field of rheumatology aiming at the promotion of evidence-based medicine by formulating practical recommendations addressing clinical problems. We performed two systematic literature reviews to determine the value of imaging modalities in UA patients. These papers served as a basis for developing recommendations on how to investigate and follow-up UA patients. (***Chapters 2-4***) In RA patients, we examined the relationship of radiological joint damage with physical functioning and more specifically if joint space narrowing is more importantly associated with impaired functioning than erosive joint damage. We also evaluated if joint damage in certain joints groups (either joint space narrowing or erosions) can explain higher HAQ scores. (***Chapter 5***)

The second part of this thesis focussed on research questions regarding disease activity. We investigated whether different versions of the DAS, with a reduced number of scored joints, without exclusion of the feet, would still be valid to use. We also wanted to ascertain that the DAS, using a patient VAS for disease activity would be as accurate as the DAS using patients VAS for general health. (***Chapter 6***) Furthermore, we studied if patients and physicians rated disease activity with a VAS differently and identified which factors explained these possible differences. (***Chapter 7***)

Remission seems to be the optimal treatment goal. However, different definitions of remission exist, based on the different composite scores of disease activity. It remains to be determined if these different remission criteria have different associations with physical disability and joint damage. We have investigated this issue in

Chapter 8. Additionally, we assessed the relationship between active disease and HRQoL: 1) Are patients displaying or achieving lower disease activity demonstrating a better HRQoL compared to patients in higher disease activity? and 2) Is there extra benefit in patients displaying or achieving remission versus patients in low disease activity? (***Chapter 9***)

The final part of this thesis comprised of the implementation of monitoring in daily clinical practice and evaluated the feasibility of autonomic systematic monitoring of physical functioning. (***Chapter 10***) In ***Chapter 11*** the findings of this thesis are summarised and discussed.

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Chapter 2

The value of conventional radiographs in undifferentiated arthritis: a systematic review

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ABSTRACT

Objective: To perform a systematic literature review on the diagnostic and predictive value of conventional radiographs (CR) in patients with undifferentiated arthritis (UA).

Methods: We performed an extended search using Medline, Embase, the Cochrane library, and abstract from the 2007 and 2008 meeting of the American College of Rheumatology and the European League Against Rheumatism. Articles were included based on predefined inclusion criteria, and quality was assessed by using validated quality scales.

Results: In total, 25 articles were included from 6003 retrieved references. Five articles described a pure UA population, 20 articles described a mixed population (mostly rheumatoid arthritis (RA) and UA). In studies on UA, erosions on CR were strong predictors of RA diagnosis (positive likelihood ratio (LR+) 3.5-10.9; odds ratio 7.6 and 8.7). In a more heterogeneous mixed population, 20 studies reporting on 11 cohorts found a relationship between CR findings and a subsequent diagnosis of RA. LR+ for erosions and/or bony decalcifications ranged from 1.8-9.7 and there was a greater prevalence of erosions and higher Sharp van der Heijde score (SvdH) in the RA group at follow up. With regard to prognosis in both UA and mixed populations, an association was found between number of abnormalities on CR and poor outcome.

Conclusion: Several studies, in pure UA and mixed populations, clearly demonstrate that CR are helpful in predicting future diagnosis of RA or worse prognosis. However, absence of abnormalities on CR does not sufficiently exclude RA or other unfavorable outcome.

INTRODUCTION

Undifferentiated arthritis (UA) is an ill-defined disease entity, since it is characterized by the absence of other diseases. Establishing an early diagnosis or prognosis in patients with UA is of major importance to obtain earlier and targeted treatment, leading to better outcomes for these patients. [1] To understand and learn more about this group of patients, "How to investigate and follow up Undifferentiated Peripheral Inflammatory Arthritis (UPIA)" was chosen as the subject for the 2009 3E (evidence, expertise, exchange) Initiative in rheumatology.

The 3E initiative promotes evidence-based medicine by formulating recommendations using both data form the literature and expert opinion. [2] Seventeen countries and almost 700 experts participated in this project. In total, ten clinical questions selected by clinicians were chosen for a systematic review. The final recommendations based on the 10 different systematic reviews can be found elsewhere.[3]

We present results of the systematic reviews of one of the ten clinical questions: "What is the diagnostic and predictive value of X-ray in UPIA? Should it be performed at baseline and repeated at what interval?"

Conventional radiographs (CR) are commonly used for arthritis patients as additional tests in clinics. CR are relatively safe, inexpensive, and widely available, which makes them a convenient test in current clinical care. Radiographs can help confirm or exclude a diagnosis such as rheumatoid arthritis (RA) or psoriatic arthritis. Abnormalities on radiographs might also be valuable in predicting other outcomes in UA, such as structural damage or impaired physical functioning.[4].

At this time there are no systematic reviews that describe the importance of this test in UA for establishing either diagnosis or prognosis, since most data are collected in patients with early RA.
We assessed the diagnostic and predictive value of CR inpatients with UA by reviewing all available literature using an extensive search strategy. As part of the 3E process, an evidence based recommendation on the use of CR was then formulated afterwards by combining the results of this review and the opinion of experts.

PATIENTS & METHODS

The selected clinical question was rephrased according to the PICO method (Patients, Intervention/Index test, Comparison, Outcome)[5], which is used to translate a clinical question

into a question with epidemiological terms in order to make a literature search possible. The population was defined as the patient with UA, and conventional radiographs as intervention.

For our search there is no relevant control group. For the diagnostic search, outcome was defined as a specific diagnosis such as RA or psoriatic arthritis. Outcome in the search on prognosis was defined very broadly, in principle as every possible unfavorable outcome (e.g., progression of the disease, radiological damage, impaired physical function) and the final selection was dictated by the available literature.

Three types of studies were considered for inclusion: [1] cohort studies in which patients from a given UA population had CR at baseline and in whom the outcome after a period of follow-up was recorded; [2] retrospective case-control studies in which patients had CR at baseline and who were known to have had UA when the baseline investigation was performed; and [3] randomised controlled trials of UA patients that implicitly addressed the question of diagnostic or prognostic value, as each arm of a trial can be seen as a separate cohort study.

Medline, Embase and the Cochrane library were searched for articles published between 1950 and February 2009. The extensive search strategy *(see web appendix: www.3eupia.com)* was developed in close collaboration with a trained librarian and consisted of three parts: target population, intervention and preferred study type (diagnostic or prognostic). Abstracts presented at the 2007 and 2008 meetings of the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) were searched using the following terms: undifferentiated, undiagnosed, unclassified, early or probable arthritis. All references of selected articles and relevant reviews were hand searched for additional articles.

The selection process consisted of two phases:(1) all titles and abstracts were checked for relevant articles; and (2) the full articles were reviewed in detail and retained or excluded based on predefined criteria. Criteria included: UA patients ≥18 years of age, presence of at least one clinically swollen joint, and use of CR to predict diagnosis or prognosis in these patients. Articles were split into two groups: a pure UA group and a mixed population, where only part of the group consisted of patients with UA.

Articles included in the review were assessed for quality using validated scales. Quality assessment of diagnostic studies was performed using a scale based on the Evidence-Based Medicine Working Group Quality.[6] Assessment of the prognostic studies was done by the Newcastle-Ottawa Quality scale looking for three items: selection, comparability, and outcome. The maximum number of stars that can be awarded to a study is 9.[7] The level of evidence was determined using the scale developed by the Oxford Centre for evidence based medicine. [8] *(see web appendix: www.3eupia.com).*

Data were extracted using a predefined format and analyzed by two researchers. If necessary, corresponding authors were contacted for additional details. Likelihood ratios (LR) and confidence intervals were extracted or calculated when possible; if these data were unavailable, descriptive results were used. The higher a positive LR (LR+) and the lower the negative LR (LR-), the higher the value of the test. LR+ > 5 and LR- < 0.2 represent strong diagnostic or prognostic evidence.[6]

RESULTS

In total, 6003 references where found via Medline and Embase using the developed search strategy, of which 115 articles where reviewed in detail *(see web appendix: www.3eupia.com)*. In total, 25 articles were included, five with a pure UA population and 20 with a mixed population. The Cochrane Library did not retrieve any relevant articles, and two abstracts from the EULAR and ACR 2007/2008 had already been included in the review. Of the five studies with a pure UA population, four were diagnostic studies and one assessed prognosis. Three of these five studies were performed using the same cohort (the Leiden Early Arthritis Cohort) but with different numbers of patients included. Inclusion criteria and baseline characteristics are presented in Table 1.

Two articles, van Aken [9] and Duer [10], found a high LR+ (Table 2) for developing RA according to ACR criteria[11], the first one for erosions according to Sharp van der Heijde (SvdH) method [12] the other for Larsen grade 1. [13] In the study by van der Helm-van Mil [14], erosions were found as predictor in a univariate analysis but not in multivariate analysis. The article by van Gaalen [15] demonstrated that in a model with and without anti-cyclic citrullunated peptide antibodies the odds ratios for developing RA were moderate (table 2). Prognosis was assessed by the study of Jansen [16]. When differentiating between mild and progressive disease at 1 year, SvdH scores at baseline are significantly different (Table 3).

Of 20 studies with a mixed population that could be included, heterogeneity in inclusion criteria or baseline characteristics was far greater than in the UA group (Table 1). In total, these studies are derived from 11 cohort studies from different countries. Most studies used different features of the radiographs which makes them difficult to compare.

In general, studies found high LR+ for erosions predicting diagnosis. When using both hand and foot radiographs, LR increased in comparison to using hands radiographs only.

Bony decalcification, on the other hand, was not very informative for diagnosing RA. LR- were too high to be considered clinically important. [17-21] (Table 2). Results from the remaining

Table 1. Baseline characteristics of the included studies.

Study	n	Age years mean (SD)	Disease duration months median (range)	Follow up months	female %	RF+ %	anti CCP+ %	SJC median (range)	% RA baseline	% UA baseline	Q
UA population											
1.Van Aken 2005 (9)	326	51* (40-62)†	4 (2-7)∞	12	54	20	18	3 (2-5)∞	NA	NA	good
2.Van der Helm 2007 (14)	590	53 (16)	NR (0-24)	12	58	25	21	3 (1-5)∞	NA	NA	good
3.Van Gaalen 2004 (15)	318	49* (16-93)†	3 (0-24)	12	55	21	21	2 (1-14)	NA	NA	moderate
4.Jansen 2002 (16)	77	49* (21-93)†	3 (0-36)	12	69	18	NR	NR	NA	NA	9*
5.Duer 2007 (10)	41	55* (17-78)†	18 (6-180)	24	85	NR	NR	4 (2-18)	NA	NA	moderate
Mixed population											
1.Devauchelle 2001 (17)	258	50 (16)	NR (0-11)	30‡ (11)§	68	26	NR	4‡ (6)§	NR	NR	good
2.Devauchelle 2004 (18)	149	50 (16)	NR	NR	69	23	NR	4‡ (6)§	NR	NR	good
3.Devauchelle 2006 (20)	258	50 (16)	NR	NR	68	26	NR	4‡ (6)§	NR	NR	good
4.Saraux 2001 (19)	270	NR	NR	29‡ (12)§	68	26	NR	NR	NR	NR	good
5.Jansen 2004 (30)	279	56*(18-83)†	4 (0-24)	24	67	37	33	NR	69	NR	8*
6.Jansen 2003 (31)	362	57* (18-82)†	4 (0-24)	24	67	37	30	NR	NR	NR	9*
7.Nielen 2005 (26)	379	56 (16)	5 (4-8)	12-24	69	31	NR	NR	NR	32	9*
8.Bukhari 2003 (33)	335	55 (14)	5 (IQR 2-10)	60	70	32	NR	8 (4-14)	47	NR	6*
9.Bukhari 2002 (32)	439	55 (14)	5 (IQR 2-10)	60	71	32	NR	8 (4-14)	48	NR	7*
10.Jensen 2004 (22)	75	50* (20-82)†	3 (1-24)	24	82	42	NR	5 (2-18)	61	39	moderate
11.Knudsen 2008 (24)	75	50* (20-82)†	3 (1-24)	12	82	40	NR	5 (2-18)	61	39	moderate
12.Klarund 2000 (23)	55	50* (20-82)†	3 (0-22)	12	68	47	NR	5 (0-18)	56	24	moderate
13.Cunnane 2001 (25)	206	46 (14-84)†	6‡ (1-24)	18	63	NR	NR	9‡ (0-28)	NR	22	good
14.Daragon 2001 (27)	32	46 (19-72)†	5‡ (3)§	12	43	NR	NR	NR	NR	20	moderate

Table 1. (Continued)

Study	n	Age years mean (SD)	Disease duration months median (range)	Follow up months	female %	RF+ %	anti CCP+ %	SJC median (range)	% RA baseline	% UA baseline	Q
15.Isomäki 1987 (35)	105	NR	NR	84	NR	NR	NR	NR	NR	NR	4*
16.Isomäki 1984 (34)	275	37 (17-64)†	NR	36	NR	35	NR	7**(4)§	NR	NR	5*
17.Visser 2002 (29)	524	49* (8-90)†	3 (0-24)	≥24	53	23	NR	2 (0-14)	30	26	8*
18.Gough 1994 (21)	177	NR	4‡ (2-15)	12	NR	NR	NR	NR	68	2	7*
19.Boire 2005 (36)	165	59* (19-85)†	3 (1-12)	30	58	41	33	10 (3-58)	81	NR	8*
20.Kuriya 2008 (28)	105	45 (15)	NR (2-12)	6	77	29	35	9 (5-17)	NR	NR	moderate

*median; † range; ∞ inter quartile range; ‡ mean; § SD; ** number of inflamed joints; n=number of patients; SD=standard deviation; RF= rheumatoid factor; anti-CCP= anti-cyclic citrullinated peptide antibodies; SJC=swollen joint count; RA=rheumatoid arthritis; UA= undifferentiated arthritis; Q=quality; NR=not reported; NA=not applicable

Table 2: Likelihood ratios extracted from the different articles

Study	Prognostic factor	Outcome	LR+ (CI)	LR- (CI)
UA population				
Van Aken 2005(9)	Erosive disease (SvdH) hands or feet CRs	RA (ACR) at 1 year	3.5 (2.1-6.0)	0.8 (0.7-0.9)
Duer 2008(10)	Larsen grade 1 hand or foot CRs	RA (ACR) at 2 years	10.9 (1.4-87.3)	0.7 (0.4-1.0)
Mixed population				
Devauchelle 2001(17)	Erosions hands CRs	RA according to panel	4.1 (1.7-9.5)	0.9 (0.8-1.0)
Devauchelle 2004(18)	Erosions feet CRs	RA according to panel	8.6 (1.9-37.6)	0.8 (0.7-0.9)
	Erosions hands CRs		5.7 (1.6-19.8)	0.8 (0.7-1.0)
	Erosions hands and/or feet CRs		6.2 (2.4-15.6)	0.7 (0.6-0.9)
Devauchelle 2006(20)	Erosions and/or decalcifications hands CRs	RA according to panel	1.8 (1.0-3.1)	0.9 (0.8-1.0)
Saraux 2001(19)	Erosions and/or decalcifications hands CRs	RA according to panel	9.7 (3.4-27.2)	0.8 (0.7-0.9)
Gough 1994(21)	Erosions hands or feet CRs	Persistent disease*	6.0 (1.9-18.7)	0.7 (0.7-0.9)

LR+=positive likelihood ratio; LR-=negative likelihood ratio; CI=confidence interval; UA=undifferentiated arthritis; SvdH=according to Sharp van der Heijde method; CRs=conventional radiographs; RA (ACR)=RA according to ACR criteria; *clinical or laboratory evidence of active disease or required therapy with slow-acting drugs at 1 year

Table 3: Additional results

Study	Prognostic factor	Outcome	Results
UA			
Van der Helm 2007(14)	Erosive disease*	RA (ACR)** at 1y	Univariate erosive disease non-RA 29(7%) RA 29(16%) p<0.001, multivariate logistic regression analysis not independent predictor
Van Gaalen 2004(15)	Erosions	RA (ACR) at 1y	OR 7.6 (2.4-24.4) p=0.001 (model without anti-CCP) OR 8.7 (2.4-31.2) p=0.001 (model with anti-CCP)
Jansen 2002(16)	SvdH score	Mild or progressive disease[a]	Mild UPA 2.0 Progressive UPA 8.0 Significantly different in these 2 groups
Mixed population			
Jensen 2004(22) Knudsen 2008(24) Klarlund 2000(23)	Erosions Larsen score>0	RA (ACR) at 1y	Both different in RA, UA and UA>RA group at 1y
Cunnane 2001(25)	Erosions	RA (ACR) at 1,5y	Number of erosions lower in UA group compared to RA
Nielen 2005(26)	SvdH score	RA according to rheumatologist at 1y	Univariate analysis SvdH score associated with diagnosis, multivariate not
Daragon 2001(27)	SvdH score	RA (ACR) at 1y	SvdH score not significantly different
Kuriya 2008(28)	Erosive disease	RA (ACR) at 6m	Erosive disease not independently predictive
Visser 2002(29)	Erosions acc. SvdH score	Persistent disease§	OR 2.75

Table 3 (continued)

Study	Prognostic factor	Outcome	Results
Jansen 2003(31) Jansen 2004(30) Nielen 2005(26)	SvdH scores	Mild vs progressive disease Functional outcome†	Baseline SvdH scores different in these groups, OR 1.0-1.1
Bukhari 2003(33) Bukhari 2002(32)	Larsen scores	Onset of DMARD treatment Larsen score	Larsen scores different in patients with different DMARD onset; Larsen scores a baseline predict scores at follow up
Isomäki 1987(35), Isomäki 1984(34)	Modified Steinbrocker's classification	Poor outcome at 3y Total outcome index	X-ray stage significantly different in patients with good and poor outcome at 3y X-ray stage correlates with total outcome index
Boire 2004(36)	Erosions	Severity***	OR 3.47

* as defined by the Sharp van der Heijde method; ** diagnosis of RA according to ACR criteria; [a]Progressive disease=delta radiographic progression≥4 or radiographic damage≥10 or HAQ≥1 at one year follow up; §arthritis in at least 1 joint and/or treatment with DMARDS or steroids in the last 3 months

†progressive disease= ≥5 points change in SvdH score and Low functional outcome= HAQ≥1 High functional outcome=HAQ<1; *** M-HAQ ≥ 1.0 or belong to the upper third group of the SvH score.

diagnostic studies suggest that numbers of erosions or SvdH scores are in general different in the patients developing RA, compared to UA, but not independently predictive [22-28] (Table 3).

When predicting prognosis, such as progressive disease, onset of Disease Modifying Anti-Rheumatic Drug treatment or functional ability, several studies with numerous scoring methods found that more severe abnormalities are related to worse prognosis. [21;26;29-36] (Tables 2 and 3) There was no literature available on how often radiographs should be repeated or on other radiographic characteristics that could be helpful in diagnosing or following patients with UA.

DISCUSSION

Our systematic review summarized and evaluated all available evidence on the diagnostic and prognostic value of conventional radiographs. The evidence found in this review together with expert opinion was used to make a clinical recommendation, as part of the 3E initiative, which promotes evidence-based medicine in rheumatology. The description of the final recommendations can be found elsewhere.[3]

Several studies in both UA and mixed populations clearly showed that finding erosions on radiographs gives a high probability for developing RA or a worse prognosis, as demonstrated by high LR+. High LR- indicated that diagnostic or prognostic value in the absence of radiographic abnormalities is low [9;10;17-21]. There was no literature available on whether

repeating radiographs during the diagnostic process or performing radiography to determine prognosis are of any value.

Even with our extensive search strategy, the available evidence from the literature for a pure UA population was scarce, certainly when compared to (early) arthritis in general. Many mixed cohorts included patients that fulfilled ACR criteria at baseline and differed in the percentage of UA patients (Table 1). Nevertheless, all the studies retrieved, in both UA and mixed populations, pointed in the same direction, with high LR+ for the diagnostic and prognostic value of erosions on CR (Table 2), which increases the generalizability of the results.

A problem in estimating the performance of CRs as a diagnostic test is that there is circular reasoning, since erosions are part of the 1987 ACR criteria for RA. This may lead to an overestimation of the diagnostic value of radiographs. Consequently, the ACR criteria as a measure of outcome are open for debate. Yet, this is the outcome that was used by the majority of the studies. It is nevertheless reassuring that the studies that used a different definition (RA as determined by a panel or by persistent disease) yielded the same results.

In conclusion, radiographs can be a valuable test in patients with UA and in mixed populations for predicting diagnosis or prognosis. These finding formed the basis for the final recommendation, given in detail elsewhere [3].

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Chapter 3

The value of magnetic resonance imaging and ultrasound in undifferentiated arthritis: a systematic review

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ABSTRACT

Objectives: To perform a systematic literature review about the diagnostic and prognostic value of magnetic resonance imaging (MRI) and ultrasound (US) in patients with undifferentiated peripheral inflammatory arthritis (UPIA) and to assess if these should be done at baseline and repeated at which interval.

Methods: Medline, Embase, Cochrane and ACR/EULAR 2007-08 abstracts were searched for diagnostic and prognostic studies of any duration examining the ability of MRI/US to predict the outcome of patients with UPIA. Sensitivity, specificity, predictive values and likelihood ratios were calculated. When available, odds ratios were extracted. Quality was appraised using validated scales.

Results: Regarding MRI, 11 out of 2595 screened references were included: 2 truly undifferentiated populations and 9 mixed populations. Bone edema (LR+=4.5) and the combination of a distinct MRI synovitis and erosion pattern (LR+=4.8) increased the probability of developing rheumatoid arthritis (RA). The absence of MRI synovitis (LR-=0.2) and the absence of a distinct synovitis pattern (LR-=0) decreased the probability of developing RA. Regarding US, 2 out of 2111 references were included, both mixed populations; no data could be extrapolated for UPIA.

Conclusions: MRI bone edema and the combined synovitis and erosion pattern seem useful in predicting the development of RA from UPIA. The value of US in UPIA is still to be determined. The absence of MRI synovitis seems useful in excluding the development of RA. No data was found about the value of repeating MRI/US. Studies evaluating MRI/US in UPIA are scarce but current knowledge strongly encourages further testing in undifferentiated arthritis.

INTRODUCTION

Within the field of imaging in rheumatic diseases, large and exciting advances have been made during the last decade. Although radiographs continue to be the most widely used tool, magnetic resonance imaging (MRI) and ultrasound (US) offer advantages through more sensitive depiction of inflammatory and destructive disease manifestations.[1]

In the context of undifferentiated peripheral inflammatory arthritis (UPIA), patients' questions will focus on the likelihood of developing a well-defined rheumatic disease and on what the future holds for disease progression, persistence, functional impairment and quality of life. These are questions about future diagnosis and prognosis. The answers to these questions are vital for clinical decision making, including the choice of treatment.[2]

This manuscript is part of the 3E Initiative (Evidence, Expertise, Exchange) in Rheumatology for 2008-09.[3-5] The resulting 10 recommendations on "How to investigate and follow-up UPIA" are described in more detail elsewhere.[5] The objective of this work was to systematically review the available literature about the following question: "What is the diagnostic and predictive value of MRI and US in patients with UPIA? Should they be done at baseline and repeated at which interval?"

METHODS

Strategy and criteria for considering studies for this review

The clinical question was structured in the PIO (Patients, Participants or Problem; Intervention or Index test; Outcomes or target conditions) format[6] and the eligible types of study were defined.

Patients were defined as "adults with UPIA". The definition of UPIA is controversial and there is no widely accepted classification criterion for this condition. During the 2008-09 3E Initiative kick-off meeting, experts decided that only patients in whom clinically apparent joint swelling (synovial proliferation or synovial effusion) was observed by the rheumatologist should be included. This is in contrast to some reports that have included patients with inflammatory joint symptoms in the absence of clinically observable joint swelling (a state usually referred as "inflammatory arthralgia"). It was also emphasised that the terms "early arthritis" and "undifferentiated arthritis" should not be considered similar or interchangeable. For the current systematic review, the participants should be those patients that, after the initial visits and diagnostic investigations, did not fulfil diagnostic/classification criteria for any rheumatologic disorder. Because we anticipated that very few studies would have included truly undifferentiated populations at baseline, we also kept a record of results from studies in mixed populations (e.g. UPIA+arthralgia, UPIA+early rheumathoid arthritis [RA]), as these could be useful for extrapolating results.

The *index test* was defined as a certain MRI feature (e.g. synovial fluid, synovitis, erosion, bone edema and tenosynovitis) or US feature (e.g. US power-doppler [PD] and US grey-scale [GS] scores), as defined in the study.

The *outcomes* were defined as the development of well-defined rheumatic diseases (e.g. RA, psoriatic arthritis) or relevant disease outcomes (e.g. remission, radiographic progression). The use of internationally validated diagnostic/classification criteria (e.g. 1987 American College of Rheumatology [ACR] criteria for RA[7]) and validated outcome measures should be given more value when appraising the definition of outcome.

Three *types of studies* were considered for inclusion: 1) cohort studies in which patients from a given UPIA population had MRI or US at baseline and in whom the outcome after a period of follow-up was recorded; 2) retrospective case-control studies in which patients had MRI or US at baseline and in whom it is known that they had UPIA when the baseline investigation was performed; and 3) randomised controlled trials of UPIA patients that implicitly addressed the question of diagnostic or prognostic value, as each arm of a trial can be seen as a cohort study.

Search methods for identification of studies, selection of articles, data extraction and analysis, and quality assessment

Details of the systematic literature search can be found in the web appendix (*see web appendix: www.3eupia.com)*

RESULTS

MRI results

A total of 1734 articles and 861 meeting abstracts were found. After title and abstract screening, 15 articles,[8-22] 3 meeting abstracts (already published or later published in article format(10, 11, 23)) and one additional paper from hand search[24] were left for full paper review. The inclusion criteria were fulfilled by 11 articles,(8-17, 23) which were included in the systematic literature review. Two articles included truly undifferentiated populations(8, 23) while the other 9 included mixed populations[9-17] at baseline. A detailed flowchart can be found in the web appendix (*www.3eupia.com)*.

MRI results (UPIA populations)

Studies characteristics´ and results for UPIA populations are summarized in tables 1 and 2.

Tamai et al[23] evaluated 129 patients with UPIA; all the patients expressed rheumatic manifestations of the wrists and finger joints at study entry. At a prospective follow-up of 1 year, 75 patients (58.1%) progressed to 1987 ACR criteria for RA.[7] Contrast enhanced MRI images

Table 1: Baseline patients' characteristics in included studies (UPIA populations)

Author, year Population, No (type)	Follow-up, months (range)	Females, No (%)	Age, median, years (range)	Disease duration, median, months (range)	SJC, median, (range)	CRP, median, mg/dl (range)	ESR, median, mm/h (range)	RF+, No (%)	Anti-CCP+, No (%)	X-ray erosions, No (%)
Duer 08 (8) 41 (UPIA)	24 (NA)	35 (85.4)	55 (17-78)	18 (6-180)	4 (2-18)	1 (<0.8-12)	8 (1-54)	14 (34.1)	NR	0 (0)
Tamai 09 (23) 129 (UPIA)	12 (NA)	100 (77.5)	NR (16-80)	3 (0.5-24)	NR (0-26)	NR (0-18.4)	NR	55 (42.6)	47 (36.4)	NR

UPIA: undifferentiated peripheral inflammatory arthritis. SJC: swollen joint count. CRP: C-reactive protein. ESR: erythrocyte sedimentation rate. RF: rheumatoid factor. Anti-CCP: anti-cyclic citrullinated peptide antibodies. NA: not applicable. NR: not reported.

Table 2: Performance of each variable at baseline (UPIA populations) for the prediction of progression to RA

Author, year; No at baseline; No (%) of final diagnosis of RA; Quality	Index test	SE (%)	SP (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR- (95% CI)
Duer 08 (8) Baseline UPIA = 41 Final RA = 11 (26.8) NOS = 8 stars, LE = 2b	1) MRI synovitis and erosion pattern of RA*	64	87	64	87	4.8 (1.7-13.2)	0.4 (0.2-0.9)
	2) MRI synovitis pattern of RA*	100	60	48	100	2.5 (1.6-3.9)	0 (NA)
	3) MRI erosion pattern of RA*	64	77	50	85	2.7 (1.2-6.0)	0.5 (0.2-1.1)
	4) MRI synovitis or erosion pattern of RA*	100	50	42	100	2.0 (1.4-2.9)	0 (NA)
	5) MRI synovitis and erosion and scintigraphy patterns of RA*	45	100	100	83	Inf	0.5 (0.3-0.9)
	6) RF+	36	67	29	74	1.1 (0.4-2.8)	1.0 (0.6-1.6)
	7) CRP >1mg/dl	64	63	39	83	1.7 (0-9-3.3)	0.6 (0.3-1.3)
	8) Larsen grade 1†	36	97	80	81	10.9 (1.4-87)	0.7 (0.4-1.0)
	9) Scintigrahy pattern of RA‡	64	74	50	83	2.5 (1.1-5.3)	0.5 (0.2-1.1)
Tamai 09 (23) Baseline UPIA = 129 Final RA = 75 (58.1) NOS = 8 stars, LE = 2b	1) MRI synovitis	91	44	69	77	1.6 (1.3-2.1)	0.2 (0.1-0.5)
	2) MRI symmetric synovitis	75	59	72	63	1.8 (1.3-2.6)	0.4 (0.3-0.7)
	3) MRI bone edema	41	91	86	53	4.5 (1.9-10.7)	0.6 (0.5-0.8)
	4) MRI bone erosion	29	91	81	48	3.2 (1.3-7.8)	0.8 (0.7-0.9)
	5) MRI bone edema and/or erosion	48	83	80	54	2.9 (1.5-5.5)	0.6 (0.5-0.8)
	6) IgM-RF	52	70	71	51	1.8 (1.1-2.8)	0.7 (0.5-0.9)
	7) Anti-CCP	57	93	91	61	7.7 (3.0-20.3)	0.5 (0.4-0.6)
	8) IgM-RF and/or anti-CCP	67	67	74	59	2.0 (1.3-3.0)	0.5 (0.4-0.6)
	9) MMP-3	36	85	77	49	2.4 (1.2-4.9)	0.8 (0.6-0.9)
	10) CRP positivity	68	70	76	61	2.3 (1.5-3.6)	0.5 (0.3-0.7)
	11) 2 of the following 3: anti-CCP+ and/or IgM-RF+, MRI symmetric synovitis, and MRI bone edema and/or bone erosion	68	76	80	63	2.8 (1.7-4.7)	0.4 (0.3-0.6)
	12) Anti-CCP and MRI bone edema	29	100	100	50	Inf	0.7 (0.6-0.8)

UPIA: undifferentiated peripheral inflammatory arthritis. SE: sensitivity. SP: specificity. PPV/NPV: positive/negative predictive value. LR+/LR-: positive/negative likelihood ratio. Inf: denominator is zero. RA: rheumatoid arthritis. NOS: Newcastle-Ottawa Scale. LE: level of evidence. MRI: magnetic resonance imaging. RF: rheumatoid factor. CRP: C-reactive protein. Anti-CCP: anti-cyclic citrullinated peptide antibodies. MMP-3: matrix metalloproteinase 3. NA: not applicable. *MRI synovitis/erosion pattern of RA: several joints, not 1st carpometacarpal (CMC1) joints. †Larsen grade 1 denotes the presence of joint space narrowing, soft tissue swelling and/or juxta-articular halisteresis. ‡Scintigraphic pattern of RA: several joints, but not distal interphalangeal joints and CMC1.

were evaluated for bone edema, bone erosion and synovitis in 15 sites in each finger and wrist. Patients who were positive for at least 2 of 3 objective measures (anti-cyclic citrullinated peptide [anti-CCP] antibodies and/or IgM-rheumatoid factor, MRI-proven symmetric synovitis, and MRI-proven bone edema and/or bone erosion) progressed to RA at 1 year with a positive likelihood ratio (LR+)=2.8 and a negative likelihood ratio (LR-)=0.4 (sensitivity [SE]=68%, specificity [SP]=76%). Furthermore, in 22 UPIA patients positive for both anti-CCP and MRI-proven bone edema who were considered to have progressed to RA at 1 year, the SP and positive predictive value (PPV) was increased to 100% (however, SE was 29%). Anti-CCP alone and bone edema alone had SP of 93% and 91%, respectively (SE was 57% and 41%, respectively). MRI synovitis had a LR-=0.2 regarding progression to RA (SE=91%, SP=44%).

Duer et al[8] investigated 41 patients with arthritis and subjective symptoms in the hand, who remained unclassified despite conventional clinical, biochemical and radiographic examinations. Patients who fulfilled 1987 ACR criteria for RA[7] or had radiographic bone erosions were excluded. Contrast enhanced MRI of the wrist and 2nd-5th metacarpophalangeal joints of the most symptomatic hand was performed and the MRI pattern was compared with the final diagnosis after a 2-year follow-up period (RA *versus* non-RA, according to 1987 ACR criteria). The combination of a distinct MRI synovitis and erosion pattern of RA (definitions can be found in table 2) had a LR+=4.8 and a LR-=0.4 (SE=64%, SP=87%) for the development of RA. When the synovitis and erosion pattern of RA was combined with a scintigraphy pattern of RA, SP and PPV increased to 100%, but at the cost of a low SE (45%). MRI bone edema was not assessed in this study. That same MRI synovitis pattern alone had a LR-=0 for progression to RA (SE=100%, SP=60%).

MRI results (mixed populations)

Studies characteristics´ and results for mixed populations are summarized in tables 3 and 4. These are populations who included not only patients with UPIA but also patients with arthralgia or already with an established diagnosis at baseline.[9-17]

US results

A total of 1250 articles and 861 meeting abstracts were found. After title and abstract screening, 3 articles(19, 20, 25) and 3 meeting abstracts (already or later published in article format(26, 27)) were left for full paper review. The inclusion criteria were fulfilled by 2 articles (mixed populations only). A detailed flowchart can be found in the web appendix (*www.3eupia.com*). Studies characteristics´ and results for the 2 mixed populations(26, 27) are summarized in tables 5 and 6.

Table 3: Baseline patients' characteristics in included studies (mixed populations)

Author, year Population, No (type)	Follow-up, months (range)	Females, No (%)	Age, median, years (range)	Disease duration, median, months (range)	SJC, median, (range)	CRP, median, mg/dl (range)	ESR, median, mm/h (range)	RF+, No (%)	Anti-CCP+, No (%)	X-ray erosions, No (%)
Mori 08 (9) 17 (UPIA + arthralgia)	27.4 (13-40)	14 (82.4)	57.7 (43-77)	NR	2.6 (0-12)	0.25 (0-1.5)	NR	10* (58.8)	4 (23.5)	0 (0)
Narváez 08 (10) 40 (UPIA + early RA)	20 (12-42)	28 (70.0)	54 (31-65)	4 (1.5-12)	8 (4)†	1.8 (0.7)†	33 (20)†	0 (0)	7 (17.5)	0 (0)
Zampogna 08 (11) 39 (UPIA + early RA)	38.4‡ (4-84)	29 (74.4)	51.3‡ (25-79)	NR (<9)	NR	NR	NR	NR	NR	NR
Tamai 06 (12) 113 (UPIA + early RA + non-RA)	12 (NA)	NR	NR	4.8‡ (NR)	NR	1.6§ (2.5)†	NR	54§ (67.5)	54§ (67.5)	NR
Solau-Gervais 06 (13) 30 (UPIA + arthralgia + early-RA)	30.6 (12-NR)	NR	46.8 (11.2)†	7.8 (6.2)†	2 (0-7)	2.2 (4.2)†	18 (14.8)†	10 (33.3)	0 (0)	0 (0)
Boutry 05 (14) 56 (UPIA? + arthralgia? + early RA, SLE, Sjögren?)	29 (4-72)	38 (67.9)	46 (17-69)	NR	NR	NR	NR	NR	NR	0 (0)
Klarlund 00 (15) 13 (UPIA + arthralgia)	12 (NA)	12 (92.3)	NR (13-68)	NR (1-13)	NR (0-11)	1 (1-1)	NR (3-24)	4 (30.8)	NR	NR
Sugimoto 00 (16) 50 (UPIA? + arthralgia + RA)	26 (4-71)	41 (82.0)	44 (19-74)	NR	NR	NR	NR	19** (39.6)	NR	0 (0)
Sugimoto 96 (17) 27 (UPIA? + RA? + non-RA?)	9.7 (NR)	24 (88.9)	46.6 (19-75)	NR	NR	NR	NR	10 (37.0)	NR	0 (0)

UPIA: undifferentiated peripheral inflammatory arthritis. RA: rheumatoid arthritis. SLE: systemic lupus erythematosus. SJC: swollen joint count. CRP: C-reactive protein. ESR: erythrocyte sedimentation rate. RF: rheumatoid factor. Anti-CCP: anti-cyclic citrullinated peptide antibodies. NA: not applicable. NR: not reported. *anti-agalactosyl IgG antibodies were measured and not RF. †Standard deviation. ‡mean. §Data available only for the 80 patients with the final diagnosis of RA. **Only 48 patients with known RF status.

Table 4: Performance of each variable at baseline (mixed populations) for the prediction of progression to RA

Author, year; No at baseline; No (%) of final diagnosis of RA; Quality	Index test	SE (%)	SP (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR- (95% CI)
Mori 08 (9) Baseline Mixed = 17* Final RA = 5 (29.4) NOS = 7 stars, LE = 2b	1) MRI criterion (MIP)† plus CARF+ and/or anti-CCP+	100	75	63	100	4.0 (1.5-11)	0 (NA)
	2) Symmetrical hand synovitis with MRI (MIP)†	100	50	45	100	2.0 (1.1-3.5)	0 (NA)
	3) CARF+	100	58	50	100	2.4 (1.2-4.7)	0 (NA)
	4) Anti-CCP+	60	92	75	85	7.2 (1.0-53)	0.4 (0.1-1.3)
	5) CARF+ and/or anti-CCP+	100	58	50	100	2.4 (1.2-4.7)	0 (NA)
Narváez 08 (10) Baseline Mixed = 40 Final RA = 31 (77.5) NOS = 6 stars, LE = 2b	1) MRI synovitis with BME or erosions	100	78	94	100	4.5 (1.3-15)	0 (NA)
	2) Anti-CCP+	23	100	100	27	Inf	0.8 (0.6-0.9)
Tamai 06 (12) Baseline Mixed = 113 Final RA = 80 (70.8) NOS = 7 stars, LE = 2b	Respectively >=1, 2 or 3 of the following: anti-CCP+; MRI symmetric synovitis; MRI BME and/or bone erosion	96 83 50	30 85 97	77 93 98	77 67 44	1.4 (1.1-1.7) 5.4 (2.4-12) 17 (2.4-115)	0.1 (0.04-0.4) 0.2 (0.1-0.3) 0.5 (0.4-0.6)
Solau-Gervais 06 (13) Baseline Mixed = 30 Final RA = 16 (53.3) NOS = 6 stars, LE = 2b	MRI OMERACT MCP erosion score >15	63	71	71	63	2.2 (0.9-5.4)	0.5 (0.3-1.1)
Boutry 05 (14) Baseline Mixed = 47‡ Final RA =28 (59.6)‡ NOS = 6 stars, LE = 2b	1) MRI MCP BME	71	95	95	69	14 (2-93)	0.3 (0.2-0.5)
	2) MRI MCP Synovitis	100	0	60	Inf	1.0 (1.0-1.0)	Inf
	3) MRI MCP Bone erosions	61	53	65	48	1.3 (0.7-2.2)	0.7 (0.4-1.4)
	4) MRI MCP Bone defects	39	79	73	47	1.9 (0.7-5.0)	0.8 (0.5-1.1)
	5) MRI MCP Tenosynovitis	68	53	90	38	1.4 (0.8-2.5)	0.6 (0.3-1.2)
	6) MRI Wrist BME	39	84	79	70	3.9 (1.3-11)	0.5 (0.3-0.9)
	7) MRI Wrist Synovitis	100	0	60	Inf	1.0 (1.0-1.0)	Inf
	8) MRI Wrist Bone erosions	100	16	64	100	1.2 (1.0-1.4)	0 (NA)
	9) MRI Wrist Bone defects	64	37	60	41	1.0 (0.7-1.6)	1.0 (0.4-2.1)
	10) MRI Wrist Tenosynovitis	96	21	64	80	1.2 (1-1.6)	0.2 (0-1.4)
Klarlund 00 (15) Baseline Mixed = 13 Final RA =5 (38.5) NOS = 7 stars, LE = 2b	1) MRI erosions	20	100	100	67	Inf	0.8 (0.5-1.2)
	2) MRI Tenosynovitis	60	63	50	71	1.6 (0.5-5)	0.6 (0.2.2.1)
Sugimoto 00 (16) Baseline Mixed = 29§ Final RA =8 (27.6) NOS = 6 stars, LE = 2b	Bilateral MRI synovitis of the same joint area (wrist, MCP or PIP)	88	90	78	95	9.2 (2.4-35)	0.1 (0-0.9)
Sugimoto 96 (17) Baseline Mixed = 27 Final RA =16 (59.3) NOS = 6 stars, LE = 2b	Bilateral MRI synovitis of the same joint area (wrist, MCP or PIP)	100	73	84	100	3.7 (1.4-9.6)	0 (NA)

Table 4 (Continued)

Author, year; No at baseline; No (%) of final diagnosis of RA; Quality	Index test	SE (%)	SP (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR- (95% CI)
Zampogna 08 (11) Baseline Mixed = 39 Final RA = 12 (30.8) NOS = 7 stars, LE = 2b	MRI rate of early enhancement ratio (REE)**, MRI relative enhancement (RE)**, morning stiffness, SJC, TJC, patient global, Ritchie index, DAS, HAQ, ESR, IgM RF, anti-CCP	1) Need for immunosuppressive treatment at the end of follow-up: predicted by higher REE and lower RE (MvA) 2) RA ACR criteria during follow up: predicted by higher RE (MvA) 3) RA ACR criteria at the end of follow-up: MRI not predictive (MvA) 4) Complete remission††: predicted by lower RE (UvA)					

RA: rheumatoid arthritis. SE: sensitivity. SP: specificity. PPV/NPV: positive/negative predictive value. LR+/LR-: positive/negative likelihood ratio. Inf: denominator is zero. NOS: Newcastle-Ottawa Scale. LE: level of evidence. MRI: magnetic resonance imaging. BME: bone marrow edema. Anti-CCP: anti-cyclic citrullinated peptides antibodies. CARF: anti-agalactosyl IgG antibodies. MCP: metacarpophalangeal joints. PIP: proximal interphalangeal joints. SJC: swollen joint count. TJC: tender joint count. DAS: disease activity score. HAQ: health assessment questionnaire. ESR: erythrocyte sedimentation rate. RF: rheumatoid factor. NA: not applicable. MvA: multivariate analysis. UvA: univariate analysis. *Initial cohort was 21 patients but 4 (19%) did not complete follow-up. †MRI criterion: MRI synovitis was diagnosed if there was significant intra-articular enhancement or periarticular synovial tendinitis after gadolinium-enhanced 3D transverse images were processed by means of the maximum intensity projection (MIP) method. ‡Data available for 47/56 patients (final diagnosis: 28 RA, 14 SLE, 5 Sjögren; not-analyzed: 2 reactive arthritis, 3 unclassified self-limited arthritis, 1 lost to follow-up, 3 uninterpretable MRI). §After exclusion of 2 patients who abandoned the study and exclusion of the data from 19 patients who fulfilled RA ACR criteria at baseline. **The MRI synovial enhancement ratio was calculated both as rate of early enhancement (REE) per second during the first 55" and as relative enhancement (RE) at t seconds; the REE shows the slope of the curve of contrast uptake and is steeper if inflammation is higher; the RE indicates the steady state of enhancement. ††Remission was defined as the absence of morning stiffness, absence of tender and swollen joint count and normal acute phase reactants.

Table 5: Baseline patients' characteristics in included studies (mixed population)

Author, year Population, No (type)	Follow-up, months (range)	Females, No (%)	Age, mean, years (SD)	Disease duration, median, months (SD)	SJC, median, (SD)	CRP, median, mg/dl (SD)	ESR, median, mm/h (SD)	RF+, No (%)	Anti-CCP+, No (%)	X-ray erosions, No (%)
Freeston 09 (26) 50 (UPIA? + Arthralgia)	12 (NA)	38 (76)	NR (21-80)†	<3 (NR)	NR	NR	NR	12* (24)	17* (35)	NR
Scirè 09 (27) 106 (33 UPIA + 73 early RA)	24 (NA)	75 (70.8)	59.5 (14.4)	3.8 (2.8)	12.5 (7.6)	1.9 (2.4)	31.8 (22.4)	41 (39)	30 (29)	NR

SJC: swollen joint count. CRP: C-reactive protein. ESR: erythrocyte sedimentation rate. RF: rheumatoid factor. Anti-CCP: anti-cyclic citrullinated antibodies. SD: standard deviation. UPIA: undifferentiated peripheral inflammatory arthritis. NA: not applicable. NR: not reported. *Data available only for 49 patients. †Range.

Table 6: Performance of each variable at baseline (mixed population) for the prediction of progression to persistent inflammatory arthritis (Freeston et al) or for the prediction of relapse (Scirè et al)

Author, year; Population, No; Final diagnosis, No (%); Quality	Index test	SE (%)	SP (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR- (95% CI)
Freeston 09 (26) Baseline Mixed = 49* (UPIA? + Arthralgia) Final pIA = 38 (77.6) NOS = 7 stars, LE = 2b	1) US GS≥1†	92	18	80	40	1.1 (0.8-1.5)	0.4 (0.1-2.3)
	2) US GS≥2†	76	64	88	44	2.1 (0.9-4.7)	0.4 (0.2-0.8)
	3) US GS=3†	47	91	95	33	5.2 (0.8-35)	0.6 (0.4-0.8)
	4) US PD≥1†	71	82	93	45	3.9 (1.1-14)	0.4 (0.2-0.6)
	5) US PD≥2†	50	100	100	35	Inf	0.5 (0.4-0.7)
	6) US FT in any finger	47	64	82	26	1.3 (0.6-3.0)	0.8 (0.5-1.4)
	7) Erosive on US‡	53	73	87	31	1.9 (0.7-5.3)	0.7 (0.4-1.1)
	8) RF+	32	100	100	30	Inf	0.7 (0.6-0.8)
	9) Anti-CCP+	45	100	100	34	Inf	0.6 (0.4-0.7)
Scirè 09 (27) Baseline Mixed = 106 (33 UPIA + 73 Early RA) Final RA = 106 (100) NOS = 7 stars, LE = 2b	1) Ultrasound (44 joints): US JC, US PD, US GS 2) SJC, RAI, DAS 3) CRP, ESR 4) Steroid use	DAS relapse after achieving a DAS≤1.6 at two consecutive visits 3 months apart, after ≥12 months follow-up: - US-PD was the only significant predictor of disease flare (OR=12.8; 95%CI 1.6-103.5; multivariate logistic regression)					

UPIA: undifferentiated inflammatory peripheral arthritis. pIA: persistent inflammatory arthritis. RA: rheumatoid arthritis. SE: sensitivity. SP: specificity. PPV/NPV: positive/negative predictive value. LR+/LR-: positive/negative likelihood ratio. Inf: denominator is zero. NOS: Newcastle-Ottawa Scale. LE: level of evidence. RF: rheumatoid factor. Anti-CCP: anti-cyclic citrullinated antibodies. US PD: power doppler ultrasound. US GS: grey scale ultrasound. US FT: ultrasound finger tenosynovitis. US JC: joint count ultrasound. SJC: swollen joint count. RAI: Ritchie's articular index. DAS: disease activity score. CRP: C-reactive protein. ESR: erythrocyte sedimentation rate. OR: odds ratio. CI: confidence interval. *1/50 patients lost to follow-up. †Bilateral MCP joints, flexor tendons and wrists were scanned and each joint was scored for GS and PD on a 0-3 semi-quantitative scale; dichotomised values on the table are for any joint, i.e. minimum of 1 joint. ‡At least one erosion in any joint.

DISCUSSION

This systematic literature review summarizes and evaluates the available evidence about the value of MRI and US in UPIA.

The results showed that MRI bone edema (LR+=4.5) is more likely to be seen in UPIA patients who will develop RA than in patients who will not develop RA and that the combination of MRI bone edema and anti-CCP positivity is highly specific for the development of RA (LR+=infinite, meaning that specificity was 100%).[23] However, the absence of both these features does not allow excluding the development of RA.[23] On the other hand, the results also showed that patients without MRI synovitis have a decreased probability of developing RA (LR-=0.2).[23]

In another study, the combination of a distinct MRI synovitis and erosion pattern with the involvement of several hand joints but not the first carpometacarpal joint was more likely to be seen in UPIA patients who developed RA (LR+=4.8) than in patients who did not develop RA.[8] The combination of such MRI pattern with a scintighraphy pattern with the involvement

of several joints but not distal interphalangeal joints and first carpometacarpal joint was even more specific for the development of RA (LR+=infinite, meaning that specificity was 100%).[8] However, again, none of these features allowed to exclude the development of RA.[8] On the other hand, the results also showed that patients without the above MRI synovitis pattern had a decreased probability of developing RA (LR-=0, meaning that sensitivity for RA was 100%).[8]

Results based on MRI studies in mixed populations(9, 10, 12-17) must be viewed with caution due to the heterogeneity of the study populations and the different measurements and outcomes that were used and made the pooling of data impossible. Overall they provide some evidence for the usefulness of MRI (bone oedema, synovitis and erosions) in predicting RA, but direct extrapolation of results to UPIA cannot be performed.

Regarding US, no studies were found in UPIA. We describe one study in a cohort of patients with very early inflammatory hand symptoms[26] and another in a population mainly with (very) early RA.[27] Again, extrapolation of results to UPIA cannot be made, although they suggest that US-PD signal and US-GS synovitis can be regarded as potential candidates for futures studies in UPIA. Their usefulness in this population is yet to be determined though.

Definite answers about the diagnostic and prognostic value of MRI and US in UPIA can only be achieved through well-conducted longitudinal studies of patients with UPIA. Studies of this kind are scarce, particularly in truly undifferentiated populations. The value of MRI and US should be compared with other potentially useful variables; this should be done not only by assessing the performance of the single variables alone, but also using multivariate logistic regression analysis with the aim to develop the best possible predicting model. This has never been done taking into account MRI and US.[28] The definition of a positive index test is also of great importance and ideally this should be done using validated and reproducible scoring systems. For the clinician, US may have some advantages due to the low-running costs and easy accessibility, however, extremity MRI is a promising answer for the costs of MRI. No data was found about the value of repeating MRI or US in UPIA and this should also be a matter of study in the future. The recent new ACR/EULAR criteria for RA[29] should also be taken into account in the future, as several of the patients we now describe as having UPIA will likely be labelled as RA patients.

In conclusion, a distinct MRI pattern of erosion and synovitis and the presence of MRI bone edema increased the probability of developing RA from UPIA; however, some UPIA patients presenting these MRI features may still remain undifferentiated, develop other diseases or have a self-limited course. The absence of MRI synovitis decreased the probability of developing RA; however, some patients without MRI synovitis may still develop RA. Regarding US

assessment, US-PD signal and US-GS synovitis are potential candidates for futures studies in UPIA. Current knowledge already provides evidence for the usefulness of MRI in UPIA and strongly encourages further testing of both MRI and US in undifferentiated arthritis.

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Chapter 4

Multinational evidence-based recommendations on "How to investigate and follow-up undifferentiated peripheral inflammatory arthritis": integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative

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ABSTRACT

Objective: To develop evidence-based recommendations on how to investigate and follow-up undifferentiated peripheral inflammatory arthritis (UPIA).

Methods: 697 rheumatologists from 17 countries participated in the 3E (Evidence, Expertise, Exchange) Initiative of 2008-2009 consisting of three separate rounds of discussions and modified Delphi votes. In a first round, 10 clinical questions were selected. A bibliographic team systematically searched Medline, Embase, the Cochrane Library and ACR/EULAR 2007-2008 meeting abstracts. Relevant articles were reviewed for quality assessment, data extraction and synthesis. In a second round, each country elaborated a set of national recommendations. Finally, multinational recommendations were formulated and agreement among the participants and the potential impact on their clinical practice was assessed.

Results: A total of 39.756 references were identified, of which 250 were systematically reviewed. Ten multinational key recommendations about the investigation and follow-up of UPIA were formulated. One recommendation addressed differential diagnosis and investigations prior to establishing the operational diagnosis of UPIA, seven recommendations related to the diagnostic and prognostic value of clinical and laboratory assessments in established UPIA (history and physical examination, acute phase reactants, autoantibodies, radiographs, magnetic resonance imaging and ultrasound, genetic markers and synovial biopsy), one recommendation highlighted predictors of persistence (chronicity) and the final recommendation addressed monitoring of clinical disease activity in UPIA.

Conclusions: Ten recommendations on how to investigate and follow-up UPIA in the clinical setting were developed. They are evidence-based and supported by a large panel of rheumatologists thus enhancing their validity and practical use.

INTRODUCTION

In clinical practice, a large number of patients who present with recent-onset arthritis have undifferentiated peripheral inflammatory arthritis (UPIA). In this context patients' initial questions will focus on their likelihood of developing a well-defined rheumatic disease and on what the future holds for disease progression, persistence, functional impairment and quality of life. These are questions about future diagnosis and prognosis. The answers to these questions are vital for clinical decision making, including the choice of treatment.

The 3E Initiative (Evidence, Expertise, Exchange) in rheumatology is a multinational effort, aimed at promoting evidence-based medicine by formulating practical recommendations addressing clinical problems.[1,2] The objective of the 3E Initiative of 2008-2009 was to develop practical recommendations on "how to investigate and follow-up undifferentiated peripheral inflammatory arthritis", by integrating systematically generated evidence and expert opinion of a broad panel of international rheumatologists. Although the term "inflammatory" in UPIA may seem redundant, the reason for its use was to clearly distinguish the target population from patients with degenerative joint disease, often called osteoarthritis or degenerative arthritis in the English medical literature.

METHODS

A total of 697 rheumatologists from 17 countries participated in the 3E Initiative of 2008-2009. Each country was represented by a scientific committee, consisting of one principal investigator and 5-13 members. The bibliographic team consisted of ten international fellows (PM, IC, WK, RK, BK, MS, LS-F, KT, WV, EV) and five mentors (DA, LC, RL, DvdH, CB), one of the mentors also being the scientific organizer (CB). The 17 national principal investigators were selected and invited by the 3e scientific organizer (CB) and each national chair was in charge of composing a national steering committee. The experts were all the members of the 17 national Steering Committees who attended the multi-national meetings for 3e Initiative.

During the first international meeting (n=113 participants), 10 clinically relevant questions on how to investigate and follow-up UPIA were formulated and selected via a modified Delphi vote. The areas addressed were fourfold: 1) the phase prior to establishing the operational diagnosis of UPIA- namely which differential diagnosis should be considered in a patient presenting with (inflammatory) arthritis and the minimal investigations necessary to consider a patient as having UPIA; 2) the diagnostic and prognostic value of clinical assessment and investigations in UPIA (history and physical examination, acute phase reactants, autoantibodies, radiographs, magnetic resonance imaging, ultrasound, genetic markers and synovial biopsy); 3) the predictors of persistence (chronicity) in UPIA; and 4) the measures of clinical disease activity in UPIA.

The clinical questions were structured using the PIO format (Patients, Participants or Problem; Intervention or Index test; Outcomes or target conditions).[3] The *patients* included "adults with UPIA". Duration of symptoms was not an exclusion criterion. The definition of UPIA is controversial and there is no widely accepted classification criterion for this condition. During the 2008-2009 3E Initiative kick-off meeting, experts decided that only patients in whom clinically apparent joint swelling (synovial proliferation or synovial effusion) was observed by the rheumatologist should be included. For our review, we systematically searched for studies of patients who did not fulfil diagnostic/classification criteria for any specific rheumatic disorder after initial assessment. Studies with mixed populations (e.g. UPIA+arthralgia, UPIA+early rheumatoid arthritis [RA]) were also retained, as these could be useful for extrapolating results. The *intervention or index test* was defined according to each question (e.g. erosions on radiographs, anti-citrullinated protein/peptide antibodies [ACPA] positivity) and the index test should have been assessed at baseline. The *outcomes* were defined as the development of well-defined rheumatic diseases (e. g. RA, psoriatic arthritis) or relevant disease outcomes (e.g. remission, radiographic progression). As diagnostic/classification criteria we accepted either internationally validated criteria (e.g. American College of Rheumatology criteria for RA[4]) or the opinion of the treating physician/investigator.

A systematic literature search for articles published up to February 2009 was carried out in Medline, Embase and Cochrane Library, using comprehensive search strategies, elaborated in collaboration with experienced librarians. The searches were limited to diagnostic and prognostic studies, using a modification of published sensitive search strategies.[5-8] No language restrictions were used. Retrieved citations were screened for titles, abstracts and full text using predefined inclusion and exclusion criteria; full read papers and review articles were hand-searched for additional references. Retained articles were graded for their methodological quality according to the Levels of Evidence of the Oxford Centre for Evidence-Based Medicine (http://www.cebm.net/index.aspx?o=1025 [accessed April 2009]).

Each question was addressed separately by independent searches. For each question, relevant data were extracted and appropriate statistics were calculated, including odds ratio, sensitivity, specificity, positive/negative predictive values and positive/negative likelihood ratios. Details and results of the literature search for each question will be published separately, while the current article describes the merging process between the evidence found for each question and the interpretation of this by the experts, having the ten recommendations as the result.

In the second round, a national meeting was held in each country (total=697 participants) to discuss the generated evidence and propose a set of recommendations. In a third joint meeting, the 17 scientific committees (n=94 participants) merged all propositions into 10 final recommendations via discussion and modified Delphi vote. The grade of recommendation according to the Oxford Levels of Evidence was attributed and the level of agreement was measured on a 10-point numerical rating scale (1=no agreement, 10=full agreement).[9]

Finally, the potential effect of each recommendation in clinical practice was assessed according to 3 impact statements voted by the rheumatologists.

RESULTS

A total of 39756 references were identified, of which 250 were systematically reviewed (table 1). The 10 multinational key recommendations are listed in table 2, with the corresponding level of evidence and grade of recommendation. The mean level of agreement among the rheumatologists was 8.7 (range 7.4 to 9.1). The percentage of rheumatologists who indicated they would change their clinical practice according to each recommendation is shown in table 3. Evidence for repeating investigations was not found for any of the questions, therefore all recommendations about this topic were based on expert opinion.

Table 1. Results of the systematic literature search for each recommendation topic

Recommendation (number an topic)	Retrieved references by systematic literature search (n)	Articles included in the systematic reviews (n)
1. Pre-UPIA differential diagnosis and investigations	540	51
2. History and physical examination	2914	37
3. Acute phase reactants	3699	18
4. Autoantibodies	13217	64
5. Radiographs	3585	25
6.1. Magnetic resonance imaging	2595	11
6.2. Ultrasound	2111	2
7. Genetic markers	3109	26
8. Synovial biopsy	6536	4
9. Predictors of persistence (chronicity)	437	7
10. Measures of clinical disease activity	1013	5
Total	39756	250

UPIA: undifferentiated peripheral inflammatory arthritis.

Table 2. Multinational recommendations on "How to investigate and follow-up undifferentiated peripheral inflammatory arthritis"

Recommendation (with level of evidence and grade of recommendation)	Agreement mean (SD)
1. All possible causes of arthritis (idiopathic, autoimmune, degenerative, infectious, malignancy, traumatic, metabolic) should be considered in the differential diagnosis. Complete history and thorough physical examination will determine the ranking order of possible differential diagnoses [5, D]. Investigations should be based on the differential diagnosis of the patient [5, D].	9.0 (1.7)
2. To establish a specific diagnosis and prognosis following presentation of UPIA, a careful systematic history and physical examination should be performed, with particular attention to age, gender [1a, A], geographic area [5, D], functional status [1a, A], duration of symptoms/ early morning stiffness, number plus pattern of tender/swollen joints [1a, A], axial/entheseal involvement and extra-articular/systemic features [5, D].	8.8 (1.3)
3. ESR and CRP should be performed at baseline in the work up for diagnosis [2b, B] and prognosis [2b, B] of UPIA and repeated when clinically relevant [5, D].	9.1 (1.4)
4. Testing of RF and/or ACPA should be performed in the evaluation of patients with UPIA, as these factors are predictive of RA diagnosis and prognosis; negative tests do not exclude progression to RA [1a, A]. If a connective tissue disease/systemic inflammatory disorder is suspected, additional autoantibody tests should be considered [5, D].	9.1 (1.2)
5. Radiographs of affected joints should be performed at baseline [5, D]. Radiographs of hands, wrists, and feet should be considered in the evaluation of UPIA, as presence of erosions is predictive for the development of RA and persistence of disease [1a, A]. These should be repeated within one year [5, D].	7.4 (2.6)
6. There is insufficient evidence to recommend the routine use of MRI and US for diagnosis or prognosis in UPIA [5, D]; in UPIA and suspicion of RA, MRI of hands and wrists could be considered for diagnosis [2b, B].	8.2 (2.0)
7. There is no genetic test that can be routinely recommended [3b, D], however HLA-B27 testing may be helpful in specific clinical settings [5, D].	8.8 (1.5)
8. Routine synovial biopsy is not recommended but can give information for differential diagnosis, especially in patients with persistent monoarthritis [2b, B].	8.8 (1.8)
9. Predictors of persistent inflammatory arthritis should be documented and include disease duration of ≥6 weeks [1b, A], morning stiffness >30 minutes [4, C], functional impairment [4, C], involvement of small joints [4, C] and/or knee [4, C], involvement of ≥3 joints [1b, B], ACPA [4, C] and/or RF positivity [4, C] and presence of radiographic erosion [1b, B].	8.6 (1.7)
10. Disease activity should be monitored [5, D], however no specific tool can be recommended [3b, C].	9.0 (1.7)

Between brackets: [level of evidence, grade of recommendation], according to the Oxford Centre for Evidence-based Medicine Levels of Evidence. Agreement was voted on a scale from 1 to 10 (fully disagree to fully agree) by the 94 rheumatologists attending the 3E Multi-National Closing Meeting. These attendees were members of the 17 scientific committees involved in the 3E Initiative of 2008-2009. SD: standard deviation. UPIA: undifferentiated peripheral inflammatory arthritis. ESR: erythrocyte sedimentation rate. CRP: C-reactive protein. RF: rheumatoid factor. ACPA: Anti-citrullinated protein/peptide antibodies. RA: rheumatoid arthritis. MRI: magnetic resonance imaging. US: ultrasound.

Table 3. Percentage of rheumatologists in the 3E Initiative who indicated for each recommendation if it would change their clinical practice

Recommendation (number an topic)	The recommendation will change my practice (%)	The recommendation is already my practice (%)	I don´t want to change my practice for this aspect (%)
1. Pre-UPIA differential diagnosis and investigations	0	96.5	3.5
2. History and physical examination	0	98.3	1.8
3. Acute phase reactants	5.4	91.1	3.6
4. Autoantibodies	1.8	96.4	1.8
5. Radiographs	16.1	48.2	35.7
6. Magnetic resonance imaging and ultrasound	17.9	64.3	17.9
7. Genetic markers	1.8	92.9	5.4
8. Synovial biopsy	8.9	83.9	7.1
9. Predictors of persistence (chronicity)	24.6	66.7	8.8
10. Measures of clinical disease activity	12.3	84.2	3.5

UPIA: undifferentiated peripheral inflammatory arthritis.

Table 4. Diagnosis reported as exclusion criteria and baseline investigations undertaken prior to inclusion as UPIA (ordered by the frequency of reporting in the retrieved literature), both in studies including patients exclusively with UPIA as well as in selected mixed populations that included a well-defined subset of patients with UPIA

A) Reported differential diagnosis prior to establishing the operational diagnosis of UPIA	
- Rheumatoid arthritis	- Sarcoidosis
- Osteoarthritis	- Soft-tissue disorders
- Spondyloarthritis (reactive arthritis, psoriatic arthritis, ankylosing spondylitis and undifferentiated spondyloarthritis)	- Polymyalgia rheumaica
	- Lyme disease
- Crystal-related arthritis	- Vasculitis
- Trauma	- Juvenile inflammatory arthritis
- Connective tissue diseases (systemic lupus erythematosus, Sjögren syndrome and myositis)	- Palindromic rheumatism
	- Fibromyalgia
- Septic arthritis	- Endocrinologic origin
	- Malignancy-related arthritis
	- Viral etiology
B) Reported investigations prior to establishing the operational diagnosis of UPIA	
- History	- Microbiologic assessment
- Tender and swollen joint count	- Anti-citrullinated protein/peptide antibodies
- Rheumatoid factor	- Radiography of the chest and/or of other affected joints
- C-reactive protein	- Urinalysis
- Physical examination	- Thyroid function tests
- Hands and feet radiographs	- C3, C4
- Full blood count	- Immunoglobulins
- Anti-nuclear antibodies	- Antibodies to extractable nuclear antigens
- Erythrocyte sedimentation rate	- Antibodies to double stranded deoxyribonucleic acid
- Biochemistry (liver function tests, glucose, urate and renal function)	- Specific serologic assessment
- HLA typing (HLA-B27 and HLA-DR)	

UPIA: undifferentiated peripheral inflammatory arthritis.

Recommendation 1. *All possible causes of arthritis (idiopathic, autoimmune, degenerative, infectious, malignancy, traumatic, metabolic) should be considered in the differential diagnosis. Complete history and thorough physical examination will determine the ranking order of possible differential diagnoses. Investigations should be based on the differential diagnosis of the patient.*

As UPIA is an operational diagnosis after excluding well-defined rheumatic diseases, the question about pre-UPIA differential diagnosis and investigations was analysed by looking at the diagnosis that were excluded in cohorts of patients with UPIA and by identifying the inclusion and exclusion criteria of these studies as well as the investigations performed before the UPIA cohort was established. RA was the most frequent diagnosis reported as exclusion criterion[10-59] and there was no standard baseline investigation undertaken prior to inclusion as UPIA (table 4).[41-60]

Experts agreed that when facing a new patient presenting with arthritis every diagnosis needed to be kept in mind as UPIA is an exclusion diagnosis. Although, the consensus was that it was impossible to name all possible diagnoses, it was felt useful to mention some major disease categories to make sure that these are considered. Experts also advised that UPIA should be constantly rethought, as patients may develop a disease that can be labelled with a specific diagnosis at anytime. Moreover, this recommendation applies only if arthritis persists, and not if it is self-limiting. Again, as the investigations will vary according to context and clinical presentation, experts felt that it would not be useful to make a list of recommended minimal investigations.

Recommendation 2. *To establish a specific diagnosis and prognosis following presentation of UPIA, a careful systematic history and physical examination should be performed, with particular attention to age, gender, geographic area, functional status, duration of symptoms/early morning stiffness, number plus pattern of tender/swollen joints, axial/entheseal involvement and extra-articular/systemic features.*

Although selected observational studies were of good quality, there was large heterogeneity with respect to the type of history and physical exam features that were described.[39,40,42-49,61-87]. Of the quantified features, advanced age,[44,83] female gender[44] and greater morning stiffness[43,44] were predictive of an eventual diagnosis of RA. A higher number of tender[44] and swollen joints,[43,44,61] involvement of small joints of hands and feet,[44,83] involvement of both the upper and lower extremities[44] and symmetrical involvement[43] were also associated with progression to RA. Similar features were associated with disease persistence[81-87] and development of erosions,[48,63,78] while self-reported functional disability (Health Assessment Questionnaire [HAQ] score)[67,76] and the presence of extra-articular features[76] were uniquely predictive of future disability, along with advanced age,[67,76] female gender[67] and longer symptom duration.[67]

Experts recognized the importance of the above mentioned evidence-based features and based on their clinical experience also highlighted the contribution of the patient's geographic area of residence, the presence of axial/entheseal involvement and the presence of extra-articular/systemic features. However, the greater relevance given to features included in the recommendation does not preclude the need to perform a careful systematic history and physical examination in every UPIA patient.

Recommendation 3. *Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) should be performed at baseline in the work-up for diagnosis and prognosis of UPIA and repeated when clinically relevant.*

Elevated ESR showed some diagnostic value for the development of RA[74,85] but no prognostic value for persistence (chronicity) or structural damage.[40,45,88] CRP appeared a poor predictor of persistent arthritis, radiological progression and functional disability.[80,89] However, there was some evidence for the usefulness of elevated CRP in predicting RA, especially when the CRP levels are higher.[48,88] In one study, CRP did not have any diagnostic value with regard to spondylarthropathy.[39] For other acute phase reactants, the evidence on diagnostic or prognostic value was scarce, negative, or controversial.[32,42,48,79,80,90-95]
Based on sparse evidence and on personal experience, regarding acute phase reactants, experts recommended that only ESR and CRP should be performed at baseline and repeated according to the clinical setting.

Recommendation 4. *Testing of rheumatoid factor (RF) and/or ACPA should be performed in the evaluation of patients with UPIA, as these factors are predictive of RA diagnosis and prognosis; negative tests do not exclude progression to RA. If a connective tissue disease/systemic inflammatory disorder is suspected, additional autoantibody tests should be considered.*

The association of ACPA and RF[11,42-44,48,50,73,96-110] with a diagnosis of RA at follow-up was compelling in the retrieved literature. The absence of ACPA or RF was diagnostically less helpful. The presence of ACPA or RF[75,106-109,111-115] also increased the probability of developing persistent synovitis or a worse radiographic outcome.[73,75,84-86,116] For anti-keratin antibodies (AKA) and anti-perinuclear factor (APF), evidence suggests diagnostic usefulness, AKA also appears to have some prognostic value.[11,96-99,107,110,114,117] For all other markers, including a variety of other autoantibodies as well as bone and cartilage biomarkers, the evidence for diagnostic or prognostic value is scarce, negative, or controversial.[57,102,118-126] The same applies to disease outcomes different from those already mentioned.[59,74,76,81,93,100,116,127,128]
The value of ACPA and RF in UPIA was recognized, and based on clinical experience, experts also advised consideration of additional autoantibody tests if non-RA systemic inflammatory disorders are suspected. The use of the general term ACPA was preferred, as the literature

describes several tests for detecting antibodies to citrullinated peptides (such as anti-CCP1 and anti-CCP2) and newer-generation tests are also expected to be used in the future.

Recommendation 5. *Radiographs of affected joints should be performed at baseline. Radiographs of hands, wrists, and feet should be considered in the evaluation of UPIA, as presence of erosions is predictive for the development of RA and persistence of disease. These should be repeated within one year.*

Radiographic erosions[43,49] and Larsen grade 1 (in a population without erosions at baseline)[20] increased the probability of developing RA from UPIA. Moreover, when comparing mild *versus* progressive disease after 1 year follow-up, Sharp/van der Heijde scores at baseline were significantly higher in the progressive disease group.[48] In another study,[44] erosions were found to be a predictor of RA in univariate but not in multivariate analysis.
Overall, studies in mixed populations also provided some evidence for the usefulness of radiographs in predicting RA.[72,88,92,109,122,129-135] In general, prognosis was worse when radiographic abnormalities at baseline were more severe.[75,91,109,116,133,136-140]
Experts recognized the clinical value of hand and feet radiographs in UPIA, and based on clinical experience also recommended that radiographs of affected joints should be performed at baseline; furthermore, experts advised that radiographs should be repeated within one year (in case of disease persistance). Moreover, although not voted to be included in the recommendation, some of the experts expressed their opinion that pelvic/sacroiliac joints radiographs should also be considered, particularly in RF and ACPA negative patients or if spondyloarthritis is suspected.
There was a slightly lower agreement about this recommendation (table 2, 7.4 agreement), with a larger proportion of experts stating that they didn't want to change their practice for this aspect (table 3, 35.7%). This lower concordance was mainly related to the inclusion of "radiographs of affected joints at baseline" and about the advice to repeat radiographs "within one year".

Recommendation 6. *There is insufficient evidence to recommend the routine use of magnetic resonance imaging (MRI) and ultrasound (US) for diagnosis or prognosis in UPIA; in UPIA and suspicion of RA, MRI of hands and wrists could be considered for diagnosis.*

Bone oedema was found to be an independent predictor of the future development of RA from UPIA[141] and the presence of a distinct MRI synovitis and erosion pattern with the involvement of several hand joints but not the first carpometacarpal joint also increased the probability of developing RA.[20] The absence of the same MRI synovitis pattern decreased the probability of developing RA.[20] Overall, MRI studies in mixed populations[101,134,142-147] provided some evidence for the usefulness of MRI (bone oedema, synovitis and erosions) in predicting

RA. Regarding US, 2 mixed populations revealed US-power Doppler signal and US-gray-scale synovitis as potential candidates for futures studies in UPIA.[148,149]
Experts recognized that MRI of the hands and wrists has already shown to be useful in predicting the development of RA from UPIA, while the value of US in UPIA is still to be determined. However data is still too scarce to recommend the routine use of any of these imaging tools. This recommendation does not dispute the fact that compared to physical examination and radiographs, both MRI and US may offer advantages through more sensitive depiction of inflammatory and destructive disease manifestations. The current recommendation pertains only to the diagnostic and prognostic value of these imaging tools in UPIA.

Recommendation 7. *There is no genetic test that can be routinely recommended, however HLA-B27 testing may be helpful in specific clinical settings.*

There was a great heterogeneity among the genetic markers that were tested.[39,40,46,50-52,65,84,127,133,150-165] The shared epitope (SE) was the most frequently studied marker. Eight studies[40,50,65,133,153-155,158] tested its diagnostic utility showing poor results. Only in one study was the positive likelihood ratio for RA relevant, but this result came from the study with the poorest quality and smallest sample size.[40] In isolation, no other genetic marker was informative of a future diagnosis in patients with UPIA. With regard to prognosis, the SE was weakly associated with a poor prognosis of arthritis in terms of development of erosions, mortality, disability and persistent synovitis.[65,127,133,163,164] Other genes were not good predictors of erosions or other less studied outcomes.
The experts acknowledged the current lack of evidence for the practical utility of genetics in UPIA. However, based on their clinical experience, experts chose to highlight that HLA-B27 may be helpful in the appropriate clinical setting, namely when spondyloarthritis is suspected.

Recommendation 8. *Routine synovial biopsy is not recommended but can give information for differential diagnosis, especially in patients with persistent monoarthritis.*

Studies had significant clinical and statistical heterogeneity.[22,23,166,167] Three broad synovial features of interest were identified in the literature: ACPA staining, immunohistochemistry and vascular patterns. In contrast to serologic ACPA testing, ACPA staining was shown not to be highly specific for a diagnosis of RA.[167] In one study, synovial histopathology seemed to differentiate between RA and non-RA.[166] The vascular pattern in undifferentiated arthritis was not specific enough to differentiate between spondyloarthritis and RA.[22,23]
The exact role of synovial biopsy in UPIA is yet to be determined and experts felt that it could not be recommended as a routine procedure. However, experts also highlighted that synovial biopsy may give important diagnostic clues, especially in some selected cases (e.g.

persistent/chronic refractory monoarthritis, suspicion of malignancy or suspicion of chronic infection, such as tuberculosis).

Recommendation 9. *Predictors of persistent inflammatory arthritis should be documented and include disease duration of ≥6 weeks, morning stiffness >30 minutes, functional impairment, involvement of small joints and/or knee, involvement of ≥3 joints, ACPA and/or RF positivity and presence of radiographic erosion.*

The question about chronicity was investigated by looking at prognostic studies that used multivariate analysis to identify independent predictors of persistence (chronicity). At baseline, the following variables were found to be independent predictors of persistent (inflammatory) arthritis: disease duration,[75,82,116] duration of morning stiffness,[75,85,86] change of functional status (measured by HAQ) at the first 3 months,[82] failure to respond 2 weeks after local treatment with intraarticular corticosteroids,[82] small joint involvement,[168] knee involvement,[85] presence of RF,[75,85] presence and level of ACPA,[75,86,168] functional status (HAQ),[169] arthritis of at least 3 joints,[75] proximal interphalageal joint involvement,[169] metatarsophalangeal joint involvement[75] and radiographic erosion at the hands and feet.[75] The magnitude of the association in the same predictor was diverse among the studies depending on the patient characteristics (namely if the population was purely UPIA or not), the study design, and the variables used to adjust for in the models.

Recommendation 10. *Disease activity should be monitored, however no specific tool can be recommended.*

Five studies evaluated the validation of different clinical measures in patients with UPIA. Validation aspects of 4 questionnaires - WHO Disability Assessment Schedule (WHODAS),[170] London Handicap Scale (LHS), Disease Repercussion Profile (DRP) and the HAQ,[171] and 3 physical measures - RA Disease Activity Index (RADAI),[172] McGill Range of Motion Index (McROMI)[173] and NOAR Damage Joint Count (NOAR-DJC),[174] were partially assessed in these studies, but none of the instruments of disease activity was fully validated for its use in UPIA. Although no instrument of disease activity has been fully validated for its use in UPIA, experts felt that it was important to recommend that there should be a conscious effort to record disease activity.

DISCUSSION

Ten multinational recommendations on how to investigate and follow-up UPIA in the clinical setting were developed, which are practical, evidence-based and supported by a large panel of international rheumatologists in the 3E Initiative.
We followed an established group decision method. A representative expert panel of 697 academic and community rheumatologists from 17 countries selected relevant questions that reflect the challenges of approaching a patient with UPIA. They openly discussed the evidence from the literature followed by a silent voting process. We used the touch pad methodology with pre-specified cut-off levels of agreement to generate the final recommendations. Several rounds of rewording and re-voting were sometimes required to reach the specified cut-off for agreement. This process highlights the International dimension of this collaboration and strengthens the current recommendations.[1,2] It ensured that the final recommendations were evidence-driven as well as clinically relevant.

Furthermore, the broad participation increases external validity and enhances future dissemination and implementation into rheumatological practice worldwide. Another main feature of the 3E Initiative was the promotion of epidemiology and systematic literature research, all participants having been updated on how to appraise published evidence.
There is widespread interest in predictive medicine. Following a strict methodology, we aimed to find all available evidence regarding each question, which resulted in a large number of reviewed articles. However, the evidence in truly UPIA populations is scarce, exposing the need to create a research agenda addressing this topic. In particular, future studies should clearly distinguish between individuals with early well-defined rheumatic diseases, individuals with UPIA and individuals with inflammatory joint symptoms but no obvious joint swelling. All these populations can be studied for predictive algorithms and results may be different depending on the study population.
The definition of UPIA is controversial and much of the literature is skewed towards early RA. The difficulty in defining UPIA is underlined by the continuous changing face of different categories of patients, which can be well illustrated by the recent new ACR/EULAR criteria for RA,[175] as several of the patients we now describe as having UPIA will likely be labelled as RA patients. Nevertheless, despite the influence that this changing may have on research and daily practice, the recommendations presented in this article are based on currently available evidence. They may help the clinician in the effective management of patients with UPIA and can be adjusted if future studies or clinical experience reveal new insights.

In summary, multinational recommendations for the investigation and follow-up of patients with undifferentiated arthritis in daily clinical practice were developed, integrating systematic

literature review and expert opinion, with the aim of promoting evidence-based medicine and ultimately improving patient care.

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Chapter 5

Insights in the relationship of joint space narrowing versus erosive joint damage and physical functioning of patients with rheumatoid arthritis

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ABSTRACT

Objective

To evaluate the contribution of joint space narrowing (JSN) and erosions in general and in four different joint groups in relation to physical disability in rheumatoid arthritis (RA).

Methods

Five-year follow-up data from the Behandel Strategieën (BeSt) trial were used, where 508 patients with recent onset RA were treated aiming at a disease activity score ≤2.4. Joint damage was assessed annually and scored according to the Sharp-van der Heijde method. Physical disability was measured three-monthly with the Health Assessment Questionnaire (HAQ). Generalized Estimating Equations analyses were performed to assess the relationship between the HAQ and JSN scores and erosions scores, separately and in joint groups.

Results

Overall, damage scores were low, and neither total JSN nor erosions showed significant effect on the HAQ (β=0.001 95%CI -0.003 to 0.004 and β=0.002 95%CI -0.001 to 0.006 respectively). Of the total damage scores per joint group, damage in the wrist shows a trend for association with physical disability displaying the largest effect size (β=0.005 95%CI 0.000 to 0.011). Also in the analysis with erosions per joint group, the wrist was most strongly related with physical functioning (β=0.016 95%CI 0.003 to 0.029); in the analysis with JSN per joint group no joint group was significantly related to the HAQ. Analysis of all erosion and narrowing scores per joint group in one model reveals only erosions in the wrist to be independently associated with impaired physical functioning (β=0.017 95%CI 0.003-0.030).

Conclusion

Joint damage in the wrist, erosions more than JSN, is associated with impaired physical functioning even in patients with early RA patients with limited overall damage after five years of tight controlled treatment.

INTRODUCTION

Joint damage is an early and potentially progressive feature of Rheumatoid Arthritis (RA) and is related to functional disability together with other factors such as disease activity and co-morbidity.[1-5] Previous research has shown that in early disease physical functioning is mostly determined by the disease activity score (DAS), whereas in late disease, it is mostly determined by the extend of joint damage.[6]

RA related joint damage on radiographs involves damage to the bone (bone mineral density loss and erosions), damage to cartilage (scored as joint space narrowing (JSN)) and damage to ligaments causing malalignment, which is sometimes also scored as part of the JSN scoring, depending on the scoring method used. [7-9] Recently it has been suggested in a cross-sectional study that JSN rather than erosiveness is associated with physical disability.[10] It is not clear whether the relation between JSN or erosions and physical functioning is influenced by the location of damage in particular joints or joint groups. Further insight in this could lead to specific site evaluations to assess treatment efficacy, and possibly to specific therapy targets. Therefore, we evaluated the contribution of JSN and erosions in general, and in four different joint groups, in relation to physical disability over time, in a cohort of patients with recent onset of RA, dynamically treated during five years in a tight control setting aimed at low disease activity.

METHODS

Patients

Data from the Behandel Strategieën (BeSt) trial were used, where 508 patients with recent onset active RA were dynamically treated according to a protocol directed by 3-monthly assessments of disease activity, aiming at a DAS ≤2.4. Patients were randomized into four different treatment strategies: 1. sequential monotherapy (n=126); 2. step-up combination therapy (n=121); 3. initial combination therapy with prednisone (n=133) and 4. initial combination therapy with infliximab (n=128). Clinical assessment of disease activity was performed 3-monthly, and included a 68/66 graded joint count for tenderness and swelling, erythrocyte sedimentation rate measurements and patient's assessment of global disease activity. This study was approved by the ethical committees of participating centers and all patients provided informed consent. More details about the BeSt study have been described elsewhere.[11] The current analysis was performed on five year follow up data.

Radiological assessments

Annual radiographs of hands, wrist and feet from baseline until year 5 were scored in random order by two observers blinded for patient identity and treatment allocation. The modification of the Sharp method by van der Heijde (SHS)[8] was used for the scoring of joint space narrowing and erosiveness on the radiographs. JSNis scored on a scale of 0-4 with a maximum total of 120 in the hands and 48 in the feet. Erosions are scored on a scale of 0 (no erosion) - 3 (large erosion) and are scored cumulatively with a maximum of 5 points per joint in the hands and with a maximum of 10 points in the feet. The maximum total erosion score in the hands is 160 and in the feet 120 points. Average scores of the two readers were used for the analysis.

Outcome assessment

Physical functioning was assessed using the Dutch version of the Health Assessment Questionnaire (HAQ).[12] The HAQ consists of 24 questions in eight different categories which are answered on a 0-3 severity scale. To calculate the total HAQ score, which ranges between 0 (no disability) and 3 (severe disability), all highest scores per category are summed up and divided by eight.

Statistical methods

Statistical analyses were performed with the software program SPSS V.17.0 (SPSS, Chicago, Illinois, USA). Generalized Estimating Equations (GEE) regression models were used to investigate the relationship between joint damage (in general and per joint group) and physical functioning during five years follow-up, while correcting for within patient correlation. The total HAQ score at the yearly visits was used as outcome for all analyses. GEE modeling was chosen as it is relatively robust against violations of normality, which is frequently the case with SHS, erosion and JSN scores.

Separate models were specified to be able to assess the effect size of the independent variable in relation to the dependent variable. Combined models were specified to evaluate the independent contribution of one dependent variable in the presence of other dependent variables. Adjustments were made for possible confounding variables time, DAS, gender, treatment group and BMI that were associated with physical functioning in the univariate analysis. P-values of ≤ 0.05 were considered statistically significant. For all analyses the unstructured covariance matrix was used, which does not assume a specific covariance structure and estimates every covariance individually for consecutive measurements. Since high disease activity was a requirement for inclusion, baseline measurements were excluded from the analysis to avoid a large contribution of high disease activity on disability.

The analyses were performed by entering variables in the model in the following three steps: 1. total score of JSN and total erosions score (in all joints) 2. total damage score (erosions and JSNtogether) per joint group and 3. JSN and erosion scores separately per joint group. For the second and third step in the analysis joint damage was evaluated in four joint groups: MCPs,

PIPs, wrists and feet. For step 1 and 3, first erosions and JSN were analyzed separately and then in one model together. Finally, separate variables for JSN and erosions in all different joint groups were entered in one model to evaluate the independent contribution of all factors. As the maximum attributable points per joint group or per feature can differ, all analyses were repeated using the percentage of the maximum total damage.

RESULTS

At baseline, patients reported severe disability with a mean (SD) HAQ score of 1.4 (0.7), which decreased to 0.6 (0.6) at t=1 year and remained stable over the years (HAQ 0.6 (0.6) at t=5 years). Joint damage at baseline, although present in the majority of this population with severe RA, was limited, with a median SHS score (IQR) of 3.0 (0.5-9.5), and 62% of patients showing joint damage <5 points SHS. At baseline, 37% of patients had no JSN and 28% had no erosions. After 5 years, these percentages had decreased to 30% and 18%, respectively. The median SHS score (IQR) at t=5 years was 7.0 (1.5-20.3).

JSN was mostly seen in the wrists with a mean (SD) JSN score of 2.9 (6.7), and to a lesser extent in the feet with a mean (SD) JSN score of 2.3 (5.2) at year 5. Erosions were most frequently seen in the feet with a mean (SD) score 4.4 (7.4) and thereafter in the wrists with a score of 1.2 (3.6). Mean percentage JSN ranged from 2.0% of the maximum score (in the PIPs) to 6.1% (in the wrists) and mean percentage erosions ranged from 1.8% (in the PIPs) to 3.7% (in the feet). More details are described in supplementary table S1 of the online published version of this paper.

The relationship of joint space narrowing and of erosions with functional disability

In the univariate analysis (*table 1*) the effect on disability of erosion score and JSN score is similar. JSN and physical functioning show a statistically significant relationship with a beta estimate (β) (increase in HAQ per point increase in JSN score) of 0.004 (95%CI 0.001-0.008). Erosions are related to physical functioning in the same order of magnitude, however this relationship is not statistically significant (β=0.003 95%CI -0.001-0.006). The main clinically relevant predictor for disability, showing the largest effect size, is the DAS (β=0.250; 95%CI 0.220 – 0.280). Other univariate predictors are (female) gender, time, BMI, baseline DAS and treatment group. When applying a multivariable model with correction for disease activity (concurrent and baseline), BMI, time, gender and treatment group, effect sizes for the erosions and JSN scores are smaller (β=0.001 and β=0.002, respectively), and the relationship is no longer statistically significant, neither separately nor combined in a model together. (*see supplementary table S2; published online only*)

Table 1 Univariate predictors of physical functioning as measured by the Health Assessment Questionnaire (HAQ).

Predictor	Beta	SE	95% CI
Erosions	0.003	0.002	-0.001– 0.006
Narrowing	0.004	0.002	0.001 – 0.008†
Age	0.002	0.002	-0.002 – 0.005
Female gender	0.142	0.048	0.048 – 0.236†
BMI	0.017	0.006	0.006 – 0.029†
Disease duration	0.016	0.019	-0.021 – 0.053
DAS	0.250	0.015	0.220 – 0.280†
DAS baseline	0.130	0.027	0.077 – 0.183†
ACPA positive	-0.029	0.049	-0.125 – 0.067
RF positive	-0.027	0.053	-0.130 – 0.076
Treatment group			
group 1	0.176	0.040	0.047 – 0.578†
group 2	0.148	0.070	0.017 – 0.279†
group 3	0.076	0.057	-0.035 – 0.188
group 4	*reference*	*reference*	*reference*
Time			
year1	*reference*	*reference*	*reference*
year 2	-0.041	0.021	-0.082 – -0.0002†
year 3	-0.025	0.024	-0.072 – 0.022
year 4	-0.001	0.025	-0.049 – 0.048
year 5	0.004	0.025	-0.044 – 0.052

CI: confidence interval; SE: standard error; BMI: body mass index; DAS: disease activity score; ACPA: anti citrillunated peptide antibodies; RF: rheumatoid factor. †$p<0.05$

Joint damage in joint groups in relation to disability

The relationship between the *total* damage scores per group and the HAQ is shown in table 2. Total damage in the wrist shows a trend for association with the HAQ and is demonstrating the largest effect size in both the separate analysis and in the analysis combining with the other joint groups (β=0.005 95% CI 0.000-0.010 and β=0.005 95% CI 0.000-0.011, respectively). In analyses including erosions and narrowing separately per joint group, only erosions in the wrist (β=0.014 95% CI 0.003-0.026) show a statistically significant relation with physical functioning (*table 3*).

When applying a model including joint space narrowing in all groups there is no statistically significant relationship of any joint group with physical functioning, but in the model for erosions in all joint groups, erosions in the wrist are found as an independent explanatory variable with a large effect size (β=0.016 95%CI 0.003-0.029). (*see supplementary table S3; published online only*)

Table 2 The total joint damage score per group in relation to physical functioning measured by the Health Assessment Questionnaire (HAQ).

Predictor	Beta	SE	95% CI
Separate models*			
Total damage score feet	-0.001	0.002	-0.005 to 0.003
Total damage score wrists	0.005	0.003	0.000 to 0.010†
Total damage score MCPs	0.003	0.004	-0.006 to 0.012
Total damage score PIPs	0.001	0.007	-0.014 to 0.015
One model*			
Total damage score feet	-0.003	0.002	-0.008 to 0.001
Total damage score wrists	0.005	0.003	0.000 to 0.011†
Total damage score MCPs	0.004	0.006	-0.007 to 0.014
Total damage score PIPs	-0.002	0.008	-0.018 to 0.014

Separate models: effect of the total damage score per joint group on physical functioning. One model: effect of the total damage score per joint group in the presence of the other joint groups. SE: standard error; CI: confidence interval; MCPs: metacarpophalangeal joints; PIPs: proximal interphalangeal joints. *Adjusted for BMI, DAS, DAS baseline, time, gender and treatment group; †trend; p<0.10

Table 3 Narrowing and erosion scores per joint group in relation to physical functioning measured by the Health Assessment Questionnaire (HAQ) in eight different models.

Predictor*	Beta	SE	95% CI
Narrowing feet	-0.002	0.004	-0.010 to 0.007
Narrowing wrists	0.005	0.004	-0.002 to 0.012
Narrowing MCPs	0.007	0.007	-0.007 to 0.020
Narrowing PIPs	0.013	0.013	-0.012 to 0.038
Erosions feet	-0.002	0.003	-0.008 to 0.004
Erosions wrists	0.014	0.006	0.003 to 0.026†
Erosions MCPs	-0.001	0.009	-0.018 to 0.017
Erosions PIPs	-0.007	0.011	-0.030 to 0.016

SE: standard error; CI: confidence interval; MCPs: metacarpophalangeal joints; PIPs: proximal interphalangeal joints. *Adjusted for BMI, DAS, DAS baseline, time, gender and treatment group; †p<0.05

Finally, in the extended model including all joint groups, both, as JSN score and as erosion score while correcting for BMI, DAS (baseline and concurrent), time, gender and treatment group, we find erosions in the wrist as the only independent predictor in the presence of all other associated factors (β=0.017 95%CI 0.003-0.030) (*table 4*).

We repeated the analyses using the percentage of the maximum score in stead of absolute scores (as the maximum attributable point can differ per feature or group), and found comparable results (data not shown).

Table 4 Independent contribution of narrowing and erosion scores within each joint group in relation to physical functioning measured by the Health Assessment Questionnaire (HAQ).

Predictor*	Beta	SE	95% CI
Narrowing feet	-0.003	0.005	-0.013 to 0.008
Narrowing wrists	-0.001	0.004	-0.009 to 0.007
Narrowing MCPs	0.008	0.010	-0.013 to 0.028
Narrowing PIPs	0.016	0.017	-0.017 to 0.050
Erosions feet	-0.003	0.005	-0.012 to 0.006
Erosions wrists	0.017	0.007	0.003 to 0.030†
Erosions MCPs	-0.002	0.014	-0.030 to 0.027
Erosions PIPs	-0.016	0.015	-0.044 to 0.013

SE: standard error; CI: confidence interval; MCPs: metacarpophalangeal joints; PIPs: proximal interphalangeal joints. *Adjusted for BMI, DAS, DAS baseline, year, gender and treatment group. †p<0.05

DISCUSSION

In a cohort of patients with recent onset of RA, over 5 years of tight controlled treatment both JSN and erosions showed only a small non significant effect on physical functioning defined by the HAQ. Of all sites evaluated with the SHS score, the wrist was the most important determinant, and erosions in the wrist were the only independent predictor of functional disability.

Previous research in patients from various early or advanced RA trials has shown that JSN, rather than erosiveness, was associated with physical functioning.[10] It has been suggested that this is due to different pathophysiological mechanisms of both types of damage.[13-15] In our cohort, we found the effect size on outcome HAQ of JSN or erosion scores was roughly the same and very small. This is probably because in this cohort of patients with early RA, treated with DAS steered tight control strategies, there was very limited radiological damage progression in general. The high agreement between the analyses using the absolute scores and those using the percentages of the maximum scores also indicates that severe joint damage, (at the highest end of the scale) was rare. In these patients disability was largely determined by disease activity even when the disease activity at baseline was discarded.

When analyzing damage per joint or joint group, we found that damage in the wrist was the main determinant of disability. As JSN frequently occurs in the wrist this finding would seem to corroborate the previously reported dominance of joint space narrowing in relation to functional disability.[16]However, our analyses showed that erosive damage, not narrowing, in the wrist was an independent predictor for functional disability. A possible explanation for the effect of wrist joint damage on functional ability may be that activities requiring wrist movement constitute a large proportion of the daily activities asked after in the questions

of the HAQ. Only questions on walking and climbing stairs, and possibly (but not likely) the questions on rising from an armless chair and getting out of bed, address activities where one would not need to use one's wrists. This predominance of wrist related activities in the HAQ of course reflects the daily activities of a species that evolved to walk on his hind legs to free up the use of hands and wrists.

This study has several limitations. Within the SHS method not only JSN as cartilage damage but also (sub)luxation from soft tissue damage is scored.[8] Based on our scores we do not know the separate influence of soft tissue damage on physical functioning. This is of course also a limitation in other studies that use the SHS score. However, for our conclusions on wrist damage this appears less important, as in the wrist, the JSN is almost exclusively determined by loss of joint space and not (sub)luxation. Also in the PIPs, (sub)luxation is rarely scored, but subluxation does influence the JSN score in MTPs and MCPs.

It has been suggested that plain radiographs are less sensitive for detecting erosive damage than alternative imaging techniques such as MRI, CT or ultrasound. We have not used these techniques, but if this has led to an underdetection of erosions in the wrist, this would mean that we have underestimated and not overestimated the effect of wrist erosions on functional ability.

JSN is also frequently seen on hand radiographs of patients with osteoarthritis, although it occurs mostly in the DIPs (not in the SHS score) and PIPs, and less frequently in the wrists.[17;18] We have not scored osteoarthritic damage separately, but as osteoarthritis frequently affects the middle aged and elderly, it is bound to be present in our population with a mean age of 54 at the onset of the study. Still, since the SHS method does not make a distinction between JSN due to osteoarthritis or RA, the combined occurrence may have enlarged the effect of JSN and thus masked the effect of rheumatoid erosions. Again, this would mean we could have underestimated the effect of erosive damage on functional disability and it could explain why in the total scores of all joints erosions are not significantly associated with functional ability. On the other hand, JSN in osteoarthritis is mostly seen in the PIPs (within the SHS score) and not that frequently in the joints assessed in the wrist[19], which may thus have influenced the relationship with the total JSN, but does not play a major role in the dominant effect of the wrist on HAQ.

We did not take large joint damage into account, which is an important determinant of physical disability.[20] However, since large and small joint damage are closely related to each other[20;21], the effect of that exclusion may be limited. It is also likely that in this cohort with relatively little damage progression in the small joints, there is even less damage in the large joints.

The correlation between narrowing and erosions scores (per joint) also influences their independent relationship with physical functioning. Separate erosion scores and narrowing scores show a substantial correlation within this data set (ρ=0.70), but the joint groups per feature correlate significantly as well (range ρ=0.21 to ρ=0.57). Especially, narrowing in the feet was strongly related with erosions in the feet, and narrowing in the wrist with erosions in the wrist. This may explain why in combined models including both features, the effect of one factor seems to dominate over the other, although both could provide relevant information.

Strong points include that we have not only assessed the damage features separately, but also included several joints groups, to see whether these may explain the relationships that were found. Also, we were able to include data of patients followed longitudinally over a period of 5 years. We believe that our patient population with recent RA, treated in a tight control setting, with limited joint damage, represents the RA patients of this and future decades. A final strong point, since joint damage does not follow a Gaussian distribution, is that we used a GEE model, which is relatively robust against violations of normality.

Because the wrist is an important determinant for disability, we may need to focus on the prevention of structural damage especially there. There is evidence that local synovitis is associated with damage progression in the same joint.[22] It has also been suggested that intra-articular corticosteroid injections suppress joint inflammation and damage progression.[23] Further research is needed to determine if local treatment in combination with effective systemic treatment has additional benefits to halt local damage progression and prevent disability.

In conclusion, in a large cohort with recent onset RA patients, treated with a tight control treatment strategy over 5 years and limited joint damage progression, the relation of such joint damage progression with functional ability as measured with the HAQ concentrates around erosions in the wrist. This may have consequences for evaluation of treatment success as well as for localized treatment strategies.

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Chapter 6

Simplified versions of the original disease activity score: validation in the BeSt trial

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ABSTRACT

Objective To evaluate three disease activity score (DAS) alternatives without the Ritchie articular index (RAI). To compare the use of patient global assessment (PGA) of disease activity versus global assessment of health (GH) in DAS, DAS alternatives and DAS28.

Methods Data from the BeSt study were used, a treatment strategy trial in early rheumatoid arthritis patients aiming at a DAS≤2.4. DAS alternatives were DAS0-1, with the RAI(0-3) reduced to a no-yes (0-1) score, DAS tender joint count (DAS-TJC53), with a 0-1 TJC in 53 separate joints, and DAS-TJC44 in 44 joints. Correlation patterns, mean difference from original, classification differences in disease activity level and patient percentages with radiological damage progression per level were determined for all scores**.**

Results In the majority of patients the scores were equal and correlation was high. Mean difference with the DAS at year 1 was -0.03 for DAS 0-1, 0.18 for DAS-TJC53 and 0.11 for DAS-TJC44. Classification agreement between scores was high (κ year 1 0.76-0.98). Patient percentages with joint damage progression were similar for all scores. DAS, DAS alternative and DAS28 perform similarly using either PGA or GH.

Conclusion Disease activity scores without the RAI perform comparably to the original DAS and may be chosen as alternatives. PGA can replace the GH in the DAS, the alternatives and DAS28.

INTRODUCTION

Measuring disease outcome in rheumatoid arthritis (RA) is important to evaluate response to treatment. Recent recommendations for management of RA propose measurement by validated composite scores including joint counts.[1;2]

The disease activity score (DAS) was the first composite measure developed to assess and compare disease activity in patients and patient groups. The DAS includes a swollen joint count in 44 joints, the Ritchie articular index (RAI)[3] for evaluation of joint tenderness in 53 joints, erythrocyte sedimentation rate (ESR) and a visual analogue scale (VAS) for patient global assessment of disease activity (PGA) or of general health (GH).[4] However, the DAS with VAS-PGA is not yet validated. DAS28 was introduced as a simplification with a no-yes swollen and tender joint count (TJC) in 28 individual joints.[5]

Although in general the usefulness and importance of the DAS and DAS28 are well accepted[6], implementation in daily practice remains challenging. Some find that DAS28 unjustly neglects the feet, but other scores might be too time consuming.[7;8] The RAI may be subjective and complicated, as it is a 0-3 graded evaluation of severity of tenderness and uses joint groups of which only the highest score per group counts.
Alternatives to the DAS, including more than 28 joints without the RAI, might be more attractive to use in daily routine or clinical trails. This study aims to evaluate three variations of the DAS compared to the original DAS. In addition, we compared DAS, DAS variations and DAS28 using VAS-GH or VAS-PGA.

PATIENTS AND METHODS

Data from the BeSt trial were used, a randomized clinical trail with three-monthly assessments aiming at a DAS≤2.4 by subsequent treatment adjustments.[9] All follow-up visits included a full 68/66 graded joint count for tenderness and swelling, as well as measurements of VAS-GH, VAS-PGA and ESR. The current analysis was performed based on 467 patients with complete data at one year follow-up.

DAS and DAS28 were calculated using the following formulae: $DAS=0.5398\sqrt{(RAI)}+0.06465(SJC44)+0.330\ln(ESR)+0.00722(VAS)$ and $DAS28=0.56\sqrt{(TJC28)}+0.28\sqrt{(SJC28)}+0.70\ln(ESR)+0.014(VAS)$. DAS alternatives were derived as follows: the DAS0-1 was calculated by the substitution of a RAI greater than0 with '1', while RAI '0' score remained '0', resulting in a maximum TJC of 26. The DAS-TJC53 was calculated with a 0=no, 1=yes TJC in the 53 joints originally assessed within the RAI, but without grouping, resulting in a maximum TJC of 53. The DAS-TJC44 was

calculated with a TJC 0=no, 1=yes in the same 44 joints that are assessed for swelling in the DAS. All DAS variations, as well as the original DAS and DAS28, were calculated with VAS-PGA and VAS-GH.

Pearson's correlation coefficients were calculated between the original DAS and DAS alternatives. The mean of these two measurements and the mean difference was calculated at year 1 and is displayed in Bland-Altman plots with limits of agreement of 1.96*SDmean difference. Patients were categorized according to previously published cutoffs into remission, low disease activity (LDA), moderate disease activity (MDA) or high disease activity (HDA).[10-14] Percentage agreement and κ statistics were calculated to assess agreement between categorization.

An area under the curve (AUC) DAS was calculated between 3 and 12 months for all scores separately using the formula: (½* DAS3 months + DAS6 months + DAS9 months + ½ * DAS12 months)/3. Baseline scores were excluded from the analysis to avoid skewness due to required HDA at inclusion.

The AUC DAS results, indicating disease activity over time, were categorized into remission, LDA, MDA and HDA. Next, the percentage of patients with a greater than 5 points Sharp van der Heijde score (SHS) progression between baseline and year 1 (consistent with the smallest detectable change and indicating rapid radiological progression) was compared in all categories for all disease activity scores. Finally, the ability of DAS alternatives to detect treatment differences at three months follow-up was assessed using the difference in scores between baseline and 3 months.

RESULTS

All patients had early (<2 years) RA and active disease at baseline with a mean (SD) DAS of 4.4 (0.9). At year 1 (n=467) median (range) RAI was 3.0 (0-52), RAI 0-1 3.0 (0-23), TJC53 4.0 (0-50), TJC44 3.0 (0-44) and TJC28 2.0 (0-28).

Correlation was high for all DAS alternatives compared to the original DAS and ranged between 0.96-0.99 ($p \leq 0.01$) at baseline and between 0.97-1.00 ($p \leq 0.01$) at year 1.
Correlation between VAS-PGA and VAS-GH at five time points was limited (ρ=0.5-0.8 $p \leq 0.01$). Nevertheless, for the original DAS, DAS alternatives and DAS28, all versions with VAS-GH correlated excellently to corresponding versions with VAS-PGA (range r=0.96-1.00 $p \leq 0.01$), both at baseline and year 1.

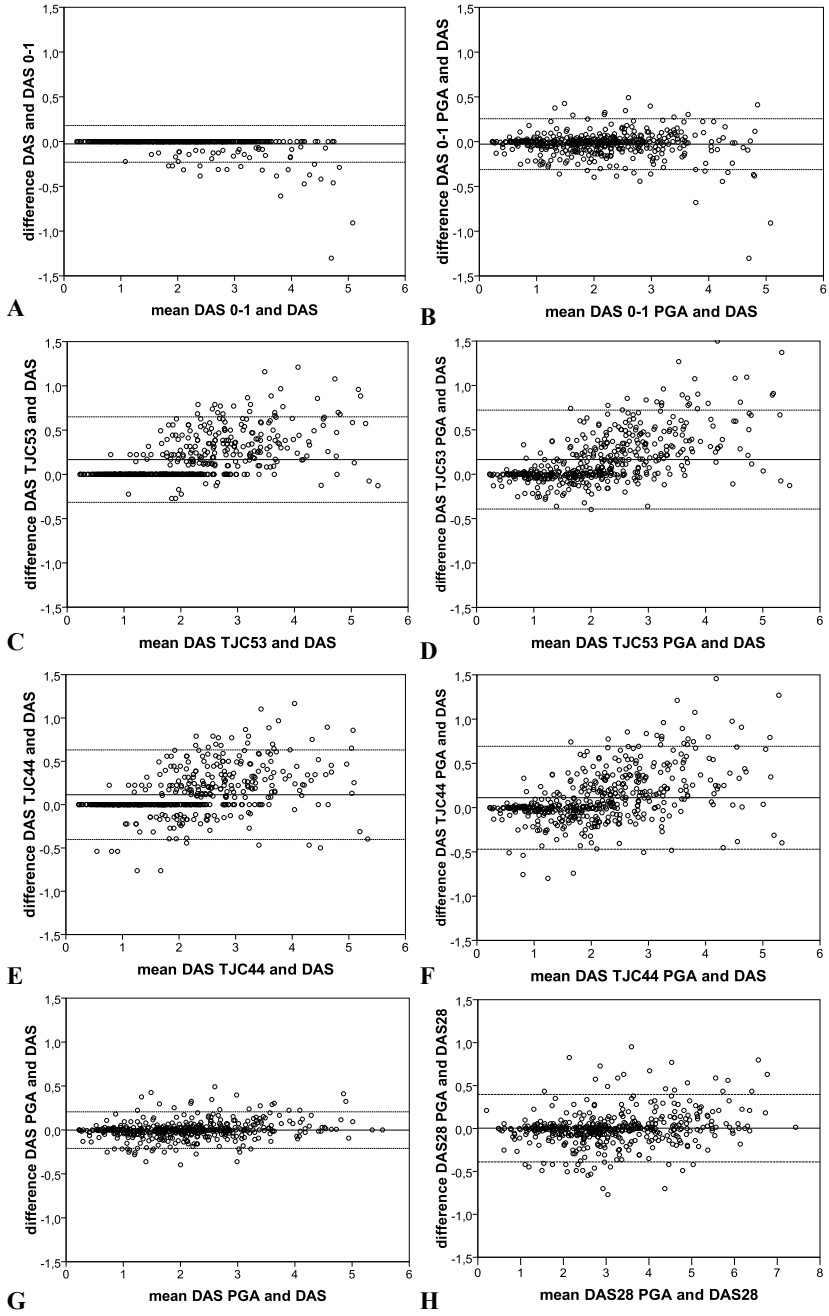

Figure 1 Mean of the 2 measurements (x-axis) versus the mean difference between the two values (y-axis) at year 1 (n=467). A DAS 0-1 GH B DAS 0-1 PGA C DAS TJC53 D DAS TJC53 PGA E DASTJC44 F DAS TJC44 PGA G DAS PGA H DAS28 PGA vs DAS28 GH

Table 1 Classification of the number of patients per disease activity category at year 1 according to the different indices, as compared with the original DAS (n=467).

		DAS			
		Remission	**LDA**	**MDA**	**HDA**
DAS PGA	**Remission**	143	7	0	0
	LDA	5	152	3	0
	MDA	0	2	123	0
	HDA	0	0	3	29
		Remission	**LDA**	**MDA**	**HDA**
DAS0-1 GH	**Remission**	148	2	0	0
	LDA	0	159	3	0
	MDA	0	0	126	2
	HDA	0	0	0	27
		Remission	**LDA**	**MDA**	**HDA**
DAS0-1 PGA	**Remission**	143	8	0	0
	LDA	5	151	6	0
	MDA	0	2	122	2
	HDA	0	0	1	27
		Remission	**LDA**	**MDA**	**HDA**
DAS-TJC53 GH	**Remission**	142	0	0	0
	LDA	6	126	1	0
	MDA	0	35	105	0
	HDA	0	0	23	29
		Remission	**LDA**	**MDA**	**HDA**
DAS-TJC53 PGA	**Remission**	138	6	0	0
	LDA	10	118	0	0
	MDA	0	37	102	0
	HDA	0	0	27	29
		Remission	**LDA**	**MDA**	**HDA**
DAS-TJC44 GH	**Remission**	142	5	0	0
	LDA	6	125	3	0
	MDA	0	31	105	0
	HDA	0	0	21	29
		Remission	**LDA**	**MDA**	**HDA**
DAS-TJC44 PGA	**Remission**	139	11	0	0
	LDA	9	118	4	0
	MDA	0	32	101	0
	HDA	0	0	24	29
		DAS 28			
		Remission	**LDA**	**MDA**	**HDA**
DAS 28 PGA	**Remission**	172	12	1	0
	LDA	6	76	11	0
	MDA	1	5	137	3
	HDA	0	0	9	36

DAS, disease activity score; GH, visual analogue scale for patient's assessment of general health; HDA, high disease activity; LDA: low disease activity; MDA: moderate disease activity; PGA: visual analogue scale for patient's global assessment of disease activity;TJC, tender joint count.

Figure 1 illustrates high agreement between DAS alternatives and the original DAS. DAS-0-1 shows a high accordance with the original DAS whereas DAS-TJC53 and DAS-TJC44 are occasionally higher as demonstrated by the higher mean difference and broader agreement limits. However, most scores remain unchanged compared with the original DAS. DAS, DAS alternatives and DAS28 perform similarly using either VAS-PGA or VAS-GH.

Categorization of all patients by different DAS is presented in Table 1. The percentage of overall agreement for all separate DAS at year 1 was high (range 82.9%-98.5%), chance corrected agreement as calculated by Cohen's κ ranged from 0.76-0.98. Significant disagreement between categorization, for example LDA versus HDA or remission versus HDA was very rare (table 1). Chance corrected agreement for all scores with VAS-GH versus VAS-PGA ranged from 0.85-0.94. Both correlation and (chance corrected) agreement between the original DAS and alternatives using either VAS score did not change over time (*see supplementary table; published online only*).

The percentages of patients with rapid radiological progression (RRP; >5 points SHS in year 1) are represented in table 2. All DAS alternatives show comparable percentages of patients with RRP within categories of disease activity level using either VAS. Overall, there are few patients with RRP in patients categorized as in remission or LDA by all composite scores.

Differences in disease activity between treatment arms (eg, treatment group 1 and 2 vs. 3 and 4) could be confirmed with all indices.

Table 2 Percentage (numbers) of patients with rapid radiological damage progression (SHS >5 points) in the first year of the study categorized according to the 'mean' disease activity level between three months and 1 year for all indices (n=386).

	Remission	LDA	MDA	HDA
DAS	9.9 (8/81)	11.0 (13/118)	19.2 (28/146)	39.0 (16/41)
DAS-PGA	10.3 (8/78)	11.9 (14/118)	18.4 (27/147)	37.2 (16/43)
DAS-0-1 GH	9.9 (8/81)	10.9 (13/119)	20.5 (31/151)	37.1 (13/35)
DAS0-1 PGA	10.3 (8/78)	11.6 (14/121)	20.0 (30/150)	35.1 (13/37)
DAS-TJC53 GH	9.1 (6/66)	12.3 (13/106)	16.6 (25/151)	33.3 (21/63)
DAS-TJC53 PGA	10.3 (7/68)	11.4 (12/105)	17.3 (26/150)	31.7 (20/63)
DAS-TJC44 GH	11.0 (8/73)	11.1 (12/108)	19.0 (28/147)	29.3 (17/58)
DAS-TJC44 PGA	10.7 (8/75)	11.5 (12/104)	17.7 (26/147)	31.7 (19/60)
DAS28	12.1 (13/107)	8.3 (5/60)	17.2 (29/169)	36.0 (18/50)
DAS28 PGA	11.2 (12/107)	8.2 (5/61)	18.0 (30/167)	35.3 (18/51)

DAS: disease activity score GH: visual analogue scale for patient's assessment of general health HDA: high disease activity LDA; low disease activity; MDA: moderate disease activity; PGA: visual analogue scale of patient's global assessment of disease activity; SHS; Sharp-van der Heijde score; TJC: tender joint count.

DISCUSSION

The original DAS is sometimes criticized for being complicated because it includes the RAI. We compared three alternatives with the original DAS with various tender joint scores and patient's assessment (by VAS) of either disease activity or GH. We found very small differences in performance of all scores. Correlation between all alternatives and the original DAS is high. All scores classify similarly patients in remission, LDA, MDA and HDA. Differences in disease activity between treatment arms could be confirmed with all indices. The percentage of patients with RRP is comparable for original and alternative scores in different disease activity levels.

Our results on the use of VAS-PGA and VAS-GH demonstrate that either can be used as suggested by the EULAR handbook[15], and affirm the single study on this subject by Khan *et al*.[16] Although individual VAS scores itself correlate only moderately, which indicates that they cover a different concept, when used as part of the DAS, DAS alternatives or DAS28 the total effect is negligible, mostly because of limited weight that is given to this component.

When categorizing patients in disease activity levels we see that DAS-TJC53 and DAS-TJC44 are classifying more MDA and HDA, less LDA and similar remission percentages. This can be explained because both DAS-TJC53 and DAS-TJC44 assess more joints separately, causing a small shift to a higher disease activity category. However, the vast majority of remission patients have none to one painful joints in which disease activity by any score, and thus remission percentages, remain the same. DAS28 shows a different pattern, with many more patients assessed as being in remission and consequently a smaller LDA group, in line with discussions about the remission definition of DAS28.[17] The percentage of patients with RRP in DAS28 remission was higher compared to the (alternative) DAS.

The slightly higher disease activity measured with both DAS-TJC44 and DAS-TJC53 with corresponding higher classification leads to less radiological damage in the HDA group of these scores. Differences are nonetheless very small. The percentages of patients with RRP were not influenced by the use of VAS-PGA or VAS-GH, neither in the alternative DAS nor in the original DAS[28].

A limitation to the current study is caused by rapid reduction in disease activity in this early severe RA population, leading to an infrequency of graded joint scores above 1, which explains the overlap between DAS0-1 and DAS. If in daily practice RAI scores of 3 are more prevalent, we expect a greater difference between the original DAS and alternative versions in higher activity levels. In modern practice were treatment is aimed at achieving remission (or at least LDA), high grading may become rare. All our results regarding DAS[28] and DAS

variants are valid at the group level and for the vast majority of patients, however for some individual patients differences between scores may be larger.

In conclusion, we have shown that scoring the presence or absence of tenderness in individual joints to calculate a disease activity score performs as good as scoring a graded tenderness score in joints groups. In daily practice or clinical studies, using a DAS alternative may be much easier than the original DAS with RAI. The score based on assessment of tenderness in the same 44 joints assessed for swelling may be most practical.

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Chapter 7

Assessment of global disease activity in RA patients monitored in the METEOR database: The patient's versus the rheumatologist's opinion.

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ABSTRACT

Objectives

To compare the patient's (PtGDA) and physician's (PhGDA) assessment of global disease activity and to identify factors that might influence these differences, as well as factors that may influence the patients and the physicians score separately.

Methods

Anonymous data were used from 2118 Dutch patients included in the METEOR database. PtGDA and PhGDA were scored independently on a 100mm visual analogue scale (VAS) with 0 and 100 as extremes. The agreement, Intraclass correlation coefficients (ICC), was calculated and a Bland Altman plot was created to visualize the differences between PtGDA and PhGDA. Linear Mixed Model analysis was used to model PtGDA and PhGDA. Logistic repeated measurements were used to model the difference in PtGDA and PhGDA (PtGDA>PhGDA vs. PtGDA≤PhGDA). Gender, age, swollen joint count, tender joint count, VAS pain, disease duration and ESR were considered as possible determinants in both models.

Results

Mean (SD) age was 57 (15) years and 67% of the patients were female. Agreement between PtGDA and PhGDA was moderate (ICC: 0.57). Patients scored on average 11 units higher (worse) than rheumatologists (95% limits of agreement: -25.2 to 47.6). Patient's perception of pain (VAS) was positively associated with a PtGDA being higher than PhGDA. Similarly, ESR and swollen joint counts were positively associated with a PtGDA being lower or equal to the PhGDA.

Conclusion

Patients rate global disease activity consistently higher than their rheumatologists. Patients base their judgment primarily on the level of pain; physicians on the level of SJC and ESR.

INTRODUCTION

The importance and use of patient reported outcomes (PROs) in health care increased during the past decades. PROs are considered valuable in measuring status and change in health care [1]. However, in addition to the PRO, similar information is also collected by the physician, e.g. assessment of level of disease activity. As patients and physicians may differ in their perception of health status, discordant observations may occur and may affect patient care. For example, patients are likely to report dissatisfaction with a treatment if their physician underestimates their perceived level of disease activity [2-4].

The 100mm visual analogue scale (VAS) is an instrument used to measure global disease activity (GDA) in rheumatoid arthritis (RA). It can be completed by the patient (PtGDA) (and is then considered then a PRO) as well as by the physician (PhGDA). Discordances between patients and rheumatologists rating their impression of GDA on a VAS have been reported; patients tend to score their GDA higher than their physician [5,6]. It is not clear which factors determine the occurrence and magnitude of these discrepancies between patient's and physicians' perceptions.

The METEOR (Measurement of efficacy of Treatment in the Era of Rheumatology) database provides data on several patient- and physician-reported outcome measures in RA. Here we have compared PtGDA and PhGDA reported in individual patients, and identified which factors determined the discordance in PtGDA and PhGDA.

METHODS

Patients

Data collected in the ongoing prospective international METEOR database were used. METEOR is an acronym for Measurement of efficacy of Treatment in the Era of Rheumatology hat has been started in 2008. METEOR is used by rheumatologists to monitor patients with rheumatic diseases. Data are collected in a central database in a completely anonymous way. Both newly diagnosed patients and patients with more advanced disease are included in de database. Measures of disease activity and Health Assessment Questionnaire data are registered every visit. Currently, the tool is used worldwide and data is available from 100 hospitals, which included more than 14.800 patients. More details on the METEOR database are described elsewhere [9] .

A sample of 2.118 patients was taken from the METEOR database covering the time span between 2008 and 2011. The number of visits (8.509 in total) varied with a range of 1 to 17 visits per patient as did time intervals between visits. PtGDA and PhGDA were measured on a 100mm visual analysis scale (VAS) with 0 (best possible) and 100 (worst possible) as extremes. PtGDA and PhGDA separately were operationalized as continuous variables. The

20mm difference between PtGDA and PhGDA was used as a binary outcome variable (patient scores higher versus rheumatologist scores equal or higher). A difference in rating of 20mm between PtGDA and PhGDA score was chosen as cutoff value, since it was considered to be a relevant discordance in previous literature[5].

Statistical analyses

Descriptive statistics were performed using the mean and standard deviation (SD) or median and interquartile ranges (IQR) as appropriate for continuous variables, and number and percentages for categorical variables.

A Bland and Altman plot was performed to visualize the differences between PtGDA and PhGDA. This is based on the standard deviation of the differences in PtGDA and PhGDA calculated from variance components in a linear mixed model (LMM), and used to construct the 95% limits of agreement [7]. The agreement between patient and physician was expressed as intraclass correlation coefficient (ICC) using variance components in a LMM with a random intercept for patients.

LMM was also used to model the PtGDA and PhGDA. Gender, age, swollen joint count, tender joint count, pain (VAS), disease duration (diagnosis until first visit) and erythrocyte sedimentation rate (ESR) were considered as possible determinants for the model.

Non-linear mixed modeling (repeated measures logistic regression) was used to model the difference in PtGDA and PhGDA as binary outcome (patient's score higher than physician's score as "event"). Gender, age, swollen joint count, tender joint count, pain (VAS), disease duration and ESR were considered as possible determinants for the model.

Software programs SAS version 9.2 and SPSS version 17.0 were used for the analyses and P-values smaller than 0.05 were considered statistically significant.

RESULTS

Of the 2118 patients, 1338 (67%) were female. The mean (SD) age at entry was 57 [15] years (table 1).

Agreement between PtGDA and PhGDA was moderate (ICC: 0.57; $p<0.01$). Patients rated their GDA on average 11mm higher (worse) than rheumatologists at the first registered visit (95% limits of agreement: -25.2 to 47.6). A few scores showed large discrepancy between the PtGDA and PhGDA score, on average 75 mm (figure 1). Patients scored the GDA significantly higher when the number of tender joint count, and VAS pain increased ($p<0.01$). VASpain ($p<0.01$), number of swollen and tender joint count ($p=0.04$ and ESR ($p<0.01$) independently contributed to an increase in GDA score by the physician. Physician's score decreased by increasing disease duration ($p=0.03$) and patient's scores increased by decreasing swollen joint count, ($p=0.04$) (table 2).

Pain (VAS), ESR and the number of swollen joints all independently contributed to the differences between patient's GDA and physician's GDA. A higher patient GDA score compared to the physicians score is positively correlated with pain (VAS). A higher or equal GDA score of the physician compared to the patient is positively correlated with ESR and swollen joint count. (Table 3)

Table 1: Baseline characteristics (Visit 1)

Variables	Patients	N total (N=2118)
Age, mean (SD)	57 (15)	1879
Female, N (%)	1338 (67)	2007
CRP, median (IQR)	5 (3-13)	167
ESR, median (IQR)	14 (6-29)	1489
DAS 28, mean (SD)	3.2 (1.4)	1408
HAQ, mean (SD)	0.9 (0.3)	575
Duration complaints until diagnosis (mo), median (IQR)	4 (1-12)	758
Duration complaints until first registered visit (yrs), median (IQR)	7 (2-15)	775
Duration diagnosis until first registered visit (yrs)median (IQR)	6 (1-13)	790
CCP positive, N (%)	212 (64)	334
RF positive, N (%)	726 (74)	987
Erosions present, N (%)	596 (65)	923
Swollen joint count 28, median (IQR)	1 (0-3)	1872
Tender joint count 28, median (IQR)	2 (0-4)	1872
VAS, median (IQR)		
Global health physician	21 (10-41)	903
Global health patient	34 (14-55)	1615
Pain patient	39 (15-60)	1476

N: number; SD: standard deviation; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; IQR: inter quartile range; DAS: disease activity score; HAQ: health assessment questionnaire; Mo: months; yrs: years; CCP: anti cyclic citrullinated peptides antibodies; RF: rheumatoid factor; VAS: visual analogue scale

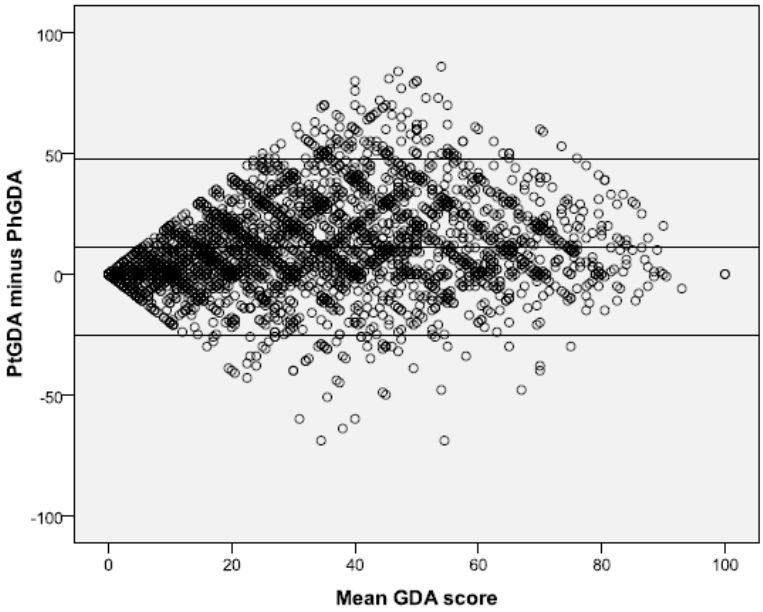

Figure 1: Bland Altman's plot: GDA patient versus GDA physician
GDA patient: global disease activity according to the patient; GDA physician: global disease activity according to the physician; PtGDA: global disease activity according to the patient; PhGDA: global disease activity according to the physician

Table 2: Linear mixed model predictors of GDA disease activity by patients and physicians

	PtGDA		PhGDA	
Variable	**β Estimate, 95% CI**	**p-value**	**β Estimate, 95% CI**	**p-value**
Male	-0.73 -2.58, 1.12	0.44	-0.25 -2.55, 2.05	0.07
Age	-0.03 -0.10, 0.03	0.33	-0.07 -0.15, 0.01	0.08
Disease duration (yrs)	-0.02 -0.11, 0.08	0.71	-0.10 -0.17, -0.03	0.03
ESR	0.04 -0.00, 0.09	0.07	0.09 0.05, 0.12	<0.01
SJC28	-0.51 -0.94, -0.09	0.02	0.53 0.02, 1.04	0.04
TJC28	0.74 0.43, 1.05	<0.01	0.41 0.03, 0.80	0.04
VAS pain patient	0.45 0.41, 0.49	<0.01	0.20 0.15, 0.25	<0.01

PtGDA: global disease activity according to the patient; PhGDA: global disease activity according to the physician; β: beta; CI: confidence interval; yrs: years; ESR: erythrocyte sedimentation rate; SJC28: swollen joint count in 28 joints; TJC28: tender joint count in 28 joints; VAS: visual analogue scale

Table 3: Non-linear mixed model predictors of GDA difference between patients and physicians

	PtGDA versus PhGDA[a]	
Variable	**β Estimate, 95% CI**	**p-value**
Male	0.18 -0.12, 0.48	0.24
Age	-0.00 -0.01, 0.00	0.38
Disease duration (yrs)	0.01 -0.01, 0.02	0.26
ESR	-0.01 -0.00, -0.02	<0.01
SJC28	-0.29 -0.37, -0.20	<0.01
TJC28	-0.04 -0.10, 0.02	0.17
VAS pain patient	0.05 -0.06, 0.06	<0.01

PtGDA: global disease activity according to the patient; PhGDA: global disease activity according to the physician; β: beta; CI: confidence interval; yrs: years; ESR: erythrocyte sedimentation rate; SJC28: swollen joint count in 28 joints; TJC28: tender joint count in 28 joints; VAS: visual analogue scale; [a] 1=patient scores higher; 0=physician scores higher or equal; reference category=0

DISCUSSION

On average, patients tend to score GDA systematically higher than rheumatologist. The agreement between both is only moderate. Determinants of the differences in scores are pain (more pain means higher GDA by the patient), and swollen joint count as well as ESR (higher SJC/ESR means higher GDA by physician). PtGDA and PhGDA separately are partly associated with the same determinants: tender joint count and pain are both taken into consideration by the patients and physicians assessment of GDA. In addition, the objective measures, swollen joint count and ESR, are taken into consideration by the physician. Expectedly, physicians put more weight on the value of ESR and SJC, whilst patients put more weight on pain.

Patients and physicians take partly the same determinants in consideration when they assess global disease activity; they both consider tender joints and pain of the patient. However the patient does not take into consideration objective measures. In fact the swollen joint count even has a negative association with PtGDA which we cannot explain. The physician takes both objective (swollen joint count, acute phase reactants and disease duration) and subjective (patients pain and tender joint count) measures in consideration in assessing the GDA. The discrepancy in factors both patients and physicians take into consideration for their

GDA assessment might lead to the systematic difference in patients and physicians scores of almost 11 units (on a scale from zero to 100) and to the only moderate agreement between patients and physicians. Other studies also reported discordances between patients and physicians in rating the GDA. Barton et al. showed that patients' GDA score was on average 15 points higher than the physicians' mean GDA score [8]. Also, the QUEST-RA study showed a higher mean GDA of patients (approximately 11 points) than GDA of physicians [5]. In concordance with the latter study, we also found a difference of approximately 11 points. However, it is questionable if 11 points is a clinical relevant discrepancy between patient' and physician' GDA score since we defined 20 points to be a difference. On the other hand, the moderate agreement between patients and physicians might support that patients and physicians rate RA disease activity differently. This confirms the statement of an earlier study that patient and physicians differ in perception of disease activity [6].

A previous study, carried out in several European countries, also showed only a moderate agreement between GDA patient and GDA physician [5]. Other studies, performed in the United States and in Europe showed low correlations and low agreement between physician and global health assessments [9, 10]. The discrepancies between the results of previous studies might suggest differences between countries in GDA of patient and physician due to cultural factors.

Our study shows that the difference in scoring might be explained by differences in the interpretation of ESR, swollen joints and pain. Pain is more likely to be associated with an equal or higher score of the patient. This statement was confirmed by the large QUEST-RA study, which studied factors on discordance between GDA of the patient and that of the physician. Pain was one of the most important factors that caused discordances. Pain increased significantly when patient scored GDA higher compared to the physician. Furthermore, the QUEST-RA also used 20mm difference in GDA score as the cut off value of a true difference between patient and physician [5].

In our study, patients with a high ESR and swollen joint count are more likely to be scored higher by the physician. A previous study confirms this result. [8]. Another study showed that, besides swollen joints, physician put more weight on ESR than patients [6].

As we can see from the results of our study, patients and physicians focus on different factors when assessing disease activity. Patients are more influenced by subjective feelings, such as pain, while physicians base their score more on objective measures, such as number of swollen joints and 'blood levels'. This is supported by previous literature [11]. Patients base their assessments on needs, priorities, experiences, expectations and attitude, which are all subjective domains. Physicians, on the other hand, rely on the patient's physical health status, which is considered more objective in nature [12, 13] .

This study has some limitations. The first is missing values, as these might not be randomly missing. Patients that perform worse in their opinion may stay at home and miss an appointment with the physician. This can result in selection of patients with unknown consequences.

Another limitation is that the included patients were not always newly diagnosed RA patients. Some patients are already treated for years and patients expectations and perceptions can change as a result of improvement or worsening of their health [14]. Therefore, long treatment duration might influence patient's assessment of GDA.

In conclusion, patients and physicians both assess GDA using partly similar determinants. Differences in GDA scores may be explained by pain, ESR and swollen joint count. Patients put more weight on pain and physicians on ESR and swollen joint count. Also cultural differences may have contributed to the moderate level of agreement between patients and physicians. We already see a difference in agreement between patient's and physician's score by comparing studies performed in several countries.

In clinical practice, it should be recommended to spend more time educating patients on how to rate the global disease activity. Patients need to be clearly informed on the difference between the disease activity and pain, as patients let pain influence their GDA score. A good understanding of the GDA score by the patient is important since a previous study showed that patients with a high PtGDA score, while having a normal ESR and low SJC and TJC, are not in remission [15].

Further research should be conducted to find out what the clinical impact is of these discrepancies between patients and physicians since previous research might suggest that treatment strategy is only based on the rheumatologist's opinion and not on the patient's opinion or the DAS28 [16]. Also differences in PtGDA and PhGDA score per country should be studied and whether GDA assessment is influenced by cultural factors.

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METEOR is a free-for-use online software program developed by the Merit Foundation and aims to improve treatment of RA by the measurement of patient outcomes and benchmarking data in a multi-national database. Data is securely sent and stored anonymously.

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Chapter 8

Association with joint damage and physical functioning of 9 composite indices and the 2011 ACR/EULAR remission criteria in rheumatoid arthritis

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ABSTRACT

Objective To compare nine disease activity indices and the new American College of Rheumatology (ACR)/European League against Rheumatism (EULAR) remission criteria in rheumatoid arthritis (RA) and to relate these to physical function and joint damage progression.

Methods 5-year data from the BeSt study were used, a randomized clinical trial comparing four treatment strategies in 508 patients with recent onset RA. Every three months disease activity was assessed with nine indices (DAS, DAS-C-reactive protein (DAS-CRP), DAS28, DAS28-CRP, Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index, and three DAS versions with adjusted tender joint scores) and were categorized into remission, low, moderate and high disease activity (LDA, MDA, HDA). In addition, the recent ACR/EULAR clinical trial and practice remission was assessed three-monthly, with 28 and 66/68 joint counts. For each index, Generalized Estimating Equations analyses were performed to relate disease activity levels and the absence/presence of remission to three-monthly assessments of physical functioning and annual radiological progression.

Results From the composite indices, CDAI and SDAI were most stringent definitions of remission and classified more patients as in LDA. DAS28 and DAS28-CRP had the highest proportions remission and MDA, and a smaller proportion LDA. ACR/EULAR remission percentages were comparable to CDAI/SDAI. The variant including CRP and 66/68 joint counts was the most stringent.
For all indices, higher levels of disease activity were associated with decreased physical functioning and more radiological damage progression. Despite differences in classification between indices, no major differences in the relation to the two outcomes were observed.

Conclusion The associations of nine composite indexes and ARC/EULAR remission criteria with functional status and joint damage progression showed high accordance, whereas the proportions of patients classified in the disease activity levels differed.

INTRODUCTION

Assessing disease activity and response to treatment is of vital importance in rheumatoid arthritis (RA), both in clinical trials and in daily practice. By early and effective suppression of inflammation, severe joint destruction and functional disability can be prevented.[1;2] The use of a tight controlled treatment approach, including frequent disease activity measurements and treatment towards a preset goal, have further improved outcomes.[3-6]
In order to measure disease activity, several composite scores have been developed, such as the Disease Activity Score (DAS)[7], the Disease Activity Score in 28 joints (DAS28)[8], the Clinical Disease Activity index (CDAI)[9], and the Simplified Disease Activity Index (SDAI)[10] as a combination of variables might represent actual disease activity better than single measures.[11] We recently validated three new variants of the original DAS with adjusted tender joint counts (TJC).[12]
All composite scores on continuous scales can be subdivided into categories (remission, low disease activity (LDA), moderate disease activity (MDA) and high disease activity (HDA)), which are nowadays also being used as tools to guide treatment decisions for individual patients. Beside these index based criteria, an international taskforce from the American College of Rheumatology (ACR) and the European League against Rheumatism (EULAR) recently developed new remission criteria for clinical practice and clinical trials.[13]
In previous studies but the number of indices compared, patient numbers or follow-up duration were limited and few studies related disease activity levels to functional ability or radiological damage progression in time. Little is known about the performance of the new ACR/EULAR remission criteria in comparison with existing index based remission definitions.[14] To be able to compare results of registries or clinical trials reliably using different composite scores, a more extended comparison is needed.
Therefore, the aims of this study were: 1. to compare classification of disease activity according to nine composite scores into remission, LDA, MDA and HDA; 2. to compare remission percentages of composite scores and new ACR/EULAR remission criteria; and 3. to relate these levels of disease activity to physical functioning and progression of joint damage.

METHODS

Patients

Five-year follow-up data of the BeSt study were used, in which 508 patients with recent-onset rheumatoid arthritis with a disease duration ≤2 years were randomized into 4 dynamic treatment strategies: 1. sequential monotherapy; 2. step-up combination therapy; 3. initial combination with prednisone; 4. initial combination with infliximab. Details have been described elsewhere.[15]Treatment was adjusted based on three-monthly measurements of

disease activity.[7;16] If DAS was >2.4 the next step of the protocol was taken. If DAS was ≤2.4 for ≥6 months the medication was tapered to monotherapy in maintenance dose. From the third year, the last disease-modifying anti rheumatic drug (DMARD) could be tapered and discontinued if DAS was <1.6 for ≥6 months in patients on monotherapy in maintenance dose. The last DMARD was restarted if DAS was ≥1.6. The study was approved by the Medical Ethics Committees, and all patients gave written informed consent.

Clinical assessments

Every three months the following variables were collected: 66 swollen joint count (SJC), 68 tender joint count (TJC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), patient's assessment of global health (VAS-GH) on a visual analogue scale (0-100mm) and physician's global assessment of disease activity (VAS-PGA).

At each time point, disease activity was calculated according to the following composite indices *(see supplementary table S1; published online only*): the original DAS with ESR or CRP (DAS; DAS-CRP), DAS28 with ESR or CRP (DAS28; DAS28-CRP), SDAI, CDAI, and 3 variants of the original DAS with adjustments in the TJC of the score.[12] In the first adjustment (DAS0-1), the same joints and joint groups are used as in the Ritchie Articular Index, but scoring only absence (0) or presence (1) of tenderness instead of grading tenderness from 0 to 3. In the second adjusted version (DAS-TJC53), grading as well as assessment of joint groups were omitted; all 53 joints of the RAI were counted separately for absence or presence of tenderness. In the last version, only 44 joints (equal to the joints assessed for swelling) were assessed for absence or presence of tenderness (DAS-TJC44). Furthermore, the presence or absence of ACR/EULAR remission was assessed using the following components: SJC≤1, TJC≤1, VAS global health ≤1cm and CRP ≤1g/dL. Four variants were used (*see supplementary table S1; published online only*): a clinical trial definition including CRP and a clinical practice definition excluding CRP, each with a 28/28 swollen/tender count and both with a 66/68 swollen/tender joint count.

At each time point, patients were classified as being in remission (yes/no) according to 9 composite indices and ACR/EULAR remission-criteria or in low (LDA), moderate (MDA) or high disease activity (HDA) according to the composite indices based on previously published cut-off points.[16-20](*see appendix supplementary table S1; published online only)* For the three simplifications of the original DAS cut-offs of the original DAS were used.

Outcome assessments

Every three months functional capacity was assessed using the Health Assessment Questionnaire(HAQ).[21] Joint damage was assessed on annual radiographs from baseline until year 5 per patient in random order using the Sharp/vdHeijde method[22], by two independent readers, blinded to patient identity. The mean scores of the two readers were used.

Statistical analysis

SPSS version 17.0 was used for all analyses. To assess the relationship between disease activity category according to nine disease activity indices, ACR/EULAR remission criteria and HAQ, four Generalized Estimating Equations (GEE) analyses were performed per index: first with HAQ per patient as continuous outcome and second with HAQ per patient as dichotomous outcome (for 3 cut-off points: HAQ>1.0, HAQ>0.5, HAQ>0).

The disease activity level was added as explanatory variable, categorized as remission, LDA, MDA and HDA, or as remission yes/no. All analyses were corrected for baseline HAQ, time, age, gender and treatment group with additional correction for time*time in the continuous HAQ analysis to approach linearity. For each disease activity level (remission, LDA, MDA, HDA or remission yes/no) and per composite score, the mean HAQ scores (continuous outcome) and probabilities of a HAQ above the cut-off (dichotomous outcome) were estimated within the GEE model. For this purpose the Estimated Marginal Means subcommand was used, which fills in the regression equation by fixing continuous values of covariates at their means and estimates HAQ values for each level of a categorical variable. This option was used to avoid differences in distribution of confounders between different disease activity levels and composite scores.

To assess the relationship between level of disease activity according to the different composite indices, ACR/EULAR remission and the progression of joint damage, four GEE analyses were performed for each composite index: first with absolute annual SHS progression per year as continuous outcome and then with annual SHS progression as dichotomous outcome (cut-off points: ≥1, ≥3, ≥5 SHS units progression per year). Since radiographs were taken annually and disease activity measured every three months, for the analysis including composite scores only, the mean disease activity per year was calculated by the following formula: (½*DAS1+DAS2+DAS3+DAS4+½*DAS5)/4 and categorized into remission, LDA, MDA and HDA. This categorical mean disease activity level per year or remission yes/no was added as explanatory variable. Remission per year was defined as ≥3 out of 4 visits remission. Only patients with complete data were used; for single missing values we used a last observation carried forward method before calculating mean disease activity per year.

The SHS analyses were corrected for total SHS at the beginning of each year, time, presence of cyclic-citrullinated peptides antibodies (anti-CCP), treatment group, age and gender. Mean progression scores and probabilities for progression were estimated for each index and each disease activity level using estimated marginal means.

The GEE method with M-dependence covariance structure was used to correct for within patient correlation, since HAQ and joint damage progression were repeatedly measured over time.

RESULTS

At baseline (n=508), patients had active disease with a mean (SD) DAS of 4.4 (0.9) and a mean (SD) HAQ of 1.4 (0.9). Mean (SD)/median (IQR) SHS at baseline was 7.1 (10.2) / 3.0 (0.5 – 9.5).

Spider diagrams

Spider diagrams (*figures 1a and 1b)* illustrate the classification into disease activity categories according to the different composite indices. Irrespective of the composite score used, more patients were classified in higher disease activity categories in year 1 than in year 5, reflecting treatment efficacy. From the composite indices, CDAI and SDAI had the most stringent definitions of remission and thus classified a relative high proportion of patients in LDA. The proportions of patients in MDA and HDA were comparable between CDAI, SDAI and DAS and DAS-CRP. DAS28 and DAS28-CRP had the highest proportions in remission and in MDA,

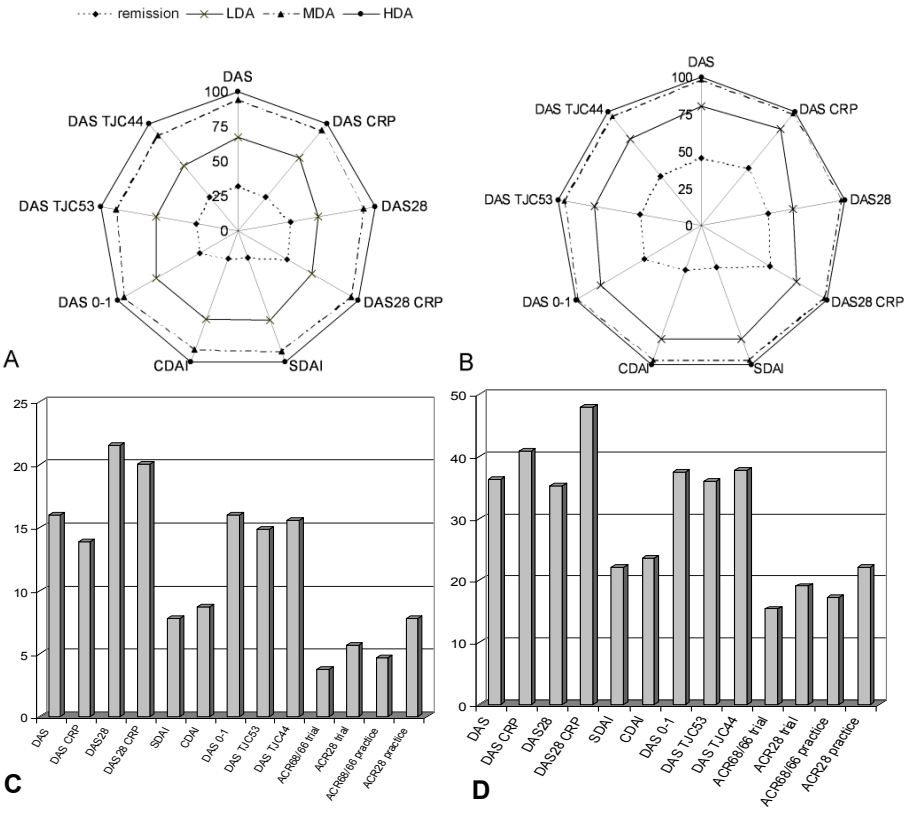

Figure 1: Spider diagrams showing the cumulative percentage of patients in remission, low, moderate and high disease activity according to the different composite indices at t=1 year (panel A, n=415) and t=5 year (panel B, n=317). Bar charts show the percentage (number) of patients in remission (>=3 visits) during the first year (panel C, n=424) and the fifth year (panel D, n=267) per remission definition.

and a relatively small proportion of patients in LDA. Of adjusted DAS versions, DAS0-1 was very comparable with the original DAS. The absolute DAS-TJC53 and, to a lesser extend, DAS-TJC44 was slightly higher than the original DAS, resulting in higher percentages of patients in HDA. Figures 1c and 1d show the remission percentages of the composite indices and ACR/EULAR remission criteria. The most stringent definition is the clinical trial definition with 66/68 joints. Clinical trial remission-criteria showed lower remission percentages than clinical practice remission-criteria, as did the criteria including a full 68/66 joint count compared with the criteria based on a 28 joint count. Numerical remission percentages per definition are presented online (*see supplementary table S2 and S3; published online only*).

Relation with functional ability

In general, predicted HAQ values among disease activity levels based on the composite indices showed high agreement *(table 1)*. As expected, HAQ values were lower when the level of disease activity was lower. Although CDAI and SDAI classified fewer patients in remission, CDAI and SDAI remission was not associated with lower HAQ scores than in other indices *(table 1)*. DAS28 variants, compared to other indices, classified the highest proportion of patients in remission and MDA and fewer patients in LDA, but HAQ levels in remission, LDA

Table 1: Mean predicted HAQ score for patients in remission, LDA, MDA and HDA.

	Remission	LDA	MDA	HDA
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
DAS	0.48 (0.40 – 0.55)	0.61 (0.53 – 0.69)	0.83 (0.75 – 0.91)	1.24 (1.14 – 1.33)
DAS CRP	0.49 (0.41 – 0.57)	0.63 (0.55 – 0.71)	0.87 (0.79 – 0.95)	1.27 (1.17 – 1.38)
DAS28	0.49 (0.41 – 0.57)	0.60 (0.52 – 0.68)	0.76 (0.67 – 0.84)	1.20 (1.10 – 1.29)
DAS28 CRP	0.52 (0.44 – 0.60)	0.62 (0.54 – 0.70)	0.80 (0.72 – 0.89)	1.28 (1.18 – 1.38)
SDAI	0.47 (0.39 – 0.55)	0.60 (0.52 – 0.68)	0.83 (0.75 – 0.92)	1.24 (1.14 – 1.33)
CDAI	0.46 (0.38 – 0.54)	0.60 (0.52 – 0.68)	0.83 (0.74 – 0.91)	1.18 (1.09 – 1.28)
DAS 0-1	0.48 (0.40 – 0.56)	0.61 (0.53 – 0.70)	0.84 (0.76 – 0.92)	1.26 (1.16 – 1.36)
DAS TJC53	0.47 (0.39 – 0.55)	0.60 (0.52 – 0.68)	0.77 (0.69 – 0.85)	1.13 (1.03 – 1.22)
DAS TJC44	0.48 (0.40 – 0.56)	0.60 (0.52 – 0.68)	0.78 (0.70 – 0.86)	1.14 (1.05 – 1.24)

Covariates and factors appearing in the model are fixed at the following values: baseline HAQ 1.4; visit 10.6; age 53.9; treatment group 1; female gender. LDA: low disease activity; MDA: moderate disease activity; HDA: high disease activity; CI: confidence interval; DAS: disease activity score; CRP: C-reactive protein; DAS28: disease activity score in 28 joints; SDAI: simplified disease activity index; CDAI: clinical disease activity index; DAS 0-1, disease activity score with RAI 0-1; TJC53: tender joint count 53 joints; TJC44: tender joint count 44 joints

Table 2: Estimated probability (95% CI) for HAQ scores>0.5 in patients in remission, LDA, MDA and HDA.

	Remission	LDA	MDA	HDA
	Probability (95% CI)	Probability (95% CI)	Probability (95% CI)	Probability (95% CI)
DAS	0.34 (0.27-0.40)	0.49 (0.42-0.57)	0.69 (0.63-0.75)	0.90 (0.86-0.93)
DAS CRP	0.34 (0.27-0.41)	0.52 (0.44-0.59)	0.73 (0.67-0.79)	0.90 (0.85-0.94)
DAS28	0.36 (0.29-0.43)	0.48 (0.40-0.55)	0.63 (0.56-0.70)	0.87 (0.83-0.92)
DAS28 CRP	0.39 (0.32-0.46)	0.51 (0.44-0.58)	0.68 (0.62-0.75)	0.90 (0.86-0.94)
SDAI	0.31 (0.25-0.38)	0.47 (0.40-0.55)	0.70 (0.63-0.76)	0.86 (0.81-0.91)
CDAI	0.31 (0.25-0.38)	0.47 (0.39-0.54)	0.70 (0.64-0.76)	0.85 (0.80-0.89)
DAS 0-1	0.34 (0.27-0.41)	0.50 (0.43-0.58)	0.70 (0.64-0.76)	0.91 (0.88-0.95)
DAS TJC53	0.34 (0.28-0.41)	0.49 (0.42-0.56)	0.65 (0.59-0.72)	0.85 (0.80-0.89)
DAS TJC44	0.35 (0.28-0.41)	0.49 (0.41-0.56)	0.66 (0.59-0.72)	0.85 (0.81-0.90)

Covariates and factors appearing in the model are fixed at the following values: previous HAQ 1.4; visit 10.6; age 53.9 treatment group 1; female gender. LDA: low disease activity; MDA: moderate disease activity; HDA: high disease activity; CI: confidence interval; DAS: disease activity score; CRP: C-reactive protein; DAS28: disease activity score in 28 joints; SDAI: simplified disease activity index; CDAI: clinical disease activity index; DAS 0-1, disease activity score with RAI 0-1; TJC53: tender joint count 53 joints; TJC44: tender joint count 44 joints

Table 3 Mean predicted delta SHS for patients in remission, LDA, MDA and HDA.

	Remission	LDA	MDA	HDA
	Mean (95%CI)	Mean (95%CI)	Mean (95%)	Mean (95%)
DAS	3.49 (-0.06-7.04)	5.50 (2.35-8.66)	7.34 (4.09-10.60)	11.70 (7.39-16.01)
DAS CRP	4.08 (0.95-7.21)	5.44 (2.34-8.55)	6.69 (3.58-9.81)	11.72 (7.09-16.35)
DAS28	3.57 (0.12-7.02)	4.61 (1.43-7.79)	6.88(3.77-9.98)	10.83 (6.83-14.83)
DAS28 CRP	3.54 (-0.03-7.10)	5.54 (2.34-8.74)	8.05 (4.80-11.30)	13.18 (8.51-17.84)
SDAI	4.01 (0.76-7.26)	4.67 (1.37-7.97)	7.39 (4.16-10.61)	11.48 (7.25-15.71)
CDAI	3.85 (0.64-7.06)	4.66 (1.41-7.91)	7.40 (4.18-10.61)	10.95 (6.89-15.00)
DAS 0-1	3.41 (-0.05-6.87)	5.45 (2.33-8.57)	7.21 (4.01-10.42)	12.66 (8.21-17.12)
DAS TJC53	3.54 (0.17-6.90)	4.78 (1.45-8.11)	6.89 (3.69-10.08)	9.92 (6.02-13.82)
DAS TJC44	3.64 (0.28-7.00)	4.92 (1.60-8.24)	7.16 (3.96-10.36)	10.24 (6.25-14.23)

Covariates and factors appearing in the model are fixed at the following values: previous SHS 10.3, year 2.8, age 53.8, treatment group 1, anti-CCP positive patients; female gender. LDA: low disease activity; MDA: moderate disease activity; HDA: high disease activity; CI: confidence interval; DAS: disease activity score; CRP: C-reactive protein; DAS28: disease activity score in 28 joints; SDAI: simplified disease activity index; CDAI: clinical disease activity index; DAS 0-1, disease activity score with RAI 0-1; TJC53: tender joint count 53 joints; TJC44: tender joint count 44 joints

and MDA were comparable to other indices. Patients in HDA according to DAS-TJC53 and DAS-TJC44 had lower HAQ scores than patients in HDA according to other indices.

Similar results were seen with regard to the probability of a HAQ score >0.5 as outcome (*table2*). Overall 34-91% of patients were limited in functioning depending on their disease activity level. HDA corresponds with a higher change of functional limitations. In general there was little difference between percentages of HAQ scores >0.5 for all composite scores,

Table 4: Estimated probability in % (95% CI) for SHS progression ≥3 units in patients in remission, LDA, MDA and HDA.

	Remission	LDA	MDA	HDA
	Probability (95% CI)	Probability (95% CI)	Probability (95% CI)	Probability (95% CI)
DAS	0.10 (0.06 – 0.15)	0.18 (0.12 – 0.25)	0.31 (0.21 – 0.40)	0.59 (0.44 – 0.74)
DAS CRP	0.12 (0.07 – 0.18)	0.19 (0.13 – 0.26)	0.33 (0.23 – 0.43)	0.61 (0.46 – 0.76)
DAS28	0.09 (0.05 – 0.14)	0.14 (0.08 – 0.20)	0.27 (0.19 – 0.35)	0.55 (0.40 – 0.69)
DAS28 CRP	0.10 (0.06 – 0.15)	0.18 (0.12 – 0.24)	0.34 (0.24 – 0.43)	0.66 (0.49 – 0.82)
SDAI	0.09 (0.03 – 0.14)	0.15 (0.10 – 0.20)	0.32 (0.23 –0.41)	0.54 (0.40 – 0.68)
CDAI	0.09 (0.04 – 0.15)	0.15 (0.10 – 0.21)	0.34 (0.25 – 0.44)	0.50 (0.37 – 0.63)
DAS 0-1	0.10 (0.05 – 0.15)	0.19 (0.12 – 0.25)	0.31 (0.22 – 0.40)	0.66 (0.51 – 0.81)
DAS TJC53	0.10 (0.05 – 0.14)	0.17 (0.11 – 0.23)	0.29 (0.20 – 0.38)	0.46 (0.34 – 0.58)
DAS TJC44	0.09 (0.05 – 0.14)	0.18 (0.12 – 0.24)	0.31 (0.22 – 0.40)	0.47 (0.35 – 0.60)

Covariates appearing in the model are fixed at the following values: previous SHS 10.3; year 2.8; treatment group 1; anti-CCP positive; female gender. LDA: low disease activity; MDA: moderate disease activity; HDA: high disease activity; CI: confidence interval; DAS: disease activity score; CRP: C-reactive protein; DAS28: disease activity score in 28 joints; SDAI: simplified disease activity index; CDAI: clinical disease activity index; DAS 0-1, disease activity score with RAI 0-1; TJC53: tender joint count 53 joints; TJC44: tender joint count 44 joints.

but the same subtle differences were found as were seen previously. In the analysis including ACR/EULAR remission definitions the same pattern was found (*table 5*). Predicted HAQ scores and probabilities for a HAQ score >0.5 were comparable for all definitions, with SDAI, CDAI and ACR/EULAR remission-criteria at the lower end of the range. Very little difference was found within the group of ACR/EULAR remission definitions. Supplementary data for other cut-off values are shown in the appendix (*supplementary table S4; published online only*).

Relation to the progression of joint damage

Table 3 shows predicted values of SHS progression for patients in different disease activity levels according to the 9 indices. All indices showed similar joint damage progression in different disease activity levels, and all composite indices showed a dose response, with a higher level of disease activity yielding more joint damage progression. Although CDAI and SDAI classifed fewer patients as being in remission, CDAI and SDAI remission were not associated with less damage progression. In the HDA category, patients with DAS-TJC53 and DAS-TJC44 had somewhat less SHS progression than patients in HDA according to other indices (*table3*). Predicted probabilities for SHS progression ≥3 units for patients in remission, LDA, MDA and HDA categories according to the 9 indices are shown in Table 4. The proportions of SHS progression between different composite indices were very similar. The percentage of CCP-positive female patients in remission showing joint damage progression varied between 9-12% for progression ≥3 units (*table 4*). The chance for progression ≥3 units in CCP- patients in remission was lower (3-4% for SHS progression ≥3, data not shown). Patients in SDAI and CDAI remission had comparable chances for progression ≥3 units compared to other indices (9% versus 9-12%). The probability for progression ≥3 units in LDA was slightly lower with

Table 5: Estimated mean predicted HAQ scores and mean SHS progression scores (95%CI) and estimated probability (95%CI) for HAQ scores>0.5 and SHS progression ≥3 units in patients in remission versus no remission. Covariates appearing in the HAQ model are fixed at the following .

	HAQ >0.5		Absolute HAQ value		SHS >= 3.0		Absolute SHS value	
	Remission Probability (95% CI)	No remission Probability (95% CI)	Remission Mean (95% CI)	No remission Mean (95% CI)	Remission Probability (95% CI)	No remission Probability (95% CI)	Remission Mean (95% CI)	No remission Mean (95% CI)
DAS	0.39 (0.32 – 0.45)	0.62 (0.55 – 0.68)	0.52 (0.44 – 0.60)	0.73 (0.64 – 0.82)	0.11 (0.06-0.16)	0.27 (0.20-0.33)	4.8 (1.3-8.3)	6.5 (3.0 – 10.0)
DAS CRP	0.38 (0.32 – 0.45)	0.63 (0.56 – 0.69)	0.52 (0.44 – 0.61)	0.74 (0.65 – 0.82)	0.12 (0.07-0.17)	0.27 (0.21-0.34)	5.2 (1.6-8.8)	6.5 (3.0-10.1)
DAS28	0.39 (0.32 – 0.46)	0.60 (0.53 – 0.67)	0.52 (0.43 – 0.61)	0.73 (0.64 – 0.82)	0.11 (0.06-0.15)	0.26 (0.20-0.33)	4.6 (1.1-8.1)	6.6 (3.3-10.2)
DAS28 CRP	0.41 (0.34 – 0.48)	0.63 (0.57 – 0.70)	0.54 (0.46 – 0.63)	0.75 (0.67 – 0.84)	0.12 (0.07-0.17)	0.28 (0.21-0.35)	5.2 (1.7-8.7)	6.7 (3.2-10.3)
SDAI	0.36 (0.30 – 0.43)	0.58 (0.51 – 0.65)	0.51 (0.42 – 0.59)	0.70 (0.61 – 0.79)	0.11 (0.04-0.17)	0.24 (0.18-0.31)	5.6 (2.2-9.0)	6.3 (2.7-9.9)
CDAI	0.37 (0.30 – 0.43)	0.58 (0.52 – 0.65)	0.50 (0.42 – 0.59)	0.70 (0.61 – 0.79)	0.09 (0.03-0.14)	0.25 (0.18-0.31)	5.3 (1.9-8.8)	6.3 (2.7-9.9)
DAS 0-1	0.39 (0.32 – 0.45)	0.62 (0.55 – 0.68)	0.52 (0.44 – 0.60)	0.73 (0.64 – 0.82)	0.11 (0.06-0.16)	0.27 (0.20-0.34)	4.8 (1.3-8.3)	6.5 (3.0-10.0)
DAS TJC53	0.39 (0.33 – 0.46)	0.61 (0.55 – 0.68)	0.52 (0.44 – 0.60)	0.73 (0.64 – 0.81)	0.12 (0.07-0.17)	0.26 (0.20-0.33)	4.8 (1.3-8.3)	6.5 (3.0-10.0)
DAS TJC44	0.40 (0.33 – 0.46)	0.61 (0.55 – 0.68)	0.53 (0.44 – 0.61)	0.73 (0.64 – 0.81)	0.12 (0.07-0.17)	0.26 (0.20-0.33)	4.7 (1.2-8.2)	6.5 (3.0-10.0)
ACR clinical trial remission 68/66 joint count	0.35 (0.28 – 0.41)	0.56 (0.49 – 0.63)	0.52 (0.43 – 0.60)	0.68 (0.59 – 0.76)	0.09 (0.02-0.15)	0.24 (0.18-0.30)	5.1 (1.4-8.7)	6.3 (2.7-9.8)
ACR clinical trial remission 28 joint count	0.34 (0.28 – 0.41)	0.57 (0.50 – 0.63)	0.51 (0.42 – 0.59)	0.69 (0.60 – 0.77)	0.10 (0.04-0.17)	0.24 (0.18-0.30)	5.2 (1.7-8.8)	6.3 (2.7-9.9)
ACR clinical practice remission 68/66 joint count	0.35 (0.28 – 0.41)	0.57 (0.50 – 0.64)	0.51 (0.42 – 0.60)	0.68 (0.60 – 0.77)	0.09 (0.03-0.15)	0.24 (0.18-0.30)	5.0 (1.3-8.6)	6.4 (2.8-10.0)
ACR clinical practice remission 28 joint count	0.35 (0.28 – 0.41)	0.58 (0.51 – 0.65)	0.50 (0.41 – 0.59)	0.69 (0.61 – 0.78)	0.11 (0.05-0.16)	0.25 (0.18-0.31)	5.2 (1.6-8.8)	6.4 (2.8-10.0)

values: previous HAQ 1.4; visit 10.6; age 53.9 treatment group 1; female gender. Covariates a appearing in the SHS progression model are fixed at the following values: SHS previous 10.2; age: 53.8; year 2.8; treatment group 1; CCP positive; female gender. CI: confidence interval; DAS: disease activity score; CRP: C-reactive protein; DAS28: disease activity score in 28 joints; SDAI: simplified disease activity index; CDAI: clinical disease activity index; DAS 0-1, disease activity score with RAI 0-1; TJC53: tender joint count 53 joints; TJC44: tender joint count 44 joints

SDAI, CDAI and DAS28 than with other indices. Patients classified in the HDA according to DAS-TJC53 and DAS-TJC44 had a lower chance to progress ≥3 units than patients in HDA according to other indices. The four versions of ACR/EULAR remission-criteria were comparably related to joint damage progression (*table5*). The probability of annual SHS progression ≥3.0 for patients in remission was 9-12%, compared with 24-28% for patients not in remission. Probabilities for progression as well as absolute SHS progression values were comparable for all definitions.
Comparable patterns were seen for annual SHS progression ≥1 and ≥5 units (*supplementary table S5; published online only*).

DISCUSSION

We compared classification into remission, LDA, MDA and HDA or remission yes/no categories with nine composite disease activity scores and ACR/EULAR remission-criteria and assessed the relationship with functional ability and radiological damage progression. Although proportions of patients classified varied between some of the score cut offs and definitions, the associations of all composite scores and remission definitions with HAQ and SHS show overall high accordance. All showed a good dose-response relationship of disease activity with HAQ and SHS progression.
This analysis expands on earlier studies comparing composite indices. We compared composite scores including 28 joint counts, and also the original DAS and several adjustments. Previous studies showed that DAS28 classifies more patients in remission[23-26], while SDAI and CDAI are strict in classifying remission[23;27], as reflected by lower remission percentages, which is in line with our results. In general, the studies that link composite scores to functional ability and radiological damage progression show that DAS28, SDAI and CDAI correlate comparably with HAQ and/or Larsen scores. They demonstrate that levels of disease activity of these indices discriminate between levels of functional state and radiological damage.[9;10;17;28]
We showed that all nine composite indices show a comparable relationship with radiological joint damage or physical functioning. Omitting grading in tender joint counts and/or omitting scoring tender joints in joint groups did not change this relationship. The same is true if acute phase reactants are left out (CDAI and clinical trial ACR/EULAR remission-criteria).
Which index should be preferred will depend on the reason for using the index and on personal preferences. In clinical practice composite scores without an acute phase reactant or a limited joint count can be used, whereas in a clinical trial setting a more elaborate composite score can be valuable. If treatment is aimed at remission, a stricter remission criterion carries a higher risk for overtreatment. However, a less strict definition may lead to residual disease activity and thereby undertreatment. SDAI, CDAI and ACR/EULAR remission-criteria classified the lowest proportion of patients in remission compared to other indices, but were not

associated with lower HAQ scores and did not lead to clinically significant less joint damage progression. DAS28 and DAS28 CRP classified the highest proportion of patients in clinical remission without compromising on HAQ and joint damage progression. However, within these indexes patient's feet are not examined which may not be appreciated. If LDA should be the target, DAS28 variants may be less useful, because DAS28 and DAS28 CRP classified fewer patients in LDA and remission together than other indices, without leading to better HAQ and progression percentages.

Our results emphasize what was seen earlier: clinical remission does not necessarily coincide with radiological remission.[29-31] The predicted probability for joint damage progression (≥3 unit) was 9-12% in anti-CCP positive patients. This suggests that there is (sub)clinical inflammation in patients with clinical remission, even with stricter definitions. An additional explanation might be that there is a delay between inflammation measured with clinical parameters and progression of joint damage visible on conventional X-rays. Part of the joint damage progression seen in patients in clinical remission might reflect disease activity that was present before onset of clinical remission.[32] Our results emphasize that a comprehensive definition of disease remission needs to include a radiological outcome.

Previous studies have showed that, early in the disease course, active inflammation (reflected in composite indices) is the main determinant of functional limitations, while in more established disease, joint damage becomes more important.[1;33;34]We analyzed the association between disease activity levels and HAQ in patients with limited joint damage during a 5 year follow up period. In more advanced disease the dose response between disease activity levels and HAQ is probably less pronounced and/or HAQ values inpatients in remission might be higher.

There is a large body of evidence supporting the benefit of targeted treatment. Less is known on what the target should be.[5;35] RCTs directly comparing LDA and remission as targets are lacking. In the BeSt study treatment was aimed at LDA. There is little difference between the mean HAQ in LDA (~0.60) and in remission (~0.50). However, progression rates in patients in LDA are considerably higher than those in patients in remission, suggesting that treatment should aim at remission. It is unknown what the gain would be on clinical and radiological outcomes while risking higher turnover in treatment options.

When outcomes are dichotomized only part of the data is being used, in contrast to using data on a continuous scale. Joint damage progression (and to a lesser extend HAQ), does not follow a Gaussian distribution. Although the GEE method is relatively robust against violations of the normal distribution, it is impossible to disentangle the complete effect of the distribution on continuous outcomes and predicted means. This may explain part of the high predicted annual progression rate, which can also be explained by unfavorable characteristics like anti-CCP positivity and treatment group. With dichotomous outcomes, the distribution is not a problem. We therefore decided to show both.

The strengths of our study are that we compared the most widely used composite indices for rheumatoid arthritis and recently published ACR/EULAR remission-criteria with different joint counts, and related classification of these indices to HAQ and Sharp-van der Heijde progression in a large group of patients. Also, all indices/criteria were repeatedly measured over time, increasing the number of observations, and were incorporated in the GEE analyses. One limitation might be that 'old' ACR remission-criteria were not included in the analyses, as not all components of these criteria were gathered three-monthly.

In conclusion, although there are differences in classification between the nine different disease activity composite indices and the ACR/EULAR remission definitions for RA, the association with functional status and joint damage progression are highly comparable. The choice of composite index is dependent on its intended use.

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Chapter 9

Is achieving remission associated with better health related quality of life than maintaining low disease activity in rheumatoid arthritis patients?

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ABSTRACT

Objective To assess if achieving remission is associated with a better health related quality of life (HRQoL) than maintaining low disease activity (LDA).

Methods Data were used of 508 patients with recent onset rheumatoid arthritis (RA) participating in the BeSt study, whose treatment was steered at LDA (DAS≤2.4), to investigate the relationship between DAS and HRQoL. Two summary scales of the Short Form-36 were used: the Physical and Mental Component Scale (PCS, MCS). Three linear mixed models were specified with PCS/MCS as dependent variable and with disease activity category, change in DAS score or change in disease activity category as independent variables. Remission was defined as DAS<1.6, or, separately, according to the ACR/EULAR remission criteria.

Results Patients in remission (DAS<1.6) compared to LDA had a significantly better PCS and MCS, with a difference of 4.0 and 1.0 points respectively (p<0.001). An increase of 1 point in DAS was associated with a decrease of 4.6 (95% CI 4.4;4.8) in PCS and a decrease of 1.6 (95% CI 1.3;1.9) in MCS. Achieving DAS-remission resulted in a 3.8 point gain in PCS compared to maintaining LDA, but no difference in MCS. Similar results were found for remission according to the ACR/EULAR criteria.

Conclusion Improvement of disease activity is associated with improvement of HRQoL, with also a clinically relevant improvement in PCS score for patients achieving remission when compared to maintaining LDA. Patients who move from LDA to remission gain 4 points in PCS, but show no significant improvement in MCS.

INTRODUCTION

Advances in treatment for RA patients have led to improved clinical and structural outcomes. Following recent recommendations, treatment should be started early and requires adjusting the medication until a target of remission or at least low disease activity (LDA) is achieved.[1;2] Achieving such a target is associated with better functional ability and less radiological damage.[3]
It remains unclear if it would be better to treat to the target of remission than of LDA as comparative studies are lacking. Also, the influence on Health Related Quality of Life (HRQoL), of achieving these different levels of disease activity is uncertain. As HRQoL reflects a more broad perspective of the influence of disease on daily life than most outcome measures, it may give more guidance on which disease activity level should be preferred.
Therefore we investigated in a low disease activity targeted cohort including early RA patients whether 1) remission or achieving remission was associated with a better HRQoL than LDA or maintaining LDA and whether 2) a change in disease activity was associated with a relevant change in HRQoL.

METHODS

Patients

Five-year follow-up data from the BeSt trial were used, where 508 patients with recent onset active RA were dynamically treated according to a step-wise treatment protocol aiming at a disease activity score (DAS) ≤2.4. Patients were randomized to four different treatment strategies: 1. sequential monotherapy; 2. step-up combination therapy; 3. initial combination therapy with prednisolone and 4. initial combination therapy with infliximab. Clinical assessment of disease activity was performed every three months, and included a joint count for tenderness and swelling, erythrocyte sedimentation rate (ESR) and patient's assessment of global disease activity. This study was approved by the ethical committees of participating centers and all patients provided informed consent. More details about the BeSt study have been described elsewhere.[4]

Outcome assessment

HRQoL was assessed with the Short Form 36 version 2 (SF-36),[5] which covers eight domains of health status: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. The SF-36 score ranges from 0 (worst) to 100 (best) and norm based scoring is available to compare different populations. Two summary measures, representing the physical component of HRQoL (physical component scale; PCS) and the mental component of HRQoL (mental component scale; MCS) are available. Both

scales cover all HRQoL domains but more weight is given to physical functioning, role-physical, bodily pain and general health in the PCS, whereas more weight is given to vitality, social functioning, role-emotional and mental health in the MCS. The SF-36 was filled out every 3 months in the first two years of treatment and yearly thereafter. A clinically important improvement from baseline for RA patients has previously been established as a minimum of 2.5 to 5 points improvement for the two summery measures.[6]

Statistical methods

Statistical analyses were performed with the software program SPSS version 20.0 (SPSS, Chicago, Illinois). Linear mixed models (LMM) were used to investigate the association between disease activity (levels) and HRQoL over time, while correcting for within patient correlation. For all analyses the unstructured covariance matrix was used, which does not assume a specific covariance structure and estimates every variance and correlation.

Two continuous outcomes, both of which normally distributed, were used for all analyses: the PCS and the MCS. Three models with these outcomes and the following independent variables were used: 1) disease activity category, 2) delta DAS (absolute), previous DAS and previous PCS or MCS score and 3) change in disease activity category (remission to LDA and vice versa) and previous PCS or MCS score.

For the first and third model, patients were categorized according to their disease activity category: high disease activity, low disease activity (based on the DAS), or remission.[7] Remission was defined as DAS<1.6,[8] or, in a separate analysis, according to the ACR/EULAR remission criteria.[9] Patients were first divided into ACR/EULAR remission yes/no, and patients not in ACR/EULAR remission were then classified into low or high disease activity depending on their DAS. The ACR/EULAR remission criteria were not designed to compare against DAS categories, but as there is no alternative classification method that allows for comparison of ACR/EULAR remission against other levels of disease activity we used this approach. In model 3, all possible changes were included in the model. We first used staying in low disease activity as reference category and then staying in remission and will only report on changing from low disease activity to remission and vice versa. Time was added as categorical covariate in all models in order to estimate the effect for each time point separately. The baseline visit was excluded because none of the patients were in remission at this visit. The following potential baseline confounders were considered: age, gender, HAQ, DAS, erosions (yes/no), anti-citrullinated protein antibodies, duration of complaints at inclusion, smoking, body mass index (BMI), alcohol intake and treatment group. None of the potential confounders importantly altered β-estimates or p-values when added to the model as separate variable, so these were not included in the final models. Values for mean HRQoL at each time point per disease activity category were calculated using Estimated Marginal Means.*(figure 1)*

RESULTS

In total 508 patients with a mean (SD) DAS at baseline of 4.4 (0.9) were included. Mean PCS (SD) was 38.8 (7.9) and mean MCS at baseline was (47.0 (11.4). At year 5, DAS was reduced to a mean (SD) level of 1.7 (0.8) while PCS and MCS had improved to a mean (SD) level of 44.8 (9.8) and 52.4 (8.6) respectively. Over 5 years (excluding the baseline evaluation), DAS-remission was recorded in 34% of the evaluations, while ACR/EULAR remission was recorded in 15%. (*table 1*)

Table 1: Percentage of patients per disease activity category using two remission definitions for year 0-5 excluding the baseline visit

	Remission: DAS<1.6 (n visits =4941)	ACR/EULAR Remission criteria (n visits=4499)*
Remission	1667 (34%)	662 (15%)
Low disease activity	1704 (35%)	2384 (53%)
High disease activity	1570 (32%)	1453 (32%)

DAS disease activity score, *n* number, *ACR* American College of Rheumatology, *EULAR* European League Against Rheumatism ; *For 442 visits, patients could not be classified because of missing values for C-reactive protein; Low disease activity: DAS ≤2.4, but not remission, High disease activity: DAS>2.4

Absolute disease activity scores in relation to QoL scores

Remission (DAS<1.6) was associated with a clinically relevant higher PCS than higher levels of disease activity, with a dose response relationship. The difference in PCS when in remission with PCS when in LDA (ß) was 4.0, and the difference with HDA 8.8, all p<0.001.(*table 2, figure 1*) Likewise, DAS categories with lower DAS were associated with higher MCS, although differences were smaller: LDA ß=1.0, HDA ß=3.1. Repeating the analyses with remission according to the ACR/EULAR remission criteria gave similar results.(*table 2)*

Table 2: Difference in absolute physical component scale score and mental component scale score for patients in low and high disease activity compared to patients in remission, defined as DAS<1.6 or according to the ACR/EULAR remission criteria

	PCS		MCS	
Remission	*ref (defined as DAS<1.6)*	*ref (defined according to ACR/EULAR criteria)*	*ref (defined as DAS<1.6)*	*ref (defined according to ACR/EULAR criteria)*
LDA	4.0 (3.5;4.4)	4.1 (3.5;4.8)	1.0 (0.5;1.5)	0.9 (0.2;1.6)
HDA	8.8 (8.3;9.4)	9.7 (9.0;10.5)	3.1 (2.5;3.7)	3.1 (2.3;3.9)

PCS physical component scale score Short form 36 (SF36), *MCS* mental component scale score SF36, *ref* reference, *DAS* disease activity score, *LDA* low disease activity (DAS ≤2.4, but not remission), *HDA* high disease activity (DAS>2.4) ; Data are presented as ß estimates (95% CI), representing the estimated difference with the reference category in PCS or MCS score

The univariable analysis showed that DAS category, gender, time, treatment group, alcohol intake, BMI and baseline DAS were also associated with outcome PCS, and DAS category, time, gender, baseline erosiveness (yes/no), baseline smoking status and baseline DAS were univariable predictors for MCS. Of the possible confounding variables none had a significant effect on the ß-estimates per disease activity category when added separately to the model, neither on the outcome PCS nor on MCS.

Changes in disease activity scores in relation to changes in HRQoL scores

Absolute changes in DAS scores were significantly associated with changes in both PCS and MCS. Patients showed an increase of 4.6 (95% CI 4.4;4.8) points in PCS when decreasing 1 point in DAS, independent of their previous DAS score and previous PCS (p<0.001). Similar results are seen for the MCS, however this difference is smaller: 1.6 (95% CI 1.3;1.9) points (p<0.001) improvement in MCS per 1 point decrease in DAS. The interaction term between previous DAS and DAS change was not significant, implying that the relationship between change in DAS and change in PSC/MCS is independent of the preceding DAS level.

Changes in DAS category in relation to change in PCS and MCS

For patients who had LDA, achieving remission was associated with a significant improvement in PCS of 3.8 points, when compared to patients who stayed in LDA, but no improvement in MCS.(*table 3*) Patients who had been in remission but flared to LDA showed a 4.0 point deterioration in PCS when compared to patients who stayed in remission, and no change in MCS.

Table 3: Change in component score (physical component scale score and mental component scale score) when achieving remission from low disease activity, and loosing remission to low disease activity, with remission defined as *DAS<1.6 and **according to the ACR/EULAR remission criteria

	PCS		MCS	
Staying in low disease activity	*ref*	*ref*	*ref*	*ref*
Achieving remission from low disease activity	3.8 (3.0;4.5)*	4.0 (3.1;4.9)**	0.5 (-0.3;1.3)*	1.0 (-0.01;2.0)**
Staying in remission	*ref*	*ref*	*ref*	*ref*
Loosing remission to low disease activity	-4.0 (-4.8;-3.2)*	-4.0 (-5.1;-2.9)**	-1.2 (-2.1;-0.3)*	-0.7 (-1.9;0.5)**

PCS physical component scale score Short form 36 (SF36), *MCS* mental component scale score SF36, *ref* reference, *DAS* disease activity score, ref reference. Data are presented as ß estimates (95% CI), representing the estimated difference in change in PCS or MCS score relative to the reference category

DISCUSSION

In this disease activity targeted treated cohort, lower disease activity was associated with better health related quality of life (HRQoL), both in the physical and mental component scale, although differences in the latter were smaller. This association was independent of the previous disease activity level and related to the final level of disease activity. A change in disease activity resulted in a change in HRQoL. We found that a clinically significant improvement of quality of life (in the physical component scale) was achieved when patients who were in a state of LDA went on to achieve remission.

To date, remission is recommended to be the optimal treatment target in RA patients,[2] but aiming for remission could increase the costs of treatment and the risk of side effects. In patients who have already achieved LDA, it is questionable if a further suppression of disease activity to a level of remission (whether based on a composite score threshold such as <1.6 in the disease activity score or based on the boolean ACR/EULAR remission criteria), also results in a further improvement in quality of life. This we have shown was indeed the case (and reversely, there was a deterioration in HRQoL if disease activity deteriorates from remission to LDA) in this LDA targeted cohort.

Previous studies have shown a cross-sectional correlation between active disease and impaired quality of life measured with generic HRQoL instruments,[10;11] and a dose-response effect of the different disease activity categories.[12;13] In longitudinal analyses over 2 years and over 10 years, it has already been suggested that an improvement in disease activity is associated with better HRQoL.[14;15] This association over a long time span may be influenced by other factors such as damage progression. As disease activity may fluctuate over time, we focused in our longitudinal analysis on shorter time intervals, and within these shorter time interval we found that improving in DAS and more specifically achieving remission is associated with improved HRQoL.

There are several limitations to our study. A DAS<1.6 may not denote true remission,[3] and the distinction with LDA (DAS ≤2.4) is relatively arbitrary. We repeated the analysis using the ACR/EULAR remission criteria, but here we were limited by the absence of associated ACR/EULAR low disease activity criteria. Instead, we again compared with 'not in ACR/EULAR remission' with established DAS categories for increased disease activity. Although according to the ACR/EULAR criteria, less patients were in remission than when using DAS remission, this did not result in a difference in the association between disease activity and HRQoL.

Second, although the association between disease activity category and HRQoL was independent of a number of patient characteristics, there might still have been residual confounding, for example caused by co-morbidity. Therefore, we cannot conclude that the achievement of remission *causes* patients to have better health related quality of life. There could be unmeasured patient traits related both to disease activity and HRQoL. A randomized clinical trial

comparing a treatment strategy aiming at LDA with a strategy aimed at remission using the same therapies would help to answer this question.

Although the change in MCS associated with achieving remission from LDA was statistically significant, it was not clinically significant. However, the mental component was also less impaired from the outset. The finding that disease activity shows a stronger relation with the physical than the mental component scale is in line with previous analyses from this study, where improvement of disease activity was associated with a smaller improvement of the MCS than the PCS,[16] and data from other cohorts.[17;18] This may be caused by the fact that in particular the mental component of HRQoL could be affected by other variables such as pain experience, psychological comorbidity, mental status, coping strategies and social networks. Also, MCS may depend more on stable patient traits such as optimism than on disease characteristics, and therefore show less variation.[19-22]

In conclusion, we have shown that a decrease in disease activity in patients with RA is associated with better HRQoL and that achieving remission after being in LDA is associated with achieving clinically significant improvement of HRQoL. This may suggest that remission is the preferred target of treatment and have implications for future (research on) goal setting in the treatment of RA.

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Chapter 10

Autonomous online Health Assessment Questionnaire registry in daily clinical practice

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ABSTRACT

Objective Tight control in rheumatoid arthritis (RA) necessitates frequent disease monitoring; patients might participate by self-assessment of their functional status. Therefore, we assessed the feasibility and acceptability of autonomous online registry of physical functioning.

Methods In two tertiary-care centers (in the Netherlands and France), consecutive RA patients were approached to perform autonomous registry of the Health Assessment Questionnaire (HAQ) in an electronic medical record. Feasibility and acceptability of autonomous HAQ registry was assessed through: (1) the percentage of acceptance; (2) the time needed to register the HAQ (the Netherlands); (3) patients' satisfaction with autonomous registry, and (4) willingness for future home-based HAQ completion, either self-declared (the Netherlands) or actual file access from home within 6 months (France).

Results In all, 214 patients were approached; 163 agreed to participate; 137 (64% of 214) had complete data which were analyzed. Median age was 56 years (range 20-78), 80% were female, median disease duration was 9 years. The median time needed to fill in the HAQ in the waiting room was 5.8 minutes; patient satisfaction was high (mean score 4.1 out of 5), self-declared willingness of autonomous registry at home was 73%. In the six-month follow-up period, 46% patients accessed their medical file from home at least once.

Conclusion Many RA patients reported willingness to self-monitor their disease online, but fewer than half of the patients actually did. To enhance patient autonomous monitoring, progress is needed in terms of internet access, continuous patient support, and importantly, convincing patients that they will benefit from autonomous monitoring.

INTRODUCTION

In patients with rheumatoid arthritis (RA), regular assessment of disease activity is recommended to evaluate the efficacy of treatment and steer treatment adjustments. [1] Although evidence suggests that a targeted treatment approach ('tight control') is superior to routine care[2,3], its implementation in current daily practice is hampered and successful implementation strategies are lacking.[4] Frequent disease monitoring necessary to perform tight control strategies may pose practical difficulties (i.e. lack of physician availability). One possible solution could be providing patients with access to electronic medical records (EMR) and obtaining autonomously registered data such as symptoms and functional ability.

Electronic registration in online files by patients has several advantages: intermediates handling data and processing are unnecessary, completeness of data can be improved and data are immediately available for all participating parties.[5] Online disease monitoring by patients could stimulate physicians to integrate frequent disease monitoring and targeted treatment adjustments into daily routine using such data.[6,7]

Many scores and questionnaires are available that could be object of autonomous electronic registration. The Health Assessment Questionnaire[8] is one of the most validated questionnaires in RA and is as informative as joint counts, radiographic or laboratory data for assessment of baseline status and change during interventions. [9]The HAQ is also predictive of long-term outcomes such as mortality and future physical disability.[10]

Before demonstrating that autonomous disease monitoring by patients is useful in terms of treatment decisions or outcomes, a first necessary step is assessment of the feasibility and acceptability of such autonomous assessment. In the present study, we assessed the feasibility of online file access and registration of the HAQ by RA patients, in a normal clinical practice setting.

PATIENTS AND METHODS

Patients

A cross-sectional (the Netherlands) and longitudinal study design (France) was used to assess the feasibility of autonomous data registry, using a patient-accessible EMR enabling online data registry. The setting comprised of two tertiary-care university hospitals, LUMC hospital in Leiden, the Netherlands and Cochin hospital in Paris, France.
A study nurse or trained student was available to include RA patients visiting the out patient department between May 2009 and June 2010. Inclusion criteria were RA, ability to under-

stand local language and willingness to fill in the EMR and evaluation form. The number of patients refusing to participate was recorded with reasons where possible, to assess both feasibility and acceptability. These study results were collected during routine evaluation of patient care and therefore ethical approval for this study was not required.

Data collection

As part of daily practice, an electronic patient file registering demographic data was created using the METEOR tool.[11] This free-of-charge tool was designed by rheumatologists for online registration of patient- and physician-derived outcomes, including composite scores for disease activity, patient's global assessment of disease activity or pain, and the HAQ[8]. Patients were provided with online access codes to gain access to their EMR in METEOR. All received a verbal instruction from study nurse or student about the system before accessing and registering their HAQ. Patients could access their file either at home, or in the waiting room before visiting the rheumatologist.

Outcome assessment

The outcome criteria were all related to feasibility and acceptability but varied between the two centers.

In the Netherlands (n=78), the assessment was performed in the waiting room before the visit to the rheumatologist with the help of a student (NAdG) if needed. Registered outcomes were: (a) the time needed for patients to fill in the HAQ and need for assistance, (b) patients' satisfaction with autonomous registry (assessed on a 0-5 Likert-scale, higher scores indicate higher satisfaction), and (c) self-declared willingness for future online HAQ registration either home-based or in the waiting room (yes/no).

In France (n=59) the outcome assessment was performed six months after the initial visit. At that time, each patient was contacted by the research nurse (ClB) and (d) self-declared autonomous access to the medical file from home within six months and (e) satisfaction with the online registry system (assessed on a 0-5 Likert scale) were collected as outcome criteria.

Statistical analyses

Analyses were descriptive for demographic characteristics and feasibility of online registry. To search for factors explaining willingness to perform online home-based data registry, univariate logistic regression analyses using the SPSS program version 17.0 or Statistical Analysis System (SAS) version 9.4, were performed. Demographic variables (age, sex, disease duration) and educational level were analyzed to explain willingness to participate in future online home-based HAQ registration (the Netherlands) or self-declared autonomous access to the EMR from home (France).

RESULTS

Participants

Of 214 eligible RA patients, 163 (76%) agreed to participate. Frequently mentioned reasons for refusal were inexperience with computer and/or internet use, and lack of time. Only few patients stated they did not want to perform autonomous disease assessments at all. In total, 137 patients (78 from the Netherlands in the cross sectional study, 59 from France in the follow-up study) completed the whole evaluation: 26 did not, either because they did not complete the evaluation (N=14, the Netherlands) or because they did not fill in the 6-month assessment (N=12, France) (*see supplementary figure S1; published online only*).

Patients had a median age of 56 (interquartile range, IQR 46-65) years and a long disease duration with a median of 8.6 (IQR 6.0-13.8) years. Most were female (80%) and 51% had received higher education (*Table 1*).

Table 1 Baseline characteristics of patients accepting to perform autonomous online registration of HAQ in two tertiary-care hospitals.

	All	France	Netherlands
Number of patients	137	59	78
Age, median (IQR), years	56 (46-65)	55 (43-61)	59 (47-67)
Female gender, n (%)	109 (80%)	48 (81%)	61 (78%)
Duration of RA, median (IQR), years	8.6 (6.0-13.8)	8.1 (6.5-13.7)	9.5 (5.8-15.0)
Educational level, n (%)			
Lower	15 (11%)	5 (9%)	10 (13%)
Medium	51 (38%)	18 (31%)	33 (43%)
Higher	69 (51%)	36 (61%)	33 (43%)

IQR, interquartile range. Medium education level: equivalent to end of high school.

Feasibility and acceptability of online registry in the waiting room (the Netherlands, n=78)

Patients needed a median (IQR) of 5.8 (4.0-8.0) minutes to access METEOR and fill in the complete HAQ *(outcome a)*. In total 58 patients (74%) needed at least some assistance during the process, although patients perceived registration as easy (mean 4.6 out of 5; SD 1.0; range 1-5). Patients were very satisfied *(outcome b)* (mean 4.1 out of 5; SD 1.1; range 1-5) with autonomous registration of the HAQ in the waiting room (*Table 2*).

The vast majority of patients reported willingness to fill in the HAQ online on a future occasion, more frequently in the waiting room (96%) than at home (73%) *(outcome c)*. Eighty-three percent said they would come to the hospital earlier, with the largest percentage (72%) agreeing maximum of 20 minutes.

Willingness to use home-based autonomous registry in the LUMC was associated with younger age (Odds ratio (OR) 0.8 95% CI 0.7-0.9) and higher educational level (OR 4.0 per level increase 95% CI 1.7-9.3) and not associated with gender, RA duration or patient satisfaction.

Feasibility and acceptability of home-based online registry in 6 months follow-up period (France, n=59)

In the six months follow-up period in the French study, 27 (46%) patients reported having accessed their online file from home at least once *(outcome d)*. The median score for patient satisfaction was 3.0 (out of 5; range 1.0-5.0), and only 19% of patients reported high satisfaction with autonomous online registration of data in METEOR *(outcome e; Table 2)*.

File access during 6 months follow-up was associated with higher satisfaction with online registry (OR 2.8, 95% CI 1.6-4.9) and longer disease duration (OR 3.4, 95% CI 1.1-10.1) and not associated with age, gender or educational level.

When the patients were asked informally by the study nurse why they did not access their file, they reported access to internet, but also perceived usefulness of the data collection, e.g. not seeing the physician using their data was not encouraging.

Table 2 Scores on survey questions for the Cochin and the LUMC hospital

	1 or 2 Negative	3 Neutral	4 or 5 Positive
1. Did you appreciate filling in the HAQ on the computer in this way? (not at all-very much)			
In the waiting room - Netherlands	6.5%	23.4%	70.1%
From home- France	47.5%	33.9%	18.6%
2. Netherlands only			
What was your opinion about filling in the HAQ in the computer program? (very difficult-very easy)	6.4%	3.9%	89.7%
Would you be capable to fill in the questionnaire with the program independently the next time? (definitely not-definitely yes)	10.3%	11.5%	78.2%

the upper and lower two scores on the five point Likert scale were combined in this table.

DISCUSSION

These data show that although many RA patients were willing to use an online EMR, either home-based or at the outpatient clinic, less than half of those who did get access used the EMR in the next 6 months. These results are disappointing, since many studies show that self management can lead to sustainable health benefits.[12,13,14]

Self-assessment is increasingly introduced in the rheumatologic field and can be combined with electronic registration to use advantages of both. Previous studies have shown that (online) computer systems are a good option for regularly capturing clinical data[15,16,17] and patient's attitudes towards these EMRs appeared positive.[18] Involvement and knowledge may then empower patients by establishing a decision-making process on equal level between rheumatologist and patients and start up the dialogue about implementation of tight control strategies.[19] This might also help to motivate patients to comply with proposed therapeutic interventions. As monthly monitoring has been shown to be superior to a less frequent monitoring schedule[2], self-assessment can assist in preserving resources for face-to-face contacts. This study shows the gap between theory and practice. Although in theory, autonomous data registry in EMRs is highly desirable, in practice in the present study willingness was limited.

This study highlights some of the limitations which impede autonomous data registration and should be taken into account when developing EMRs or implementation strategies.[20]
A first limitation is related to online access. To optimize patient involvement and online monitoring of disease-related data such as the HAQ, internet access and computer facilities for home access are the first necessities. The most common reason not to participate was lack of computer/internet experience and/or facilities. Access to internet is available for 69% of the French population and for 87% of the Dutch population, compared to 68% in the European Union and 77% in the United States (*internet world stats*). On the other hand, registry in the out patient clinic itself does overcome problems in facilities and has the advantage of immediate availability and more awareness, creating enhanced collaboration between patient and health care provider.

A second limitation relates to EMR software, which needs to be easy to use. Having been instructed and assisted during their first use of METEOR, most patients were confident that they could fill in the HAQ autonomously in subsequent visits. Data security may be of concern to patients, especially in online systems, but very few patients actually indicated this as a reason not to participate. METEOR is password protected and patientidentifying information is encrypted and complies with data protection legislation. A third important limitation which may hamper autonomous registry relates to patients, and physicians. Patients have to feel that autonomous HAQ registration is beneficial to them and need to get feedback on their efforts. This concept is related to shared decision-making and will need adaptation from both patient and physician. Also, if patients fill in the HAQ autonomously this might allow more time during the outpatient visit to discuss other issues with the rheumatologist.
A fourth limitation is the choice of which data are registered autonomously. In current clinical practice, it appears the HAQ is not widely used[21], even though it has been demonstrated to be a useful score[9], and monitoring physical ability is advised by current guidelines.[1] Patients need to be educated about the value of the HAQ and its scoring system and receive feedback

from their rheumatologists on their status. This will create a feeling of personal benefit for patients.[20] Each of these aspects should be addressed, when implementing patient autonomous data registry.

There are several limitations to this study. First, although issued from out patient clinics without selection, patients may not be representative of all patients in a rheumatologic clinic. Only approximately three-quarters of all patients participated, and comparative demographic data for patients refusing participation are unavailable. Selection bias is possible, since patients unlikely to use the online HAQ tool probably declined to participate. The high educational level in this sample could indicate that these patients are more eager to take part in disease assessment.

Furthermore, self-reported willingness may have been positively influenced because of socially desirable behavior. Although reported willingness in advance was high, self-reported home-based autonomous assessment in METEOR during six months of follow-up was substantially lower. It may also indicate that patients prefer registration on site rather than at home, which might explain the discordance in satisfaction between the two centers. A final limitation may be that extensive support by health care providers was available in this study, but may not be in other centers. However, these limitations only strengthen the conclusions of our study, since we can consider that the conditions in the present study were favorable for patients to perform autonomous registry.

In conclusion, the present study indicates that a majority of patients are willing to self-assess their disease status by registering a HAQ in an online medical file, but fewer than half of the patients actually did so from home within 6 months. This is a potentially feasible way to involve patients and to obtain regular disease assessments in the era of tight control, but patients need to experience more personal benefit. If this is achieved, online HAQ registration could lead to improved disease monitoring, quicker treatment decisions and ultimately better outcomes.

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METEOR is a free-for-use online software program developed by the Merit Foundation and aims to improve treatment of RA by the measurement of patient outcomes and benchmarking data in a multi-national database. Data is securely sent and stored anonymously.

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Chapter 11

GENERAL DISCUSSION

In the treatment of rheumatoid and undifferentiated arthritis major advances have been made in the last decades, due to improved earlier treatment as well as reliable estimation of disease activity by means of composite scores and intensified monitoring strategies (tight control), specifically aimed at pre-defined goals in outcome (treat to target).[1-3] Recent guidelines underscore the importance of goal setting and targeted treatment, which can be applied in practice by setting remission as preferred target and adjusting the medication until this target is achieved.[4-6] To complement composite scores measuring disease activity, radiological evaluation of damage to joints, and questionnaires such as the Health Assessment Questionnaire (HAQ) for functional ability and the Short Form 36 (SF-36) for quality of life are frequently introduced to assess the efficacy of therapeutic interventions.[4;5;7]

However, as outcomes of disease are improving with earlier treatment, questions regarding the usefulness of these traditional outcome measures arise. This thesis focuses on the following questions: What should be monitored in patients with undifferentiated or rheumatoid arthritis? Which imaging modalities should be used and which characteristics or abnormalities should be looked out for? How can the treating physician evaluate disease activity and what is the role of the patient in the monitoring process? What level of disease activity has to be set as a treatment goal? And last but not least: how can measurement strategies be implemented in daily clinical practice?

IMAGING IN UNDIFFERENTIATED ARTHRITIS

The value of measuring structural damage and the optimal method of assessment in rheumatoid arthritis (RA) patients have become matters of debate, as in our current era with targeted treatment strategies the amount of joint damage as seen on conventional radiographs has become very little. It has been shown that a one point increase in the Sharp-van der Heijde score (SHS) (which includes joint space narrowing (JSN) and joint erosions on radiographs of both hands and feet), corresponds with a 0.01 point deterioration in the HAQ score [8], where a change in HAQ of around 0.20 is clinically relevant. As in recent disease activity steered studies we have observed that in most patients during a 1-2 year follow-up period median levels of SHS progression scores remain below five points, [1-3;9] radiological outcome will affect functional ability only after years. Still, some patients do show rapid radiological damage progression, even after early aggressive treatment and a DAS steered regime.[8;9] If these patients could be identified before damage progression occurs, possibly using sensitive imaging techniques at presentation, effective treatment could be administered to prevent irreversible damage. It has also been suggested that more sensitive tools than conventional radiographs are needed, especially in early and undifferentiated disease, to identify those UA patients at

risk of deterioration to chronic and damaging disease. More sensitive imaging options may be magnetic resonance imaging (MRI) and ultrasound (US) investigation.

In ***Chapters 2*** and ***3*** we have assessed the diagnostic and prognostic value of three imaging techniques in undifferentiated peripheral arthritis: conventional radiographs, MRI and US. Our literature review concerning conventional radiographs (***Chapter 2***) revealed that the presence of erosions is predictive of a future diagnosis of RA or a poor prognosis of UA. Studies concerning solely UA populations were scarce, as most studies also included patients with arthritis who fulfilled the 1987 classification criteria for RA, reflecting a chronic disease state. Furthermore, since the presence of erosions on conventional radiographs is one of the seven classification criteria (where four are required to classify as RA), the performance of our test is overestimated. On the other hand, no widely accepted validated alternative for establishing a diagnosis of RA was present. No studies were available that showed other radiographic features than erosions to be predictive of a diagnosis of RA or poor prognosis in UA. Also, no evidence was found on the preferred frequency of radiographic assessment. The preferred areas to radiograph were the hands, but if the feet were also radiographed, this provided additional value.

Few studies were found on the value of MRI and US in UA. Most studies were performed in a population including both UA and RA (***Chapter 3***). MRI features that have shown of value in UA patients for predicting a diagnosis of RA, are bone edema, MRI synovitis and erosion patterns in the hands. For US, only in studies with both UA and RA patients, we found that ultrasound power Doppler signals and gray scale ultrasonography may be of value in predicting disease flare or persistence of arthritis. For neither imaging modality data was available on preferred frequency of follow-up imaging.

More recent literature (published after our review) on MRI and US has shown that including presence of MRI bone edema in a model aiming at prediction of progression to classifiable RA in UA patients has added value [10], but more extensive validation is necessary.[11] A recent initiative formulated recommendations regarding the use of imaging in RA patients based on the combination of systematic literature reviews and expert opinion and advised conventional radiographs of hands and feet as initial imaging technique for the assessment of joint damage. However, MRI and/or US may be used for prediction of a future diagnosis of RA in UA patients and patients with diagnostic uncertainty, or as assessment of (subclinical) inflammation in patients who are in clinical remission. It has also been suggested that these enhanced techniques may be of value in disease activity monitoring, predicting therapy response and establishing prognosis.[12] There are however, no long term follow-up studies yet that can match early abnormalities on MRI and/or US with later relevant and irreversible damage on conventional radiographs.

The results of the systematic literature reviews on imaging were integrated with the results of the other reviews on the remaining clinical questions and combined with clinical expertise of an international panel of rheumatologists in order to formulate recommendations on how to investigate and follow-up UA patients. (***Chapter 4***)

Features and sites of joint damage on radiographs in relation to physical functioning

The relationship between joint damage and physical functioning has been extensively described in the literature.[13-15] Recently, it has been suggested that JSN may impose a larger effect on physical decline than joint erosions [16], although some questions regarding this relationship remain.[17] Moreover, unknown to date was whether damage in specific joints, which are included in our current scoring method, is more prominently related to functional impairments. In ***Chapter 5*** we have shown that separate JSN and erosion scores in our cohort of patients with recent onset RA treated in a tight controlled setting, were not related to functional disability measured by the HAQ. However, when considering joint groups (e.g. feet, wrists, metacarpophalangeal joints and proximal interphalangeal joints), we found that joint damage in the wrist, and more specifically erosive damage, was independently preditive of a worse HAQ score.

This implies that damage especially in the wrist has a major impact on patient's physical functioning. This finding also raises the question whether site-specific treatment (for example corticosteroid injections) may be able to locally prevent joint damage and thus improve daily physical functioning. Additional research is needed to further assess the association of damage in specific joint areas on MRI and US with functional decline.

Disease activity in Rheumatoid Arthritis

One of the composite scores most often used to measure disease activity, the disease activity score (DAS), combines clinical and laboratory results as indicators of disease activity in one continuous score to yield a more complete estimate of active disease.[18;19] The original DAS has been adjusted several times, diminishing the number of counted joints or the time needed for calculation.[20-22] Although widely used in clinical trials, the DAS is not systematically used in clinical practice world-wide.[23] Implementation may be stimulated by simpler and faster ways of DAS measurement or calculation. In ***Chapter 6*** we have assessed three variations of the DAS in which the tender joint count component is differently registered, but keeping both hands and feet included. These variations have the advantage of easier scoring and calculation, without the exclusion of the feet (as seen for example in the DAS28), which are frequently involved in RA.[19] Instead of the graded Ritchie Articular Index (RAI) [24], we used a 0-1 tender joint count in the same joint(groups) (DAS 0-1), a tender joint count in 53 separate

joints (DAS TJC53) and a tender joint count in 44 separate joints (DAS TJC44) to calculate the DAS.

Overall, we have demonstrated that these three versions of the DAS show a high correlation with the original DAS and classify the different disease activity levels similarly (*convergent validity*). A similar degree of radiological progression across categories of all DAS versions was observed, demonstrating construct validity, and with all DAS versions differences in disease activity between the treatment arms in our study could be found after three months follow-up (*discriminate validity*). However, scores with the adjusted versions DAS-TJC53 and DAS-TJC44 were higher, leading to shifts in classification mostly from the low and moderate disease activity category into the higher categories, but not importantly affecting the classification into the remission category. As the overall validity of the DAS versions appeared comparable, which DAS variation is preferred may therefore depend on more practical arguments. Since the RAI remains difficult to calculate, physicians and other health care providers may want to choose a composite score with a reduced non-graded joint count including the feet, such as the DAS TJC44.

We also compared the use of two patient derived visual analogue scales (VAS) within the DAS: the VAS for patient's global assessment of disease activity (VAS-PGA) and the VAS for general health (VAS-GH) (***Chapter 6***). Both are used in daily practice, although the DAS validation was based on the latter.[18] We found that within the composite score DAS these can be used interchangeably, without importantly affecting the score of the DAS. Yet, differences between VAS-PGA and VAS-GH are considerable, and their correlation with each other is low. Possibly, the concepts that these two scores cover differ in the minds of patients scoring the questions, which may also be related to the phrasing of the questions. While global disease activity may be perceived as primarily as reflecting arthritis activity, general health may be experienced as a broader concept,maybe influenced by co-morbidity as well. Within the DAS limited weight is given to these components and therefore the use of both VAS scores in practice is possible. Yet, as these VAS scores may be used as individual scores as well, attention should be given to the observed difference. Moreover, when VAS-PGA and VAS-GH are used solitary this decreases face validity as compared to using a composite measure with the inclusion of a laboratory measure or a physician derived judgement.[25]

In ***Chapter 7*** we compared a VAS score for assessment of global disease activity derived from patients (PtGDA) with the same VAS score derived from physicians (PhGDA), based on data from the METEOR database.[26] We found that patients consistently score their disease activity higher than physicians, on average 11 points (on a scale of 100), confirming results of previous studies.[27-29] The higher rating of patients compared to physicians was associated with higher pain perception by patients, whereas when physicians scored higher, this was related

to higher ESR and/or higher swollen joint counts. A possible explanation is that patients in their judgment attribute more influence on their perceived discomfort, whereas physicians tend to be driven by more objective variables. This would align with the observation that patients and physicians differ in their disease perspectives on active disease.[30] As a patient VAS is part of the new ACR/EULAR remission criteria[31;32], patients with a high VAS and no other signs of active disease may be classified as not in remission, consequently triggering treatment adjustments (when targeting at remission), that aim at reducing inflammation that is not present.[32] However, this also indicates that for some patients remission according to the physician based on joint counts and laboratory measures, is not perceived as complete disease control.

Using various definitions, drug free remission as ultimate treatment goal, can be achieved in 9-25% of all RA patients, as demonstrated in several recent clinical trials.[33] However, the optimal way to define remission (either drug free or not) is still a matter of debate. Several composite measures, such as DAS, DAS28, SDAI and CDAI have specific cutoff values to define remission.[34-36] In ***Chapter 8*** we investigated the relationship of nine composite indices plus the newest ACR/EULAR remission criteria[31;32] with physical functioning and radiological damage to gain further insight into their differences in definition of remission. We have shown that SDAI, CDAI and ACR/EULAR definitions are more stringent in defining remission than the other composite measures, as fewer patients were able to reach that state. However, these more stringent definitions were not associated with clinically relevant better HAQ scores or lower SHS scores. To define remission more stringently seems therefore clinically not very relevant with regard to joint damage progression and physical functioning. Whether (steering towards) stricter remission definitions lead to better outcomes on the long term, or higher quality of life, better symptom control and less flares remains to be determined.

In addition, some definitions have been shown to allow more residual disease activity than others[37-39] and defining remission using less strict definitions could thus give a false sense of security, as (subclinical) disease activity can remain. That radiological progression is not necessarily haltered during clinical remission is demonstrated in our study by the prediction of radiological damage progression for some of the patients in remission. Future research should give direction on how to identify the patients with continued damage progression despite appearing in clinical remission, so that we will be able to treat them appropriately thereby preventing both over and under treatment. We believe that all remission definitions that were evaluated showed good construct validity and that the choice of the preferred measurement instrument can be based on other factors, such as practicality.

Quality of life and disease activity

Health Related Quality of Life (HRQoL) is among one of the most broad outcome measures reflecting a wide range of variables determining general well-being in the presence of disease.[40] Different measures for HRQoL exist, both general and disease specific instruments.[41] In the BeSt study, HRQoL was measured three-monthly (in the first two years of the study) using the Short Form 36[42], a generic measure consisting of the following eight factors: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. We investigated the relationship of two summary scale measures, the Physical Component Scale (PCS) and the Mental Component Scale (MCS) (both using all factors, yet with different weights) with the DAS. (***Chapter 9***)
We found that a lower DAS was related with a clinically significantly higher and thus better HRQoL for both the PCS and MCS, although in the MCS the difference was less than the previously established clinically important level of improvement (e.g. >2.5 points).[43] A decrease in DAS was related to an improvement in HRQoL and more specifically, a lowering of disease activity to the level of remission was associated with a clinically relevant better PCS, independent of the previous level of DAS. This relationship was not found for the MCS, which may be explained by the MCS depending on other factors such as pain experience, comorbidity and coping strategies as oppose to the PCS.[44-46]

The PCS results may suggest that a goal as strict as remission is to be preferred over one of low disease activity, since this would result in better quality of life for patients. As our analysis was based on a LDA steered cohort, future research should focus on the comparison of steering treatment at remission and LDA and compare the achieved level of HRQoL between these groups for definite conclusions on the preferred treatment goal.

Disease monitoring in daily practice

Patients have demonstrated a positive attitude towards electronic health records and such records could perfectly be used for regular monitoring of disease, either by the patient himself or by health care providers.[47-49] In ***Chapter 10*** we have assessed the feasibility of online HAQ registry by patients, either from their homes or at the outpatient clinic. We learned that, although at the outpatient clinic the majority of patients indicated to find registry easy and valuable, in a follow-up setting for registry at home only a minority indeed declared to have registered the HAQ. This questions the feasibility of uncontrolled registry at home. An explanation may be that patients have given socially desirable answers, not matching their actual actions. Another possibility is that initially patients may have had the intention to fill in the questionnaire, but in the end refrain from using the system, as they do not perceive direct benefits from registration. Without feedback on their efforts and knowledge about benefits of these efforts, initiatives promoting regular disease assessment are bound to fail.

GENERAL CONCLUSIONS AND FUTURE PERSPECTIVES

This thesis focused on disease monitoring in both RA and UA patients with respect to value of imaging, the assessment of disease activity, the preferred treatment target and the implementation in daily practice.

Which imaging modalities should be used in patients with arthritis and which characteristics should be looked out for?

Structural damage assessment in patients with rheumatoid or undifferentiated arthritis can be performed with conventional radiographs, MRI or US. Conventional radiographs of hands, wrists and feet are valuable in early undifferentiated disease to predict future diagnosis and prognosis, but for MRI and US little evidence was available on their value. However, recent studies have implied that these techniques may be able to establish active disease in UA patients.[50;51] As more treatment advances are made and radiological damage may further diminish, these techniques might in time replace the traditional radiographs, especially to establish subclinical disease activity (e.g. in patients in remission) and possibly continued joint damage progression.[12]

It needs to be further investigated how abnormalities on MRI and/or US relate to limitations in physical functioning and especially HRQoL, which directly represents the patient's well-being. Also, it is not sure to date if these abnormalities, for example in patients in clinical remission, are treatable, and what the magnitude of the possibly improved outcomes would be.

Radiographs may still be used to evaluate structural abnormalities related to previous periods of active disease.[52] In RA patients extra attention may be given to radiographic damage in the wrists, given the high impact of localized damage in this area on physical functioning. Future research should establish if local intra-articular therapy can prevent or halt local damage progression and stabilize or improve functional ability. If localized damage on alternative techniques such as MRI or US also highly impacts on physical functioning remains to be determined.

How can the treating physician evaluate disease activity and what is the role of the patient in the monitoring process?

When treating patients with arthritis, specifically rheumatoid arthritis but possibly other forms of chronic arthritis as well such as undifferentiated arthritis, disease activity assessment with a composite score including the feet should be regularly performed to steer treatment decisions. Inclusion of the feet is essential, as RA frequently affects the feet and remaining active disease in these joints may influence the measurement of disease activ-

ity.[37] These measurements can be performed by physician using several composite scores, of which some are more practical than others, but all relate to physical functioning and structural damage similarly. Another option is the assessment of active disease by patients. Yet, we have seen that physicians and patients do not score active disease similarly and factors which are predicting their score differ. Within composite scores, the inclusion of "objective" measures such as laboratory measures and signs on physical examination filters out these differences between patients and physicians, although the question remains if disease activity measured based on laboratory results and physician derived judgment captures the complete construct of active disease. Factors such as pain relief, fatigue or coping strategies should also be carefully monitored and addressed in order to accomplish primarily a more in depth understanding and secondly an improvement of the actively experienced disease by these patients.[3334]

What level of disease activity should be the goal of our treatment?

The preferred treatment target still remains a matter of debate. According to treat to target recommendations, the primary goal of treating the patient with rheumatoid arthritis is "to maximise long-term health-related quality of life through control of symptoms, prevention of structural damage, normalisation of function and social participation" while "abrogation of inflammation is the most important way to achieve this goal."[4] We have seen that achieving a goal as strict as remission leads to improved outcomes in terms of radiological damage, physical functioning, and most importantly HRQoL. Yet, the differences with a low disease activity state are small and not always clinically relevant. On the other hand, as continued structural damage progression is possible even in patients in clinical remission[53;54], we believe that the lowest possible disease activity state should be reached. Remission can be defined with a composite score such as the DAS, which does include the feet, in contrast to the new ACR/EULAR remission criteria. Another advantage over the Boolean version of the ACR/EULAR remission criteria is that composite measures do not solely allow single variables to determine whether a patient is in remission or not, which can be problematic such as with the patient derived VAS score. Future research should directly compare treatment strategies steering at remission and LDA and focus on HRQoL as an outcome.

How can measurement strategies be implemented in current daily practice?

Although many of our resources are used for research on new treatment (strategies) of RA patients and on the development of such strategies, relatively little attention is given to their implementation in practice. Research regarding successful implementation is scarce and few implementation strategies have been shown valuable.[23;55] Yet, there is an increased pressure for registry of disease status, also from insurance companies requiring objective arguments for reimbursement of treatment with expensive therapies. [56] Quality indicators aiming at spe-

cific diseases including RA are now steering and forcing certain changes in the organisation of our health care.[4;6]

Patient engagement in this changing healthcare system is becoming more and more important. Patients need to be part of it and be educated about their role in this process. They need to be aware of the importance of regular disease assessment for their disease outcome and how they can participate in this assessment. ICT solutions, such as electronic patient files, may support their involvement in this disease monitoring process. Furthermore, patients need to receive feedback from their health care providers on their efforts in monitoring, their outcomes and the consequences of these results for the management of their disease, possibly including treatment alterations.

In conclusion, to improve management and outcomes of patients with undifferentiated and rheumatoid arthritis, physicians should regularly assess disease activity using composite measures and strive for remission by appropriate treatment adjustments according to the treat to target paradigm. Patients have to be actively engaged in the management of their disease by regularly assessing their daily physical functioning and HRQoL. Treatment can be aimed at the lowest possible state of disease activity, without symptoms, physical limitations and with a good HRQoL. Additional future research should principally aim at directly comparing treatment strategies with different treatment goals with the inclusion of newer imaging techniques to identify subtle signs of disease activity and/or damage, and secondly at their implementation. Successful implementation of the best strategies and measuring techniques in current daily practice can ultimately lead to better care and outcomes for patients with arthritis.

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Chapter 12

Nederlandse samenvatting

In de behandeling van ongedifferentieerde (UA) en reumatoïde artritis (RA) is in de afgelopen decennia veel vooruitgang geboekt. Met name de mogelijkheid tot vroege behandeling met DMARDS ("disease modifying anti rheumatic drugs") gecombineerd met een betrouwbare schatting van de ziekteactiviteit door middel van samengestelde scores (de zogenaamde 'composite scores') en intensievere controle strategieën ("tight control"), specifiek gericht op pre- gedefinieerde doelen in uitkomsten ("targetted treatment") hebben bijgedragen aan een enorme verbetering in prognose van RA patiënten. Recente richtlijnen onderstrepen ook het belang van het stellen van een behandeldoel met frequente evaluaties, hetgeen in de praktijk uitgevoerd kan worden door frequente metingen van ziekteactiviteit en zo nodig therapieaanpassingen tot het behandeldoel is bereikt. Naast het meten van de ziekteactiviteit kan radiologische schade aan gewrichten middels Röntgen- foto's in kaart worden gebracht en kunnen vragenlijsten worden afgenomen zoals de Health Assessment Questionnaire (HAQ) voor het inschatten van dagelijks functioneren en de Short Form 36 (SF-36) om de kwaliteit van leven te meten. Al deze maten kunnen worden meegenomen bij het beoordelen van de effectiviteit van therapeutische interventies.

Met de op dit moment betere resultaten van behandeling is het de vraag of deze traditionele meetinstrumenten op dit moment nog wel voldoen. Dit proefschrift richt zich daarom op de volgende vragen**:** Wat moet worden gecontroleerd bij patiënten met UA of RA? Welke beeldvormende technieken kunnen worden gebruikt en welke kenmerken op deze beeldvormende technieken moeten worden geëvalueerd? Hoe kan de behandelend arts ziekteactiviteit evalueren en wat is de rol van de patiënt hierin? Welk niveau van ziekteactiviteit kan als streefdoel van de behandeling worden ingesteld? En last but not least: hoe kunnen onze meetstrategieën in de dagelijkse klinische praktijk worden geïmplementeerd?

Beeldvormende technieken in ongedifferentieerde artritis

De waarde van het meten van structurele gewrichtsschade in RA patiënten en de optimale evaluatiemethode van deze schade staat ter discussie. Met de huidige behandelingsstrategieën is de hoeveelheid gewrichtsschade op Röntgenfoto's drastisch afgenomen tot op het niveau dat pas na jaren actieve ziekte de mate van progressie van Röntgenschade daadwerkelijk het functioneren zal beïnvloeden. Echter, bij een klein deel van de patiënten is er wél sprake van snelle radiologische schade progressie, zelfs met vroege ziekteactiviteit gestuurde en intensieve behandeling. Als deze patiënten zouden kunnen worden geïdentificeerd voordat deze schade optreedt, eventueel met behulp van gevoeligere beeldvormende technieken, kan een effectieve behandeling op tijd worden toegediend om onomkeerbare schade te voorkomen. Er is gesuggereerd dat gevoeligere technieken dan de conventionele röntgenfoto (zoals echografie en magnetic resonance imaging (MRI)) daarvoor in aanmerking zouden komen, om vooral in het begin van de ziekte op het moment dat er nog sprake

is van een ongedifferentieerde artritis die UA patiënten te identificeren met kans op een progressief en persisterend ziekte beloop.

In de ***hoofdstukken 2 en 3*** hebben we door middel van literatuur onderzoek de diagnostische en prognostische waarde van drie beeldvormende technieken geëvalueerd in ongedifferentieerde artritis: MRI, echografie en conventionele Röntgenfoto's. Het blijkt dat erosies op Röntgenfoto's van UA patiënten voorspellend zijn voor een toekomstige diagnose van RA, en tevens voorspellend voor een slechter beloop van de ziekte. Het aantal verrichte studies specifiek in deze UA populatie was beperkt, de meeste studies waren verricht in een groep patiënten waarvan een deel vroege RA patiënten was, die al aan de 1987 RA classificatie criteria voldeden. Aangezien de aanwezigheid van erosies op conventionele röntgenfoto ook onderdeel is van deze classificatie criteria, wordt op die manier de waarde van deze 'test' overschat. Echter, er bestaat geen algemeen aanvaarde andere gevalideerde definitie van RA. Er werden geen studies gevonden over de waarde van andere karakteristieken die zichtbaar kunnen zijn op Röntgenfoto's. Data over gewenste follow-up frequentie van het nemen van Röntgenfoto's werd niet gevonden. Om afwijkingen in kaart te brengen is het nuttig de handen te fotograferen, maar de evaluatie van ook de voeten gaf additionele informatie.

Er werden maar weinig studies gevonden over de waarde van MRI en echografie in UA patiënten. De meeste studies werden uitgevoerd in een gemengde populatie van zowel UA en RA patiënten.(***hoofdstuk 3***). Beenmergoedeem, synovitis en het erosiepatroon op MRI hebben prognostische waarde in UA patiënten om een toekomstige RA diagnose te voorspellen. Doppler signalen en 'gray scale synovitis' zichtbaar met echografie, kunnen van waarde zijn bij het voorspellen van opvlamming van de ziekte of het persisteren van de artritis. Ook voor echografie was niet duidelijk geen wat de gewenste follow-up frequentie zou moeten zijn.

Recentere literatuur (gepubliceerd na onze review) laat zien dat het meenemen van de aanwezigheid van beenmergoedeem op MRI, binnen een model om een toekomstige RA diagnose te voorspellen in UA patiënten, toegevoegde waarde heeft [10], maar dit dient verder te worden gevalideerd. De geformuleerde aanbevelingen van een recent initiatief aanbevelingen met betrekking tot het gebruik van beeldvorming bij RA patiënten adviseren als eerste conventionele röntgenfoto's van handen en voeten te maken voor de beoordeling van gewrichtsschade. Echter, MRI en/of echografie kan worden gebruikt voor het voorspellen van een toekomstige diagnose van RA in UA patiënten en bij patiënten met onduidelijkheid over de diagnose of bij de evaluatie van (subklinische) inflammatie bij klinische remissie. Er is ook gesuggereerd dat deze verbeterde technieken van waarde kunnen zijn bij het monitoren van de ziekteactiviteit, het voorspellen van de reactie op therapie en het voorspellen van de prognose. Er zijn echter geen lange termijn follow-up studies die evalueren of vroegtijdige

afwijkingen op MRI en en/of echografie goed correleren met latere gewrichtsschade op conventionele röntgenfoto's.

De resultaten van deze twee systematische literatuur onderzoeken werden geïntegreerd met de resultaten van de andere literatuur studies betreffende UA patiënten en gecombineerd met de klinische expertise van een internationaal panel van reumatologen om aanbevelingen te formuleren over hoe UA patiënten te onderzoeken en te vervolgen. De resultaten daarvan leest u in ***hoofdstuk 4***.

De relatie van het soort gewrichtsschade en de locatie daarvan met dagelijks functioneren

De relatie tussen gewrichtsbeschadiging en fysiek functioneren is uitvoerig beschreven in de literatuur. Recentelijk is gesuggereerd dat gewrichtsspleet- versmalling een groter effect op het dagelijks functioneren heeft dan erosies [16], hoewel enkele aspecten hiervan nog onopgehelderd blijven. Tot op heden was onbekend of schade op specifieke gewrichtslocaties prominenter gerelateerd zijn aan de functionele beperkingen. In ***hoofdstuk 5*** hebben we aangetoond dat afzonderlijke JSN en erosie scores an sich niet gerelateerd waren aan verminderd dagelijks functioneren. Echter, bij het analyseren van schade per gewrichtsgroep (voeten, polsen, metacarpofalangeale gewrichten en proximale interfalangeale gewrichten), vonden we dat de schade (erosies en gewrichtsspleetversmalling) in de pols, en dan met name de erosieve schade, onafhankelijk predictief waren voor een slechtere HAQ score. Dit houdt in dat de schade met name in de pols een grote invloed heeft op het fysieke functioneren van de patiënt. Deze bevinding werpt ook de vraag op of behandeling per locatie (bijvoorbeeld door middel van injecties met corticosteroïden) in staat zijn om lokaal gewrichtsschade te voorkomen en daarmee het dagelijks functioneren te waarborgen. Aanvullend onderzoek is nodig om schade in specifieke gewrichten of in gewrichtsgroepen op andere beeldvormende technieken zoals MRI en echografie te relateren aan functioneren.

Ziekteactiviteit in reumatoïde artritis

De meest gebruikte composite score om ziekte te meten is de DAS (disease activity score) welke klinische en laboratoriumresultaten als indicatoren van ziekteactiviteit combineert om zo een volledigere inschatting van actieve ziekte te maken. De oorspronkelijke DAS is meerdere malen aangepast, onder andere door het verminderen van het aantal gescoorde gewrichten en door de berekening van de totale score te vergemakkelijken. Hoewel de DAS veel wordt gebruikt in klinische studies, wordt de DAS niet systematisch toegepast in de klinische praktijk. Om de implementatie van DAS metingen in de praktijk te stimuleren, kan wellicht een versimpeling van de DAS meting of de berekening daarvan een goede bijdrage leveren. In ***hoofdstuk 6*** hebben we drie varianten van de DAS geëvalueerd, waarin de pijnlijke gewrichten op een andere gemakkelijkere manier werden gescoord, waarbij tevens

de voeten werden gescoord. Juist omdat de voeten vaak betrokken zijn bij RA. [19] In plaats van de gegradeerde 'Ritchie articular index' (RAI), gebruikten we een ja/nee pijn score in dezelfde gewrichten/gewrichtssgroepen. (DAS 0-1), een ja/nee pijnscore in 53 afzonderlijke gewrichten (DAS TJC53) en een ja/nee pijnscore in 44 afzonderlijke gewrichten (DAS TJC44) en vergeleken deze varianten met de originele DAS.

De varianten vertonen een hoge correlatie met de originele DAS en classificeren van de verschillende levels van ziekteactiviteit ongeveer gelijk (convergente validiteit). Er werd een vergelijkbare mate van radiologische progressie in alle categorieën van alle DAS versies waargenomen, waaruit blijkt construct validiteit, en met alle DAS versies konden verschillen in activiteit van de ziekte tussen de behandelingsgroepen in ons onderzoek na drie maanden follow-up worden aangetoond (discriminante validiteit). Echter, de scores gescoord met de DAS-TJC53 en DAS-TJC44 waren hoger, waardoor verschuivingen optraden in de ziekteactiviteit categorieën, en wel met name bij patiënten in lage ziekteactiviteit (volgens de originele DAS) die vervolgens werden ingedeeld als gemiddelde ziekteactiviteit. Dit gold niet voor de patiënten in remissie. Gezien het feit dat alle versies vergelijkbare resultaten lieten zien, kan de keuze van composite score gemaakt worden op basis van praktische argumenten. Aangezien de gradeerde RAI lastig blijft te scoren en te berekenen , zouden zorgverleners een composite score kunnen kiezen die dit heeft vereenvoudigd, zoals bijvoorbeeld de DAS TJC44, waarbij toch de voeten zijn geïncludeerd.

We vergeleken visuele analoge schalen (VAS) die beide worden gebruikt als onderdeel van de DAS: enerzijds de VAS voor de algemene indruk van de patiënt betreffende ziekteactiviteit (VAS-PGA) en anderzijds de VAS voor de algemene gezondheid (VAS-GH) (***hoofdstuk 6***). Beide worden gebruikt in de dagelijkse praktijk, hoewel de DAS gevalideerd is op basis van de laatste. We vonden dat binnen DAS deze scores door elkaar kunnen worden gebruikt, zonder dat dit een belangrijke invloed heeft op de uiteindelijke score van de DAS. Toch verschillen VAS-PGA en VAS-GH apart aanzienlijk van elkaar en de correlatie tussen beide is laag. De interpretatie door patiënten van de achterliggende concepten die deze twee scores meten, lijkt te verschillen. Dit zou onder andere te maken kunnen hebben met de formulering van de vragen. Terwijl globale ziekteactiviteit gezien kan worden als een gevolg van artritis activiteit, kan de algemene gezondheid ervaren worden als een ruimer begrip, wellicht beïnvloed door factoren als co-morbiditeit. Aangezien binnen de DAS het toegekende gewicht voor de VAS beperkt is, is gebruik van beide VAS scores in de praktijk goed mogelijk. Echter, om deze VAS scores afzonderlijk te kunnen gebruiken moet er aandacht gegeven worden aan de verschillen aangezien hierdoor de indruksvaliditeit kan verlagen omdat geen lab waardes of een oordeel van een arts wordt gebruikt.

In ***hoofdstuk 7*** vergeleken we de VAS-score voor de beoordeling van de globale ziekteactiviteit beoordeeld door patiënten (PtGDA) met dezelfde VAS score voor ziekteactiviteit beoordeeld door artsen (PhGDA). Hiervoor werden gegevens gebruikt uit de METEOR database. We vonden dat de patiënten consequent hoger scoren dan artsen, gemiddeld 11 punten (op een schaal van 100), iets wat eerder gezien werd in andere studies. Een hogere score van patiënten in vergelijking met artsen was geassocieerd met een hogere pijnperceptie door patiënten, terwijl indien artsen hoger scoorden, dit was gerelateerd aan hogere bezinking en een hoger aantal gezwollen gewrichten. Een mogelijke verklaring is dat patiënten zich in hun oordeel meer laten beïnvloeden door hun gevoel van ongemak, en dat artsen meer worden gedreven door objectievere variabelen. Dit klopt met de waarneming dat patiënten en artsen verschillen in hun perspectief van actieve ziekte. Aangezien de patiënt VAS onderdeel is van de nieuwe 'boolean' ACR / EULAR remissiecriteria, kunnen patiënten met slechts een hoge VAS en geen andere tekenen van actieve ziekte, geclassificeerd worden als niet in remissie. Dit kan leiden tot therapie aanpassingen (indien behandeling gericht is op remissie), wellicht voor behandeling van inflammatie die niet daadwerkelijk aanwezig is. Lastig is dus dat door sommige patiënten remissie die gedefinieerd wordt volgens de arts op basis van gewrichtsscores en laboratorium maten, niet gezien wordt als volledige controle van de ziekte.

Medicatie vrije remissie als ultiem behandeldoel, gedefinieerd volgens diverse uitkomstmaten, kan in 9-25% van alle RA patiënten worden bereikt. Echter, de optimale manier om remissie te definiëren (met of zonder medicamenteuze therapie) is nog steeds onderwerp van discussie. Verschillende composite scores, zoals DAS, DAS28, SDAI en CDAI hebben met behulp van specifieke cutoff waarden remissie gedefinieerd. In ***hoofdstuk 8*** onderzochten we de relatie tussen negen composite scores plus de nieuwste ACR / EULAR remissie criteria met fysiek functioneren en radiologische gewrichtsschade om meer inzicht te krijgen in de verschillen in remissie definities. We hebben aangetoond dat SDAI, CDAI en ACR / EULAR definities strenger zijn bij het definiëren van remissie dan de andere composite scores, zodat minder patiënten in staat waren om die toestand te bereiken. Nochtans waren deze strengere definities niet geassocieerd met klinisch relevante betere HAQ scores of lagere SHS scores. Het strenger definiëren van remissie lijkt daarom klinisch niet erg relevant (met betrekking tot gewrichtsschade en fysiek functioneren). Of (sturen op) remissie volgens strengere definities leidt tot betere resultaten op de lange termijn, of een hogere kwaliteit van leven, een betere symptoomcontrole en minder ziekte opvlammingen, moet nog worden bepaald.

Een aantal definities laat meer residuele ziekteactiviteit toe dan andere en het definiëren van remissie met minder strikte definities zou dus een onterecht gevoel van veiligheid geven want het is mogelijk dat er toch (subklinische) ziekteactiviteit aanwezig blijft. Dat radiologische progressie tijdens klinische remissie niet noodzakelijkerwijs afwezig is, wordt ook terug gezien in onze studie door de voorspelling van radiologische schade progressie

bij enkele patiënten in remissie. Toekomstig onderzoek moet richting geven aan hoe de patiënten te identificeren zijn die schade progressie hebben ondanks klinische remissie, zodat we hen adequaat kunnen behandelen en zowel over- als onderbehandeling kunnen voorkomen. Wij zijn van mening dat alle remissie definities die werden geëvalueerd goede construct validiteit toonden en dat de keuze van de gewenste meetinstrumenten kan worden gebaseerd op andere factoren, zoals bijvoorbeeld praktische factoren.

De relatie tussen kwaliteit van leven en ziekteactiviteit

Gezondheid gerelateerde kwaliteit van leven (Health Related Quality of Life; HRQoL) behoort tot een van de meest brede uitkomstmaten, omdat het een groot aantal variabelen meeneemt om het algemeen welzijn in aanwezigheid van de ziekte te bepalen. Er bestaan verschillende meetinstrumenten voor het in kaart brengen van HRQoL, zowel algemene als ziekte specifieke instrumenten. In de BeSt studie, werd HRQoL gemeten om de drie maanden (in de eerste twee jaar van de studie) met behulp van de Short Form 36, een generiek instrument dat bestaat uit de volgende acht factoren: fysiek functioneren, rolbeperkingen door fysieke gezondheidsproblemen, pijn, algemene gezondheidsbeleving, vitaliteit, sociaal functioneren, rolbeperkingen door emotionele problemen, en geestelijke gezondheid. Deze factoren kunnen gesommeerd worden in een lichamelijke en een psychische schaal: de Physical Component Scale (PCS) en de Mental Component Scale (MCS) (beide maten gebruiken alle factoren, echter met verschillende gewichten). Wij onderzochten in ***hoofdstuk 9*** de relatie van de PCS en MCS met de DAS.

We vonden dat een lagere DAS geassocieerd was met een klinisch significant hogere en dus betere kwaliteit van leven, voor zowel de PCS en MCS. Echter, voor de MCS was het verschil minder dan de eerder vastgestelde klinisch belangrijke verbetering van >2,5 punten. Een afname in DAS hing samen met een verbetering van de kwaliteit van leven en met name een verlaging van ziekteactiviteit tot op het niveau van remissie, was geassocieerd met een klinisch relevante betere PCS, onafhankelijk van het voorgaande niveau van DAS. Deze relatie werd niet gevonden voor de MCS, wat kan worden verklaard doordat de MCS afhankelijker is van andere factoren, zoals pijn, co-morbiditeit en coping-strategieën, in tegenstelling tot de PCS.

De PCS resultaten lijken te suggereren dat remissie als doel te prefereren is boven lage ziekteactiviteit, omdat dit zou leiden tot een betere kwaliteit van leven voor patiënten. Onze analyse was gebaseerd op een lage ziekteactiviteit gestuurd cohort, dus zal toekomstig onderzoek zich moeten richten op de vergelijking van het niveau van kwaliteit van leven in een remissie versus lage ziekte activiteit gestuurd cohort om definitief conclusies te trekken over het te prefereren behandeldoel.

Ziekte monitoring in de dagelijkse klinische praktijk

Patiënten vertonen een positieve houding ten aanzien van het gebruik van elektronische patiënten dossiers, welke perfect zouden kunnen worden ingezet voor het monitoren van ziekte. Dit kan gedaan worden door de patiënt zelf dan wel door de zorgverlener. In ***hoofdstuk 10*** hebben we de haalbaarheid van het online registeren van de HAQ door patiënten beoordeeld zowel thuis als op de polikliniek. We hebben geleerd dat hoewel op de polikliniek de meerderheid van de patiënten aangeeft het registeren gemakkelijk te vinden en waardevol, vervolgens in een follow-up studie thuisregistratie slechts door een minderheid verricht wordt. Dit werpt vragen op over de haalbaarheid van thuisregistratie. Een verklaring hiervoor kan zijn dat patiënten sociaal wenselijke antwoorden hebben gegeven, niet in overeenstemming met hun daadwerkelijke gedrag. Een andere mogelijkheid is dat patiënten in eerste instantie de bedoeling hebben gehad de vragenlijst in te vullen, maar uiteindelijk daarvan hebben af gezien omdat ze geen directe voordelen van registratie zagen. Het is belangrijk om feedback te geven aan patiënten over hun registratie en de voordelen van deze inspanningen en het regelmatig monitoren te bespreken, omdat anders initiatieven ter bevordering van regelmatige ziekte monitoring gedoemd zijn te mislukken.

Algemene conclusies en toekomstperspectieven

Dit proefschrift richt zich op het monitoren van ziekte in zowel RA als UA patiënten en kijkt daarbij naar de waarde van de beeldvorming, het beoordelen van ziekteactiviteit, het vast te stellen behandeldoel en de implementatie van monitoring in de dagelijkse praktijk.

Welke beeldvormende technieken dienen te worden gebruikt bij patiënten met artritis en welke kenmerken daarvan zullen in ogenschouw genomen moeten worden?

Het in kaart brengen van structurele schade bij patiënten met RA of UA kan gedaan worden met conventionele röntgenfoto's, MRI of echografie. Conventionele röntgenfoto's van handen, polsen en voeten zijn waardevol in het begin van ongedifferentieerde ziekte om de toekomstige diagnose en prognose te voorspellen, maar voor de aanvullende waarde van MRI en echografie werd weinig bewijs gevonden. Echter, recente studies hebben gesuggereerd dat deze technieken in staat zijn om actieve ziekte aan te tonen in UA patiënten. Naarmate de behandeling van RA en ongedifferentieerde artritis zich verder ontwikkelt, en mogelijk de radiologische schade nog verder afneemt, zouden deze technieken conventionele Röntgenfoto's kunnen vervangen bijvoorbeeld om subklinische ziekteactiviteit vast te stellen bij patiënten in klinische remissie met progressieve gewrichtsschade.

Het moet nader worden onderzocht hoe de afwijkingen op de MRI-en en/of echografie relateren aan beperkingen in fysiek functioneren en met name ook aan gezondheid gerelateerde kwaliteit van leven, een maat die rechtstreeks het algemeen welzijn van de patiënt beoogt te

meten. Ook is het op dit moment niet zeker of deze afwijkingen, bijvoorbeeld bij patiënten in klinische remissie, te behandelen zijn en wat de winst met betrekking tot bijvoorbeeld HRQoL of lichamelijk functioneren zou zijn bij behandeling.
Röntgenfoto's kunnen worden gebruikt om structurele afwijkingen te objectiveren na voorgaande perioden van actieve ziekte. Bij RA patiënten zou extra aandacht gegeven kunnen worden aan de schade ter plaatse van de pols, gezien de hoge impact van schade in dit gebied op het fysieke functioneren. Toekomstig onderzoek moet vaststellen of lokale intra-articulaire therapie deze plaatselijke schade kan voorkomen of progressie kan remmen en of dit ook tot de gewenste verbetering dagelijks functioneren leidt. Of gewrichtsschade op specifieke locaties gemeten met MRI of echo ook relateert aan fysiek functioneren is niet bekend.

Hoe kan de behandelend arts ziekteactiviteit meten en wat is de rol van de patiënt bij het regelmatig meten van ziekteactiviteit?

Bij de behandeling van patiënten met artritis, met name RA, maar mogelijk ook andere vormen van chronische artritis en UA, moet het meten van de ziekteactiviteit met een composite score, met inbegrip van de voeten, regelmatig worden uitgevoerd om behandeling goed te kunnen sturen. Het mee scoren van de voeten is daarbij essentieel, omdat bij RA de voeten vaak meedoen en dit dus invloed heeft op de ziekteactiviteit. Deze metingen kunnen door de arts worden uitgevoerd met diverse composite scores, waarvan sommige praktischer zijn dan andere, die echter alle op een vergelijkbare manier relateren aan fysiek functioneren en structurele schade. Een andere optie het meten van ziekteactiviteit door patiënten. Echter, we hebben gezien dat artsen en patiënten verschillen in hun mening over actieve ziekte en de factoren die hun scores voorspellen verschillen. In de composite scores zitten naast de VAS "objectievere" maten van ziekteactiviteit, zoals de bezinking of gewrichtsscores, wat de verschillen tussen patiënten en artsen compenseert. Aan de andere kant is het de vraag of met deze objectievere factoren wel de daadwerkelijke ziekteactiviteit in kaart gebracht wordt en of dit niet meer lastiger te meten factoren bevat. Factoren zoals pijn, vermoeidheid en coping-strategieën moeten ook in ogenschouw genomen worden om een beter begrip, en anderzijds een verbetering van de ervaren actieve ziekte bij deze patiënten te bewerkstelligen.

Welk niveau van de ziekteactiviteit moet het doel van onze behandeling zijn?

Het na te streven doel van behandeling blijft nog steeds onderdeel van discussie. Volgens recent geformuleerde aanbevelingen moet het primaire doel van de behandeling van de patiënt met reumatoïde artritis zijn: "het waarborgen van de gezondheid gerelateerde kwaliteit van leven op de lange termijn, door middel van symptoom controle, het voorkomen van structurele schade, het normaliseren van functioneren en de maatschappelijke participatie te maximaliseren", waarbij het supprimeren ontsteking is de belangrijkste manier is om dit

doel te bereiken." We hebben gezien dat het bereiken van een doel zo streng als remissie leidt tot betere resultaten met betrekking tot radiologische schade, fysiek functioneren, en vooral HRQoL. Toch zijn de verschillen met het streven naar een lage ziekteactiviteit klein en niet altijd klinisch relevant. Aan de andere kant weten we dat de voortschrijdende structurele schadeprogressie zelfs bij patiënten in klinische remissie mogelijk is. Dit is een argument vóór het streven naar de laagst mogelijke ziekteactiviteit. Remissie kan worden gedefinieerd met een composite score zoals de DAS, die wel de voeten meeneemt, in tegenstelling tot de nieuwe ACR / EULAR remissie criteria. Een ander voordeel over de 'boolean' versie van de ACR / EULAR remissiecriteria is dat het resultaat van de DAS berekening een continu getal is, in tegenstelling tot de recente ja/nee remissie criteria waarbij een factor het totale oordeel zelfstandig kan bepalen wat tot problemen kan leiden zoals bij de VAS gescoord door de patiënt. In de toekomst zal onderzoek zich moeten richten op het direct vergelijken van behandelingsstrategieën sturend op verschillende behandeldoelen en daarbij focussen op kwaliteit van leven als uitkomst.

Hoe kan regulaire ziekte monitoring in de huidige dagelijkse praktijk worden geïmplementeerd?

Hoewel veel van onze beschikbare middelen gebruikt worden voor onderzoek naar nieuwe behandelingen of behandelstrategieën voor artritis patiënten, wordt relatief weinig aandacht besteed aan de implementatie van regulaire ziekte monitoring. Er zijn weinig implementatie studies beschikbaar en de studies die er zijn, hebben teleurstellende resultaten. Toch is de druk om regelmatig ziekteactiviteit te registreren hoog, mede opgelegd door verzekeringsmaatschappijen die objectieve argumenten eisen om dure behandelingen al dan niet te vergoeden. Deze kwaliteitsindicatoren die worden vastgesteld voor diverse ziekten dwingen nu bepaalde veranderingen af in de organisatie van onze gezondheidszorg voor RA patiënten.

Het betrekken van patiënten bij de behandeling wordt in de huidige gezondheidszorg steeds belangrijker. Patiënten moeten deel uitmaken van het behandelproces en onderwezen worden over hun rol in dit proces. RA patiënten moeten zich bewust zijn van het belang van regelmatige ziekte monitoring voor hun uiteindelijke ziekte uitkomst. Het is van belang dat zij weten hoe zij kunnen deelnemen aan deze evaluaties. ICT-oplossingen, zoals elektronische patiëntendossiers, kunnen de betrokkenheid van patiënten bij ziekte monitoring ondersteunen. Daarnaast moeten patiënten feedback krijgen van hun zorgverleners op hun ziektemonitoring, hun behandelresultaten en de gevolgen van deze resultaten voor eventueel noodzakelijke behandelaanpassingen.

Tot slot, om het monitoren en de uitkomsten van patiënten met UA en RA te verbeteren, moeten artsen regelmatig ziekteactiviteit beoordelen met composite scores en streven naar remissie door de behandeling daarop te sturen. Patiënten moeten actief worden betrokken

bij het monitoren van hun ziekte door het regelmatig zelf beoordelen van hun dagelijks functioneren en van hun kwaliteit van leven. Behandeling kan worden gestuurd op het laagst mogelijke niveau van ziekteactiviteit, waarbij patiënten klachtenvrij zijn, geen fysieke beperkingen hebben met daarbij een goede kwaliteit van leven. Toekomstig onderzoek zal gericht moeten zijn op directe vergelijking van behandeling- en monitor strategieën met verschillende behandeldoelen, gebruik makend van nieuwere beeldvormende technieken om subtiele tekenen van de ziekteactiviteit en/of schade te identificeren, en ten tweede het gebruik daarvan. Succesvolle implementatie van de beste monitoring en behandelstrategieën in de dagelijkse klinische praktijk kunnen dan uiteindelijk leiden tot betere zorg en uitkomsten voor patiënten met artritis.

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CURRICULUM VITAE

Rosanne Koevoets werd geboren in Goes op 13 oktober 1981. Na het afronden van het Voorbereidend Wetenschappelijk Onderwijs, is zij medische biologie gaan studeren aan de Universiteit van Amsterdam. In 2000 is zij overgestapt naar de studie geneeskunde aan de Erasmus Universiteit te Rotterdam en in 2007 behaalde zij aldaar haar artsendiploma. Zij is daarna werkzaam geweest als arts-assistent op de afdeling cardiologie in het Lange Land ziekenhuis en op de acute opname afdeling van de psychiatrie bij de BAVO te Rotterdam. In 2008 startte zij met haar promotie promotietraject in het Leids Universitair Medisch Centrum, waarbij zij betrokken is geweest bij het 3e initiatief, METEOR en de BeSt studie. Momenteel is zij werkzaam in het Universitair Medisch Centrum Utrecht als dermatoloog in opleiding.

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