# Patient Outcomes in the Treatment of Rheumatoid Arthritis
## Informing tapering decisions

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**COLOFON**

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# Patient Outcomes in the Treatment of Rheumatoid Arthritis
## Informing tapering decisions

## Patiëntgebonden factoren bij de behandeling van reumatoïde artritis
### relatie met opbouw en afbouw van medicatie

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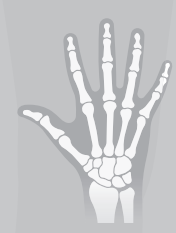
# Chapter 1

## Introduction


# INTRODUCTION



## Rheumatoid arthritis

Rheumatoid arthritis (RA) is one of the most prevalent chronic inflammatory diseases (1). Incidence in Western countries ranges from 9 to 45 cases per 100000 per year, with lower incidence observed in South European countries (2). Estimated prevalence ranges from 0.3% to 0.8% (2) and females are about three times more often affected than males (3).

The etiology of the disease is not completely understood. Increased concordance rates in twins and an increased risk associated with a positive family history suggest genetic factors play a role in the pathogenesis (1). In addition, genome-wide association studies have identified more than a hundred loci associated with RA risk, most of which implicate immune mechanisms (1). Environmental factors have been linked to the disease as well. Smoking, lower socioeconomic status and periodontal disease have been associated with an increased risk of RA (1).

## Impact

As a chronic disease, RA carries a substantial burden for both individual patients and society (1, 4). RA is a systemic disease that primarily involves inflammation of the joints (1). If left untreated, chronic inflammation of the joints causes articular destruction and bone erosions, leading to decline and functional disability. (5) Extra-articular manifestations may occur as well, among which rheumatoid nodules, pulmonary involvement, vasculitis and systemic comorbidities (1).

At the individual level, RA is not only associated with pain and disability due to joint inflammation, but also carries a burden extending beyond the joints and has been associated with an increased risk of several comorbidities (5). An approximately 2-fold higher cardiovascular risk has been reported for patients with RA compared with the general population (6), that cannot be entirely explained by shared risk factors (7) and is likely a consequence of systemic inflammation (8). A 2-fold increased risk of hip and vertebral fractures has been reported (9), which can be contributed to bone loss due to disease activity, physical inactivity and glucocorticoid use (8). In addition, an approximately 8-fold increased risk for developing interstitial lung disease was found in an inception cohort of RA patients compared with controls (10). Infection risk is increased in RA patients as well, which may be attributed either to an impaired immune system due to the disease or to effects of immunosuppressive therapy (5). An increased risk for certain malignancies has been associated with RA, among which lymphomas and lung cancer (11). Use of TNF-inhibitors has been reported to increase the risk of melanoma and non-melanoma skin cancer (12, 13).

At the level of society, RA has a large impact and leads to increased costs, both due to direct and indirect medical costs, such as reduced work capacity and decreased societal participation (1, 14).

## Psychosocial aspects

Apart from physical comorbidities, RA has been associated with increased levels of psychosocial distress, such as fatigue, anxiety, depression and cognitive impairment (5). Compared to the general population, prevalence of depression is about 1.5 times higher in RA patients (15) and is estimated to occur in 13-20% of patients (16). The prevalence may be as high as 40% when mild depressive symptoms are included (17). Anxiety often overlaps with depression and occurs 2-4 times more frequently in patients with RA (18). Apart from the burden depression and anxiety inflict by themselves, they also affect disease activity and treatment response. Higher anxiety and depression scores have been associated with significantly less remission rates at follow-up visits (19, 20). Fatigue is a common symptom in inflammatory disease. Also in RA patients, fatigue is significantly more pronounced compared with controls (21, 22) and tends to have a non-resolving character (23). Despite the association between fatigue and inflammation, negative associations have been found between baseline erythrocyte sedimentation rate and fatigue 1 year later (24) and two meta-analyses concluded that biologicals only have a small effect on reducing fatigue (25, 26). Associations have also been found for fatigue with pain, depression, anxiety and lack of social support (27-29).

Decreased work performance and work disability are observed in patients with RA (14, 30) and have been related to worse treatment response (31). Taking all aspects together, the burden of RA leads patients to experience a significantly impaired quality of life (5). Compared to age- and sex-matched controls, RA patients have lower scores on both the physical and mental domains as measured by the Short Form-36 (SF36) (5, 8). Although treatment results in improvements in health-related quality of life, scores in both physical and mental domains remain below those of age- and sex-matched healthy controls (5).

Overall, we may conclude that there is evidence that RA is associated with higher levels of psychological distress, which likely contributes to the lower levels of health-related quality of life of RA patients experience. There is also some evidence for an association between anxiety and depression and disease activity. However, the body of evidence is not yet complete. Most studies focused on single psychosocial factors only or were performed in established RA patients. Also, the nature of the relationship between psychosocial factors such as anxiety and depression and disease activity score (DAS) remains unclear. Therefore, in this work, we aim to study the impact of a broad range of psychosocial factors (anxiety, depression, fatigue, coping style) on patients with early RA, with a special interest on DAS.

## Management

Therapeutic management of RA consists of the application of disease-modifying anti-rheumatic drugs (DMARDs). These agents target inflammation and, by definition, also reduce structural damage progression in RA (1). There are two major classes of DMARDs: Synthetic DMARDs and biological DMARDs. Synthetic DMARDs can be further divided into conventional synthetic and targeted synthetic DMARDs (1). Conventional synthetic DMARDs are the oldest class of agents, examples of which are methotrexate, sulphasalazine and hydroxychloroquine. Use of these agents has evolved empirically and their modes of action are still largely unknown (1). On the contrary, biological and targeted synthetic DMARDs have been developed to modulate specific targets in the inflammation process (1).

Current EULAR recommendations (32) for treatment of RA are based on the following principles:

1. Early treatment
2. Treat-to-target
3. Tight control

Early treatment means that therapy with DMARDs should be initiated as soon as the diagnosis of RA is made. Treat-to-target implies that treatment should be aimed at reaching a target of remission or low disease activity in every patient. Tight control is the frequent monitoring of patients for disease activity, so that treatment can be timely adjusted.

For newly diagnosed patients, the guidelines state that treatment should be initiated with a (combination of) conventional synthetic DMARDs, of which methotrexate should be part. Low dose glucocorticoids should be considered as a part of the initial treatment strategy for up to 6 months, but should be tapered as rapidly as clinically feasible (32). In case the treatment target is not achieved with the first DMARD strategy, guidelines recommend the addition of a biological DMARD if poor prognostic factors are present. In the absence of such factors, another conventional synthetic DMARD strategy should be attempted first. In case a first biological DMARD has failed, patients should be treated with another biological DMARD (in case of a failed TNF-inhibitor a second TNF-inhibitor may be attempted) (32). Whether or not starting with combination of synthetic DMARDs leads to improved outcomes over starting with methotrexate alone remains controversial (1) and current guidelines accept both strategies (32). An important argument against the use of a combination strategy are the increased toxicity and discontinuations compared to methotrexate alone, while several studies show no differences in disease activity scores are observed at 6 months and beyond (1). On the other hand, in tREACH it was observed that patients initiating with combination DMARD therapy achieve remission more quickly, resulting in less biological use and improved functional outcomes at 1 year

of follow-up (33). At last, it should be noted that, even if detailed guidelines are available, rheumatologists may not fully adhere to them in clinical practice. For instance, the IRIS study reported that over 96% of participating rheumatologists stated to agree with the EULAR recommendations to start DMARD treatment as early as possible after diagnosis and that MTX should be part of the first treatment strategy (34). However, when measuring the actual performance, the rheumatologists only applied these guidelines in 67% and 60% of the recorded patients respectively (34). The recommendation that composite measures should be recorded regularly was agreed upon by 83% of rheumatologists, but only in 54% of patients were composite scores actually recorded in ≥50% of patient visits (34).

## Remission and tapering

Conceptually, remission has been defined as the total absence of all articular and extra-articular inflammation and immunologic activity related to rheumatoid arthritis (35). As the assessment of such a state is not feasible, instead the concept of clinical remission is used in practice. (36) Both in clinical practice and in clinical trials, a cut-off point of <2.6 on the 28-joint Disease Activity Score, or <1.6 on the original DAS is often used to define remission. However, use of these definitions has been criticized, as signs of joint inflammation may clearly be present despite a score indicating remission (36). For this reason, the ACR/EULAR committee has advocated the use of more stringent remission criteria for use in clinical trials (36).

Still, regardless of the definition used, disease control can be obtained in an increasing number of patients (37). For example, in Norwegian patients registered in the NOR-DMARD registry, remission rates have doubled over the past decade to 40% (38). Similar patterns have been observed in the ESPOIR cohort, in which 50% of early RA patients were in DAS28 remission and 65% in DAS28 low disease activity 5 years after disease onset. The growing population of patients with RA in remission can be attributed for a great part to a paradigm shift that has taken place over the past two decades in the treatment of RA, in which concepts early diagnosis, tight-controlled treatment and treat-to-target are central (39). Another important factor has been the rapid development of new anti-rheumatic drugs, especially the biological DMARDs (37).

As a consequence of this success, a new question has emerged whether de-escalation or even stopping of DMARD therapy should be considered in patients that have reached long-standing remission (37). This question is important for several reasons (37). First, in case of a symptom-free disease state, the benefits of continuous treatment should still outweigh the risks associated with long-term use of that treatment, both of which may be difficult to establish. Second, the costs of DMARDs, in particular bDMARDs, are high. As healthcare resources are under growing economic pressure, potential overtreatment of patients in remission should be avoided. This could make resources available for other

patients in need of expensive treatments. Third, a potential cure of RA could can only be distinguished from mere suppression of inflammation by DMARDs after therapy has been de-escalated. (37) Due to the potential benefits, the option to de-escalate treatment in patients in sustained remission has also been included into recent treatment guidelines (32). However, treatment de-escalation may come with certain risks as well. A systematic review and meta-analysis on the withdrawal of biological agents in RA found that withdrawing biologics decreased the probability of maintaining low disease activity and remission and found a small but significantly increased risk for radiographic progression (40). Identification of patients that would gain most benefit, or harm, from treatment de-escalation would therefore be preferable, but is not yet possible (37).

To further optimize the management of RA patients, rheumatologists need to be able to make informed decisions based on the best available evidence. Therefore, a second aim of this work is to study the effects of treatment de-escalation in patients with low disease activity or remission to aid rheumatologists in making informed decisions. A special focus will be on the tapering of conventional synthetic DMARDs, as recent literature on this topic is lacking.

### Summary and aims

Despite the advances that have been made in the medical treatment of RA (39), challenges to further optimize care for patients remain. Two of these challenges will be the focus of this work: First, despite the better medical outcomes the burden of disease in RA patients is still higher compared to the general population, which may be attributed, at least in part, to higher levels of psychological distress patients experience (5). Second, continuous medical drug treatment for patients in remission is only justified if the benefits outweigh the disadvantages such as potential overtreatment, safety considerations and treatment costs (37). These challenges resulted in the main objectives of this thesis:

1. To study the impact of psychosocial factors on patients with early RA, with special interest in the relationships between psychosocial factors and disease activity score and achievement of treatment goals
2. To study the effects of treatment de-escalation in patients with low disease activity or remission and aid rheumatologists in making informed decisions with regard to treatment de-escalation

### Overview

In chapter 2, we will describe the burden of disease, quality of life and health care consumption of patients diagnosed with RA during the first year of follow-up and compare them to patients diagnosed with joint complaints without synovitis.

In chapter 3 we will evaluate the associations between psychosocial factors and disease activity at subsequent visit during the first 15 months of follow-up.

In chapter 4, we will describe the prevalence and pattern of fatigue in patients diagnosed with early RA during the first year after diagnosis. Factors associated with worsening and recovering of fatigue over time in patients with low or high levels of fatigue at baseline are investigated.

In chapter 5, predictors for attaining remission within the first 6 months of treatment and sustained remission at 6 and 9 months are explored.

In chapter 6, we will investigate the tapering of conventional synthetic DMARDs in patients with early arthritis in sustained remission during 2-year follow-up of the tREACH trial.

In chapter 7, we will present a systematic literature review of publications on RA patients tapering or discontinuing synthetic or biologic DMARDs. Main focus will be on reported flare rates, radiographic progression and time to achieve re-remission after flare.

In chapter 8, we will explore doctor's preferences for de-escalating DMARDs in rheumatoid by means of a discrete choice experiment. In this study, we will investigate which factors rheumatologists deem important in their decision to de-escalate medication and the relative importance. Differences between rheumatologists will be explored as well.

In chapter 9, we will provide a general discussion of the main findings of this thesis and their relevance to clinical practice. Methodological considerations and their potential implications on the findings will be discussed. Finally, several recommendations for future research will be presented.

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# Chapter 2

## Quality of life and health care use in patients with arthralgias without synovitis is similar to that of patients diagnosed with early RA: Data from an early arthritis cohort

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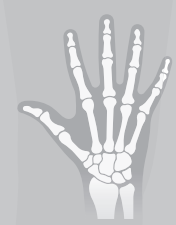


## ABSTRACT

### Objective

To compare the burden of disease and its development over time in patients being referred to an early arthritis cohort being diagnosed either as having arthralgias without synovitis or as having rheumatoid arthritis (RA).

### Methods

Patients being diagnosed as having arthralgias without synovitis or RA were selected from the REACH cohort. Data were collected on clinical and psychological characteristics, demographics, pain scores (Rheumatoid Arthritis Disease Activity Index), functional ability (Health Assessment Questionnaire), health related quality of life (HRQOL, Short Form-36), fatigue (Visual Analogue Scale and Fatigue Assessment Scale) and health care utilization (HCU) at baseline, 6 and 12 months of follow-up. Burden of disease measures (pain, functional ability, fatigue and HRQOL) and HCU levels were plotted over time for both groups. A Poisson regression model for repeated data was used to identify determinants of HCU for both groups.

### Results

At baseline, 330 patients with arthralgias without synovitis (non-synovitis, NS group) and 244 RA patients (RA group) were included. Overall, burden of disease measures and HCU levels were very similar between groups. Both groups showed improvement over time with respect to pain scores, functional ability, HRQOL and HCU levels. Independent predictors for high HCU were identified: More pain, worse physical health and external locus of control in the NS group and longer duration of complaints, chance locus of control and worse physical functioning in the RA group.

### Conclusion

Despite the absence of an inflammatory diagnosis, patients with arthralgias without synovitis experience a similar burden of disease compared to RA patients.

## INTRODUCTION

Over the past decade, early arthritis clinics have been established around the world (1). Main goal of these clinics is the early detection and treatment of rheumatoid arthritis, which has been shown to result in a more favorable course of disease (2-4). Although many of the patients referred to early arthritis clinics are diagnosed as having early rheumatoid arthritis (RA) and benefit from early treatment of their condition, another part of the referred patients do not show any physical signs of an underlying inflammatory disease and are unlikely to develop RA in the future. Patients in this second group are referred to the rheumatologist with complaints that very much resemble those of early arthritis, but for whom no signs of arthritis can be found at physical examination. However, despite the absence of an underlying inflammatory condition, a previous study suggested that these patients experience a similar burden of disease as early RA patients or patients with other inflammatory joint conditions do (5). Formal diagnoses, as well as a clear understanding of the processes underlying the complaints, are usually lacking in this patient group. As a result, the consequences on functional ability, health and general well-being, as well as the progression of health complaints over time are unknown. Furthermore, despite the high burden of disease, standardized treatment regimens are usually absent for this category of patients. It is unclear what strategies these patients adopt to deal with their complaints after visiting the rheumatologist being diagnosed as non-synovitis.

Aim of the present study was to to compare the burden of disease and its development over time in patients being referred to an early arthritis clinic being diagnosed either as having arthralgias without synovitis or as having rheumatoid arthritis (RA). To do this, we set out to answer to the following questions:

1. What are the quality of life, perceived pain, perceived fatigue, functional ability and health care consumption levels in patients with arthralgias without clinical synovitis compared to those of RA patients and how do these domains evolve over time?
2. Which factors are associated with higher health care consumption levels in patients with arthralgias without clinical synovitis and patients with RA?

## PATIENTS AND METHODS

### Study population

Patients in this study were selected from the Rotterdam Early Arthritis CoHort (REACH) (5). All patients participating before June 2009 that gave permission to send questionnaires were included. Patients were excluded if diagnosed with non-RA arthritis at any moment during the 12 months of follow-up (Figure 1).

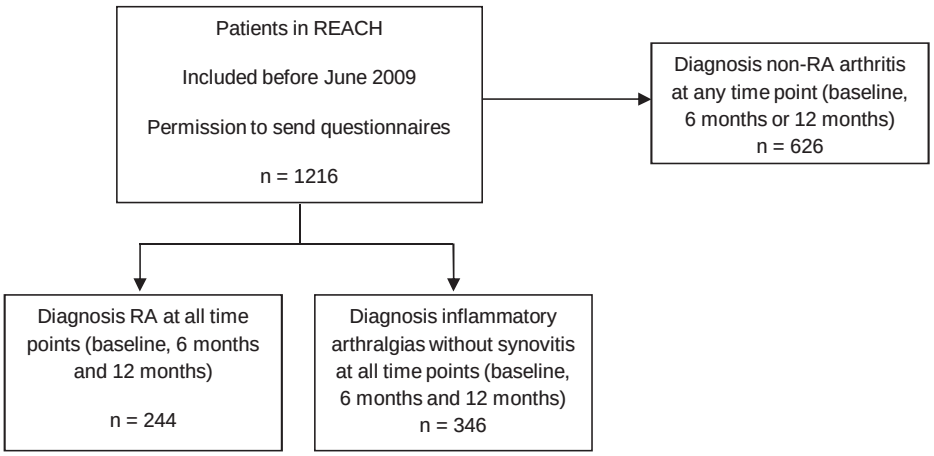


**Figure 1.** Inclusion and follow-up of patients with RA and patients with arthralgias without synovitis.

The REACH is a prospective inception cohort set up in the greater Rotterdam area in July 2004. Patients were recruited at their first consultation either via the general practitioner or via the outpatient rheumatology clinic of 5 hospitals.

Patients in the REACH cohort were included if they fulfilled either or both of the following criteria:

1) having synovitis in at least one joint on clinical examination
2) having pain, stiffness or loss of function in at least two joints accompanied by at least two of the following criteria: morning stiffness > 1 hour; unable to clench a fist in the morning; pain when shaking someone's hand; pins and needles in the fingers; difficulties wearing rings; difficulties wearing shoes; a family history of RA; unexplained fatigue lasting less than one year.

Patients were excluded if their symptoms existed for more than 12 months, or if symptoms resulted from trauma or overuse. This study was approved by the ethics committees of the 5 participating hospitals. All patients gave written informed consent.

## Measures for burden of disease

*Pain*

Pain was assessed using the Rheumatoid Arthritis Disease Activity Index (RADAI) questionnaire (6). The RADAI was modified so that two questions regarding the activity of joint inflammation were excluded. Sumscores were calculated on a scale of 0-10, higher values indicating more symptomatic disease.

*Functional ability*

Functional ability was assessed by the Health Assessment Questionnaire (HAQ) (7). The HAQ ranges from 0 to 3, higher scores indicating more disability.

*Health related quality of life*

Health related quality of life (HRQOL) was assessed by the Medical Outcome Study Short Form-36 Health Survey (SF-36). The SF-36 is a generic 36-item questionnaire covering 8 dimensions: physical functioning (PF), physical role functioning (RP), bodily pain (BP), general health (GH), vitality (VI), social functioning (SF) and mental health (MH) (8, 9). To provide a global measure of physical and mental functioning, component summary scores (physical component scale (PCS) and mental component scale (MCS) respectively) were calculated from the 8 separate dimensions of the SF-36. The 8 dimensions and 2 summary scores may range from 0 to 100, a higher score indicating a better HRQOL.

*Fatigue*

Fatigue was measured by questionnaire using 2 different scales: A visual analogue scale (VAS) and the Fatigue Assessment Scale (FAS). The VAS is a continuous scale, ranging from 0 to 100. Total FAS scores can range from 10 to 50 (10). On both the VAS and the FAS, higher scores indicate higher levels of fatigue.

*Health care use*

Health care utilization (HCU) was assessed by a questionnaire at baseline, 6 months and 12 months of follow-up. At each point, patients were asked to report the number of visits for joint complaints for general practitioners, medical specialists, physiotherapists, nurse specialists, occupational physicians and other health care providers (to be specified by the patient). If any health care provider was consulted, patients were asked to report the number of visits.

To evaluate overall use of care, a combined HCU measure was constructed as follows: visits to GP + visits to a medical specialist + visits to a physiotherapist / 5 + visits to alternative health care providers. Since generally, multiple sessions for physiotherapy are prescribed we chose a correction factor of 5 (based on the distribution of our data, 15% had more than 5 visits to a physiotherapist at baseline) to be applied for its contribution to the combined measure.

## Clinical and demographic characteristics

*Clinical characteristics*

A trained research nurse took a standardized history and conducted a physical examination at baseline, after 6 months and after 12 months. Tender and swollen joint counts were computed evaluating 53 joints and 44 joints respectively (as required to calculate

the original Disease Activity Score (DAS) (11)). The presence or absence of synovitis was confirmed by the treating rheumatologist. Diagnoses were obtained directly from the treating rheumatologists or chart reviews.

*Demographic characteristics and lifestyle*

Patients were asked about their age, sex and ethnicity. Education was categorized as low (primary school, lower and intermediate secondary schooling or intermediate vocational training), intermediate (higher secondary schooling or intermediate vocational training), and high (higher vocational training or university). Employment status was defined as having paid employment (yes/no). Living status was ascertained and patients were classified as living alone or with others. Body mass index was categorized into obese (≥ 30 $kg/m^2$) or non-obese (< 30 $kg/m^2$).

## Psychosocial characteristics

*Coping style*

Coping style was assessed using the Coping of Rheumatic Stressors (CORS) questionnaire (12-14). The questionnaire consists of 2 scales: "decreasing activities to cope with pain" and "pacing to cope with limitations". Sum scores were computed. A higher sum score indicates more frequent use of the coping strategy.

*Locus of control*

Perceived control over health outcomes was measured by the Multidimensional Health Locus of Control Questionnaire (MHLC). The MHLC assesses 3 different dimensions of perceived health control by means of 3 scales: "internal", "external" and "chance" (15, 16). The "internal" scale reflects the belief that people are personally responsible for their own health. The physician scale reflects that a physician is responsible for one's health. The "chance" scale reflects the belief that health depends on chance, luck or fate. The subscale scores range from 6 to 36, a higher score indicating that a patient's belief is stronger in that particular health locus of control. The scales are not opposite ends of the same spectrum. Thus, it is possible to have, for example, both internal and physician beliefs about health status at the same time.

*Anxiety / depression*

Anxiety and depression were ascertained using the Hospital Anxiety and Depression Scale (HADS) (17, 18). The HADS was originally developed to identify anxiety disorders and depression among patients in non-psychiatric hospital clinics. Both the anxiety and depression subscales range from 0 to 21, higher scores indicating more anxiety or depression.

### Statistical analysis

Characteristics of the study population were described using simple descriptive analysis techniques. Baseline differences between groups among continuous variables were tested with the unpaired t-test or with the Wilcoxon rank-sum test if data were not normally distributed. Categorical variables were tested using Pearson's chi-square test.

Determinants of HCU were evaluated using Poisson regression analyses for repeated data. A 6-month time-lag model was chosen, implying that the measurement of a risk factor was related to the outcome measured 6 months later. For variables that measured overlapping constructs (HADS and SF-36 MCS, HAQ and SF-36 PCS, Tender Joint Count and RADAI) or were highly correlated (coping with pain and coping with limitations), one variable was selected for inclusion into the model. Covariates that were collected solely at baseline were included into the model as time-independent covariates. All univariate analyses were performed taking into account the evolution of HCU over time. For the multivariable models, first variables were selected based on their level of significance in the univariate analysis ($p \leq 0.20$). Then backwards stepwise selection was performed, while covariates month, age and sex were included by default. Missing covariates were imputed with their corresponding individual value at 6 or 12 months of follow-up. If neither of these were available the group mean was imputed. Subsequently, missing values at 6 months of follow-up were imputed with their corresponding baseline values and missing values at 12 months of follow-up were imputed with their corresponding values at 6 months. All statistical analyses were performed with the statistical package STATA (12.0 SE) using $p \leq 0.05$ as level of statistical significance.

## RESULTS

### General characteristics

At baseline, 330 patients with inflammatory arthralgias without synovitis (non-synovitis, NS group) and 244 rheumatoid arthritis patients (RA group) were included. Of 244 patients in the RA group, 166 (68.0%) fulfilled the ACR1987 criteria and 171 (70.1%) fulfilled ACR2010 criteria. One-hundred-twenty-four patients (50.8%) fulfilled both criteria, 42 (17.2%) fulfilled ACR1987 criteria only, 47 (19.3%) fulfilled ACR2010 criteria only and 31 (12.7%) fulfilled neither criteria.

On average, patients in the RA group were older (54.0 years versus 45.0 years), were more often males, had lower education, were more often unemployed, had a shorter duration of complaints (103 versus 136 days), had more tender joints (9 versus 4), had higher pain scores (RADAI, 3.3 versus 2.5) and had higher functional disability scores (HAQ, 1 versus 0.6) than patients in the NS group (Table 1).

**Table 1.** Baseline clinical, demographic and psychosocial characteristics of non-synovitis (n=330) and rheumatoid arthritis (n=244) patients.

| | Non-synovitis (n=330) | | Rheumatoid arthritis (n=244) | | P-value |
|---|---|---|---|---|---|
| **Clinical and demographic characteristics** | | | | | |
| Age, mean [n] (sd) | 45.0 [330] | (12.4) | 54.0 [244] | (13.7) | **< 0.001**[a] |
| Female, n (%) | 282/330 | (85) | 165/244 | (68) | **< 0.001**[b] |
| Dutch ethnicity, n (%) | 251/309 | (81) | 188/229 | (77) | 0.823[b] |
| Education, n (%) | | | | | **0.008**[b] |
| Low | 154/310 | (50) | 145/230 | (59) | |
| Intermediate | 96/310 | (31) | 54/230 | (22) | |
| High | 60/310 | (19) | 31/230 | (13) | |
| Living alone, n (%) | 40/312 | (13) | 38/231 | (16) | 0.266[b] |
| Paid employment, n (%) | 204/313 | (65) | 127/231 | (52) | **0.017**[b] |
| BMI, mean [n] (sd) | 26.8 [321] | (5.1) | 26.4 [219] | (4.6) | 0.376[a] |
| Duration of complaints, median days, [n] (range) | 136 [329] | (7 – 380) | 103 [244] | (7 – 373) | **< 0.001**[c] |
| Tender joint count, median [n] (range) | 4 [328] | (0- 26) | 9 [241] | (0 – 45) | **< 0.001**[c] |
| RADAI (0-10), median [n] (range) | 2.5 [304] | (0 – 8.4) | 3.3 [225] | (0- 9.5) | **0.004**[c] |
| HAQ (0-3), median [n] (range) | 0.6 [310] | (0- 2.3) | 1 [229] | (0- 2.9) | **< 0.001**[c] |
| Fatigue (FAS), median [n] (range) | 22 [307] | (10 – 48) | 21 [225] | (10 – 47) | 0.177[c] |
| Diagnosis, n(%) | | | | | N/A |
| Tendinopathy | 48/330 | (15) | | | |
| Joint complaints (other) | 201/330 | (61) | | | |
| Fibromyalgia | 11/330 | (3) | | | |
| Osteoarthrosis | 70/330 | (21) | | | |
| Comorbid conditions, n (%) | | | | | 0.382[b] |
| None | 83/320 | (26) | 76/232 | (31) | |
| 1 | 124/320 | (39) | 80/232 | (33) | |
| 2 | 66/320 | (21) | 44/232 | (18) | |
| 3 or more | 47/320 | (15) | 32/232 | (13) | |
| **Psychosocial characteristics** | | | | | |
| Coping with pain (8-32), median [n] (range) | 14 [310] | (8 – 29) | 15 [229] | (8 – 30) | **<0.001**[c] |
| Coping with limitations (8-40), median [n] (range) | 20 [310] | (10 – 37) | 23 [229] | (10 – 40) | **<0.001**[c] |
| Locus of control, median [n] (range) | | | | | |
| Internal (6-36) | 21 [307] | (7 – 32) | 21 [231] | (6 – 34) | 0.541[c] |
| External (6-36) | 17 [307] | (6 – 34) | 20 [231] | (9 – 35) | **<0.001**[c] |

**Table 1.** Baseline clinical, demographic and psychosocial characteristics of non-synovitis (n=330) and rheumatoid arthritis (n=244) patients. (*continued*)

| | Non-synovitis (n=330) | | Rheumatoid arthritis (n=244) | | P-value |
|---|---|---|---|---|---|
| Chance (6-36) | 19 [307] | (6 – 35) | 20 [231] | (6 – 36) | 0.585[c] |
| Anxiety (HADS (0-21)), median [n] (range) | 6 [309] | (0 – 21) | 5 [231] | (0 – 18) | 0.151[c] |
| Depression (HADS (0-21)), median [n] (range) | 3 [309] | (0 – 18) | 4 [229] | (0 – 18) | 0.067[c] |
| SF36 | | | | | |
| PCS (0-100), median [n] (range) | 39 [306] | (12 – 59) | 32 [225] | (9- 58) | **<0.001[c]** |
| MCS (0-100), median [n] (range) | 54 [306] | (20 – 70) | 54 [225] | (21 – 74) | 0.343[c] |

[a] Student t-test
[b] Fisher's exact test
[c] Wilcoxon rank-sum test

## Psychosocial characteristics, functional ability and fatigue

Psychosocial characteristics were very similar between groups (Table 1). Although significant differences were found on coping with pain and limitations (CORS), physical health (SF-36 PCS) and external locus of control, differences are too small to have clinical relevance. Pain scores (RADAI) decreased over time in both groups (Figure 2A) from 2.9 (95%-CI 2.7-3.1) to 2.1 (95%-CI 1.8-2.3) and 3.4 (95%-CI 3.1-3.7) to 1.8 (95%-CI 1.6-2.0) in the NS and RA group respectively. A trend was seen for higher pain scores at baseline and lower pain scores after 6 and 12 months in the RA group. Baseline functional ability (HAQ) scores were worse in the RA group but decreased over time (Figure 2B). HAQ scores remained more or less constant over time in the non-synovitis group. Fatigue scores, as measured with the fatigue assessment scale (FAS), were similar in both groups and remained constant over time (Figure 2C). Fatigue scores measured on a visual analog scale (VAS), were similar in both groups and decreased from 55 (95%-CI 52-57) and 51 (95%-CI 48-54) at baseline to 47 (95%-CI 44-51) and 42 (95%-CI 38-46) after 12 months in the NS group and RA group respectively (Figure 2D). HRQOL (SF-36 subscales) was comparable or somewhat lower for the RA group, improving over time for both groups (Figure 3). However, HRQOL remained considerably lower than the population average in both groups.

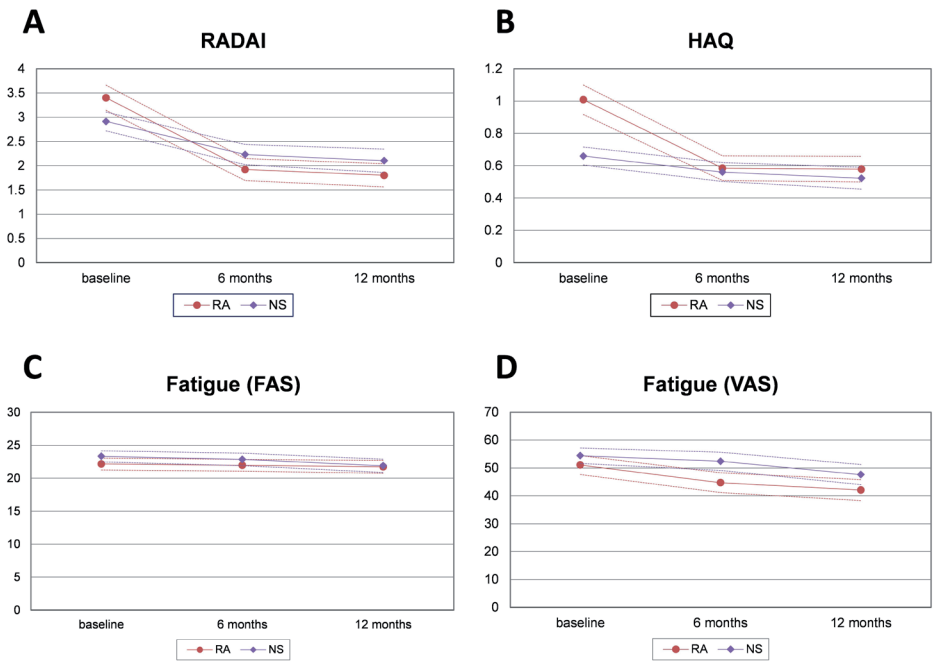


**Figure 2.** Evolvement of pain scores (RADAI) (panel A), functional ability (HAQ) (panel B), fatigue measured with the FAS (panel C) and fatigue measured with the VAS (panel D) over time in patients with arthralgias without synovitis and patients with rheumatoid arthritis. Dotted lines indicate 95%-confidence intervals.

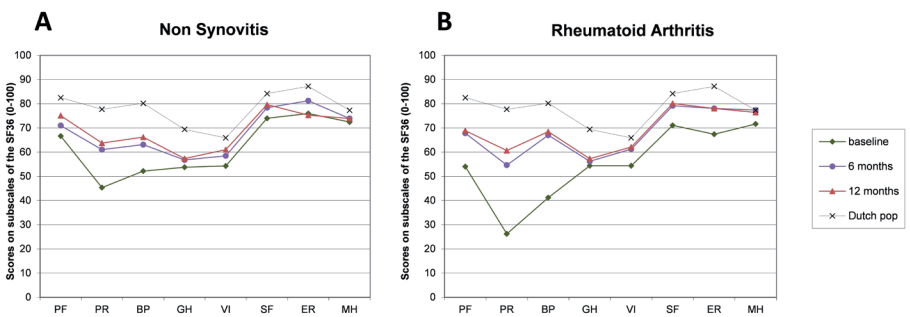


**Figure 3.** Health related quality of life in patients with arthralgias without synovitis (panel A) and patients with rheumatoid arthritis (panel B), as measured by the SF-36 components physical functioning (PF), physical role functioning (PR), bodily pain (BP), general health (GH), vitality (VI), social functioning (SF), emotional role functioning (RE), and mental health (MH). Averages for the general Dutch population aged >25 years are shown.

## Health care utilization

HCU decreased over time in both groups and was similar in both groups, except for more visits to medical specialists in the RA group, which one would expect (Figure 4). In the NS group, high levels of HCU were associated in the multivariable Poisson analysis with increased pain (IRR 1.10, 95%-CI 1.02–1.17), worse physical health (IRR 0.98, 95%-CI 0.96-0.99) and external locus of control (IRR 1.04, 95%-CI 1.01-1.07) (Table 2) and in the RA group with shorter duration of complaints (IRR 1.53, 95%-CI 1.17-2.00), worse physical functioning (IRR 0.98, 95%-CI 0.97- 0.99) and low chance locus of control (IRR 1.03, 95%-CI 1.01-1.05) (Table 2).

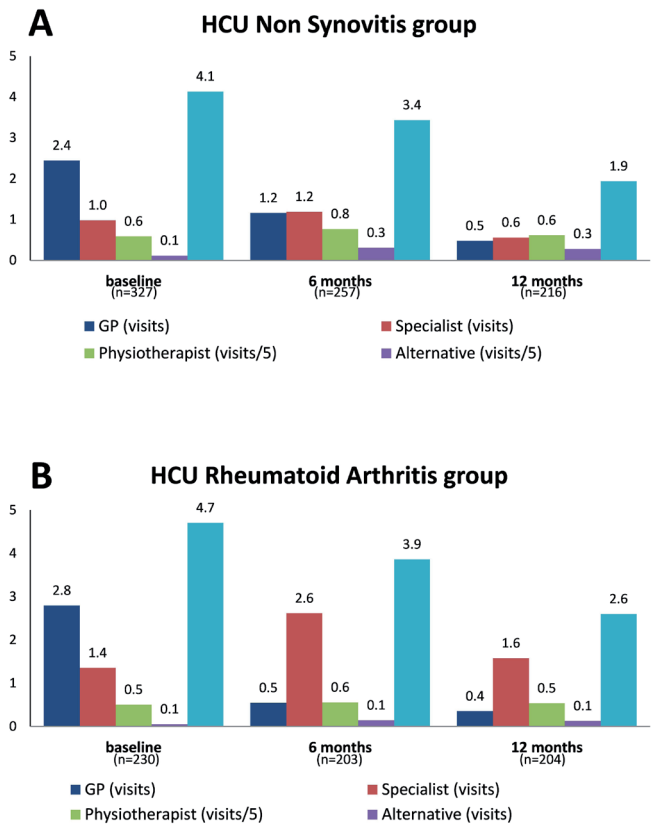


**Figure 4.** HCU in patients with arthralgias without synovitis (panel A) and patients with rheumatoid arthritis (panel B) during the 6 months prior to baseline, 6 and 12 months of follow-up, by type of health care provider.

**Table 2.** Multivariable Poisson regression for repeated data[b]: Determinants for combined HCU over the first year for non-synovitis and rheumatoid arthritis patients.

| | Multivariable model | | | Multivariable model | | |
|---|---|---|---|---|---|---|
| | Non-synovitis | | | Rheumatoid arthritis | | |
| | **IRR** | **p** | **95%-CI** | **IRR** | **p** | **95%-CI** |
| Month | **0.944** | **0.000** | **0.922 – 0.967** | **0.962** | **0.000** | **0.942 – 0.982** |
| Age[a] | 1.001 | 0.858 | 0.990 – 1.013 | 1.000 | 0.992 | 0.992 – 1.008 |
| Female sex | 1.110 | 0.597 | 0.755 – 1.630 | 1.085 | 0.465 | 0.872 – 1.348 |
| Duration of complaints | | | | | | |
| 90-180 days | | | | 0.922 | 0.476 | 0.737 – 1.153 |
| >180 days | | | | **0.653** | **0.002** | **0.500 – 0.852** |
| Pain (RADAI) | **1.095** | **0.009** | **1.023 – 1.172** | | | |
| External locus of control[a] | **1.036** | **0.018** | **1.006 – 1.066** | | | |
| Chance locus of control[a] | | | | **0.972** | **0.004** | **0.953 – 0.991** |
| SF36 PCS | **0.975** | **0.000** | **0.963 – 0.987** | **0.980** | **0.000** | **0.971 – 0.988** |

[a] baseline
[b] backwards selection was applied; variables month, age, sex were included by default

## DISCUSSION

Overall, we observed that the burden of disease, as measured by pain, disability, fatigue and quality of life, and health care consumption levels are very similar between patients with arthralgias without synovitis compared to patients with rheumatoid arthritis. Our results indicate that, despite the absence of an underlying inflammatory process, patients with arthralgias without synovitis experience a burden of disease that is similar to that of patients diagnosed with early rheumatoid arthritis, at least during the first year of follow-up. Pain scores, functional ability, HRQOL and health care consumption levels improved over time in both groups. Fatigue scores improved only marginally (VAS fatigue) or not at all (Fatigue Assessment Scale) in both groups. Groups differed most with respect to baseline disability scores (HAQ), which were higher in the RA group. Small differences were observed with respect to health care consumption levels, that were somewhat higher in the RA-group, and HRQOL scores (SF-36 subscales), that were either similar or somewhat worse in the RA group. The finding that HCU levels in the NS-group are quite similar to those observed in the RA-group is surprising. RA patients are actively being treated for their disease and have regularly scheduled visits with their rheumatologist, which accounts for a large part the health care consumption levels observed. Patients in the NS-group, on the other hand, probably seek care for different reasons. Possibly searching for a diagnosis and relief for their symptoms.

In existing literature, studies on burden of disease measures and health care consumption in RA patients are sparse and absent in patients with arthralgias without synovitis. In a prospective cohort study of 183 patients with early rheumatoid arthritis included between 1985 and 1989, Lindqvist et al. found that median HAQ scores increased from 0.8 at baseline to 1 after one year of follow-up (19). In contrast, we found that median HAQ scores decreased in the RA group from 1.0 at baseline to 0.6 after 12 months. These differences are probably a consequence of the availability of more effective treatment regimens nowadays. In accordance to our findings, a study comparing four cohorts of patients with early rheumatoid arthritis found that pain scores (VAS) decreased in all cohorts during the first year of follow-up (20). In the Dutch cohort, pain scores decreased from 3.9 at baseline to 2.6 at 1 year of follow-up (20).

Despite substantial improvements in pain, functional ability and HRQOL scores, we only observed a modest improvement in fatigue scores as measured on the visual analog scale (VAS), while no improvement in fatigue scores was seen on the FAS. Possibly, the FAS is less sensitive than the VAS for the detection of subtle changes in fatigue. We did not find any studies investigating levels of fatigue in NS patients in current literature. However, in line with our findings, studies investigating the effect of treatment with conventional or biologic DMARDs on VAS fatigue scores in RA patients, found improvements, but with small effect sizes, as well (21, 22).

Second aim of this study was to identify factors associated with high HCU levels in patients with arthralgias without synovitis and patients with RA. Our multivariable Poisson regression analyses showed that overall HCU was associated with worse physical health in both groups. Differences between the groups were found for duration of symptoms at baseline (>6 months) and high chance locus of control, that were associated with lower HCU in the RA group, while higher pain scores and external locus of control were associated with higher HCU in the non-synovitis group. We could not find any previous studies in which HCU was assessed in an early arthritis cohort. In a cross-sectional study among 1200 patients with established RA, Jacobi et al. found that overall high use of care was associated with younger age, female sex, longer disease duration and having 2 or more comorbidities (23). We could not confirm a relationship for age, sex and comorbidity. These discrepancies could be explained by the smaller sample size of our study, or the difference between patients in the two studies (long standing RA in the Jacobi study versus newly diagnosed RA in our study). Moreover, Jacobi found increased disease duration to be associated with high HCU, while we found a longer duration of complaints to be associated with less HCU.

This study has several strengths and weaknesses. Strong points include the fact that data were obtained prospectively and repeatedly within an early arthritis cohort. Determinants for HCU were analysed using a Poisson model for repeated data, taking into

account progression of the outcome over time. Possible weaknesses of this study are the relatively small sample sizes of the two patient groups. Possible determinants for HCU might not have been detected due to this. Also, HCU was measured using questionnaires, introducing a potential for recall bias. Recall bias could have led to both an over- and an underestimation of HCU, although underreporting was found to be the more common problem when using questionnaire data (24). In either case, as disease burden is very similar among groups, we would expect that if recall bias indeed is present, it would be similar among groups. This would then lead to non-differential misclassification of health-care use, resulting in a dilution of effect sizes for determinants of HCU in our Poisson regression models. Therefore, the relatively weak effect sizes observed in the multivariable analyses for determinants of HCU might be a consequence of non-differential misclassification of HCU due to recall bias. Another limitation might be that some patients diagnosed with fibromyalgia (n=10) were among the patients in the non-synovitis group, because fibromyalgia was not an a priori exclusion criterion. This could have biased the results for the group. However, excluding the 10 patients with fibromyalgia (3.6% of total) from the analysis of determinants of HCU in the non-synovitis group did not substantially change the results as previously found (data not shown). Also, the finding that HRQOL is similar between groups pertains only to the first year of follow-up. Further observation is required to see if this is still true later on. Another limitation could be that patients in the non-synovitis group were selected on the basis that they did not develop any form arthritis during the first 12 months of follow-up, while they might be developing arthritis later on. Patients in our cohort were followed-up for 24 months. Therefore, we checked whether patients in the NS-group had developed any form of arthritis at 24 months of follow-up or beyond. At 24 months of follow-up, 4 patients in the NS-group had developed arthritis. Two patients were diagnosed with RA, 1 patient was diagnosed with polyarthtritis and 1 patient was diagnosed with oligoarthritis. Beyond 24 months of follow-up, 8 more patients developed a form of arthritis. Five patients were diagnosed with RA, 2 patients were diagnosed with psoriatic arthritis, and one patient was diagnosed with synovitis due to osteoarthritis. However, excluding the 12 patients developing arthritis beyond 12 months of follow-up from the analysis did not significantly change the results (data not shown).

## CONCLUSION

In conclusion, we found that the burden of disease, as well as health care use (HCU), in patients with arthralgias without synovitis is comparable to that of patients with rheumatoid arthritis. Although both groups show improvements in pain scores, quality of life

and reduction of HCU over time, only a modest improvement was seen for fatigue in both groups.

Health related quality of life in the non-synovitis group remains substantially lower compared to the general population. We therefore believe that, after synovitis is sufficiently ruled out by the rheumatologist, patients should be offered further support and monitoring by their general practitioner. Depending on the burden of health complaints, the emphasis could lie on helping patients to better cope with their complaints, for instance through psychological interventions. However, if any joint swelling does occur in the future, patients should be referred back to a rheumatologist for further examination.

## ACKNWOLEDGEMENTS

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# Chapter 3

## Effects of psychosocial factors on monitoring treatment effect in newly diagnosed RA patients over time: Response data from the tREACH study

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## ABSTRACT

### Objectives

To investigate 1) whether psychosocial factors have an additional effect on disease activity and 2) which compounds of psychosocial factors are the most influencing ones during the first year of RA treatment.

### Methods

Fifteen months follow-up data were used from patients included in tREACH; an RCT comparing initial triple DMARD therapy (iTDT) to methotrexate monotherapy (iMM) with glucocorticoid bridging in both groups. Patients were evaluated every 3 months and treated-to-target. Associations between DAS at 3, 9 and 15 months and psychosocial factors anxiety, depression, fatigue and coping with pain at the previous visit were assessed by multivariable linear regression correcting for demographic, clinical and treatment related factors.

### Results

N=265, 251 and 162 patients were available for analysis at 3, 9 and 15 months of follow-up respectively. Baseline anxiety and coping with pain were associated with DAS at 3 months. Coping with pain at 6 months was associated with DAS at 9 months. Fatigue at 12 months was associated with DAS at 15 months. Psychosocial factors were moderately correlated to each other. Effects on DAS were mainly through DAS components tender joint count and global health.

### Conclusion

Psychosocial factors have an additional effect on DAS throughout the first year of treatment in early RA. A change in pattern was observed from anxiety and coping with pain being associated with subsequent DAS at baseline towards fatigue being associated with subsequent DAS at 12 months. Due to the explorative nature of this study, more research is needed to confirm this pattern.

## INTRODUCTION

Rheumatoid arthritis is a common autoimmune disease and is associated with progressive disability, early death and socioeconomic costs (1). Disease progression can be tackled by early treatment with DMARDs, using tightly controlled and treat-to-target strategies (2, 3). This target has been proposed in guidelines as remission or low disease activity, which is commonly measured in clinical practice by composite scores such as DAS and DAS28 (4). Recently published studies show that with this regime a response rate between 40-80% can be reached within 1 year (5, 6). Several patient and disease characteristics, such as baseline disease activity (7, 8), age (7, 9) and sex (7-9) have been reported that may explain part of the variability in response rates. However, a large part of the variability remains unexplained, suggesting that other, unidentified, factors may be at play as well. Recent interest has gone out to the influence of psychosocial factors. Several studies have reported significant associations between baseline levels of anxiety and/or depression and subsequent disease activity scores or its components (10-12). However, effects of psychosocial factors after treatment has been initiated on disease activity have not been extensively studied. Knowing and understanding the effect of psychosocial factors underlying disease activity and treatment response could provide important information for selection of therapy, evaluation of response, and even targeted psychological interventions aimed at optimizing patient outcome (13). In this study, we aimed to answer the following questions: 1) Is there, apart from an effect by patient and disease related factors, an additional effect of psychosocial factors on the disease activity during the first year of treatment in an early RA population. 2) Which compounds of psychosocial factors are the most influencing ones during the disease course?

## METHODS

### Study population

Fifteen months follow-up data were used from the tREACH cohort, for which a detailed description of the inclusion criteria and protocol can be found in the original tREACH paper (6). In short, patients with early arthritis (duration of complaints < 1 year) and a high risk of developing persistent arthritis (score >6 points on Visser model (14)) were eligible. Of the included patients, 97% fulfilled the ACR/EULAR 2010 criteria for RA (4). Patients were randomized to the following induction treatment strategies: Triple DMARD therapy (iTDT; methotrexate (MTX) 25 mg/week, sulphasalazine 2000 mg/day and hydroxychloroquine 400 mg/day or MTX monotherapy 25 mg/week (iMM). Both groups received bridging therapy with glucocorticoids (triamcinolone acetonide 80 mg or methylprednisolone 120 mg once by intramuscular injection or oral prednisone 15 mg for 4 weeks, thereafter tapered by 5

mg/week). Patients were evaluated every 3 months. In case DAS was >2.4, patients were switched to a TNF-blocker combined with MTX 25 mg/week. If sustained remission (DAS<1.6 at 2 consecutive visits) was achieved, medication was tapered according to protocol. Detailed information on the medication scheme can be found in the original tREACH paper (6).

## Outcomes

Outcomes were the disease activity scores (DAS) at 3, 9 and 15 months of follow-up.

## Psychosocial factors

Psychosocial factors, measured at baseline, 6 and 12 months of follow-up, included anxiety and depression (hospital anxiety and depression score (HADS)), fatigue (Fatigue Assessment Scale (FAS)) and coping with pain (Coping with Rheumatic Stressors) and are explained in more detail below:

Coping with pain: Coping with pain was measured by the Coping with Rheumatic Stressors (CORS) questionnaire. The list contains 8 questions about coping with pain (Cronbach's alpha 0.88). Scores range from 8-40 (15).

Depression and anxiety: The Hospital Anxiety and Depression Scale (HADS) was used to measure depression and anxiety. The scores for depression and anxiety range between 0 to 21, higher scores indicating symptoms related to more anxiety or depression (16).

Fatigue: Fatigue was assessed using the Fatigue Assessment Scale (FAS). Questions were asked about the fatigue status of the patient. The score ranges from 10 to 50, higher score indicating higher levels of fatigue (17).

## Demographic, disease related and treatment related factors

Age, sex, rheumatoid factor (RF) and anti-citrullinated protein (ACPA) status were assessed at baseline. For this study, initial treatment strategy was included as a binary variable, indicating methotrexate monotherapy with GC bridging (coded 1) versus initial triple DMARD therapy with either oral or intramuscular GC bridging (coded 0). At follow-up visits, medication increase was defined as a dose increase or switch towards other medication. Medication decrease was defined as a dose decrease or discontinuation of medication. Medication increase and decrease included as binary variables also.

## Statistical analyses

*Missing data*

In those patients having an outcome DAS available, missing values in covariates at the previous visit (see Supplemental Table 1) were completed using multiple imputation with chained equations (mi impute chained procedure in STATA). Given that the largest missing rate observed was 42.3% (Supplemental Table 1) , a number of m=50 imputations was chosen, taking into consideration the rule of thumb that the number of imputations

should at least be equal to the percentage of incomplete cases (18). To avoid bias, imputation models were constructed such that all variables used in the analysis models were included in the imputation models (18). Before imputation, continuous variables were transformed to normality using the "nscore" package for STATA by Mark Lunt (19) and transformed back to their original scale afterwards, ensuring imputed values cannot lie outside the observed data range (19). The complete specification of imputation models can be found in Supplement 1.

*Analyses*

Multivariable linear regression analyses were performed for psychosocial factors, measured at baseline, 6 months and 12 months of follow-up, on outcome disease activity score (DAS) at 3, 9 and 15 months of follow-up respectively and correcting for demographic, disease-related and treatment-related factors.

First, DAS was regressed against each individual psychosocial factor, controlling for DAS and medication change at previous visit and baseline factors age, sex, RF and ACPA positivity. Then a full model was build containing all 4 psychosocial factors together and controlling for the same factors. Backward elimination was performed on the full model until remaining psychosocial factors were significant. Statistical analyses were performed using STATA 14.1 (StataCorp, 4905 Lakeway Drive College Station, Texas, USA). P-values <0.05 were considered statistically significant.

## RESULTS

Two-hundred-eighty-one patients were available for analysis, 161 of whom had outcome DAS available at all three visits (completers) Overall, mean age was 53 years, 190 (68%) were female (Table 1). Mean baseline DAS was 3.36 and 95% fulfilled the ACR/EULAR 2010 criteria for RA (6) (Table 1). Completers and non-completers were similar with respect to baseline characteristics, except for a slightly higher percentage of completers being RF-positive and fulfilling the ACR/EULAR 1987 criteria (Table 1).

### Association after 3 months of treatment

Analyses of each psychosocial factor individually, correcting for age, sex, RF, ACPA and baseline DAS, revealed that higher levels anxiety, coping with pain and depression were associated with a higher DAS at 3 months of follow-up. After applying backward elimination on the full model, anxiety and coping with pain were independent predictors for DAS at 3 months of follow-up. In sensitivity analysis by bootstrap samples, anxiety and coping with pain were selected in 65.3% and 56.7% of samples, whereas depression and fatigue were selected in <15% of samples (Table 2).

**Table 1.** Baseline characteristics.

| | All patients (n=281) | Completers (outcome DAS available at 3, 9 and 15 months) (n=161) | Non-completers (outcome DAS missing at 3, 9 or 15 months) (n=120) | P-value[1] |
|---|---|---|---|---|
| *Demographic* | | | | |
| Age | 53 (14) | 53 (14) | 53 (14) | 0.981 |
| Sex, female, n(%) | 190 (68) | 104 (65) | 86 (72) | 0.210 |
| | | | | |
| *Disease-related* | | | | |
| Duration of complaints, days, mean (sd) | 166 (91) | 168 (87) | 164 (97) | 0.662 |
| RF-positive | 228 (81) | 138 (86) | 90 (75) | 0.023 |
| ACPA-positive | 226 (80) | 133 (83) | 93 (78) | 0.286 |
| Fulfilling ACR/EULAR 1987 criteria | 189 (67) | 118 (73) | 71 (59) | 0.013 |
| Fulfilling ACR/EULAR 2010 criteria | 267 (95) | 154 (96) | 113 (94) | 0.571 |
| DAS, mean (sd) | 3.36 (0.96) | 3.39 (0.97) | 3.33 (0.95) | 0.648 |
| HAQ, mean (sd) | 1.00 (0.66) | 0.97 (0.65) | 1.03 (0.67) | 0.496 |
| tSvHs, median (IQR) | 0 (0-0) | 0 (0-0) | 0 (0-0) | 0.266[2] |
| | | | | |
| anxiety (HADS), mean (sd) | 5.8 (3.7) | 5.8 (3.9) | 5.8 (3.5) | 0.861 |
| depression (HADS), mean (sd) | 4.6 (3.4) | 4.5 (3.4) | 4.6 (3.4) | 0.843 |
| fatigue (FAS), mean (sd) | 22.2 (7.0) | 22.6 (7.3) | 22.0 (6.8) | 0.542 |
| coping with pain (CORS), mean (sd) | 15.5 (5.2) | 16.2 (5.2) | 15.0 (5.1) | 0.058 |

[1] Differences between completers and non-completers were tested. Student's t-test and Pearson's Chi-squared test were used as appropriate, unless specified otherwise

[2] Wilcoxon rank-sum test

Abbreviations:

- ACPA: Anti-Citrullinated Protein Antibodies
- ACR: American College of Rheumatology
- CORS: Coping with Rheumatic Stressors
- DAS: Disease Activity Score
- EULAR: European League against Rheumatism
- FAS: Fatigue Assessment Scale
- HADS: Hospital Anxiety and Depression Scale
- HAQ: Health Assessment Questionnaire
- IQR: Interquartile range
- RF: Rheumatoid Factor
- sd: standard deviation
- tSVHS: total Sharp van der Heijde Score

## Association after 9 months of treatment

In the per factor analysis of psychosocial factors, correcting for age, sex, RF, ACPA and DAS at 6 months, coping with pain was associated with DAS at 9 months and fatigue showed a borderline significant association. After backward elimination, coping with pain remained as significant predictor for DAS at 9 months of follow-up. In sensitivity analyses on bootstrap samples, coping with pain was selected in 59.2% of samples and fatigue in 20.4% of samples.

**Table 2.** Multivariable linear regression analysis of psychosocial factors at baseline, 6 and 12 months on DAS at 3, 9 and 15 months respectively. All analyses are corrected for age, sex, RF, ACPA, initial treatment group, medication change at previous visit and DAS at previous visit.

| | Multivariable, per factor | | | Multivariable, full | | | Multivariable, after backward elimination | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **beta** | **P** | **95% CI** | **beta** | **P** | **95% CI** | **beta** | **P** | **95% CI** | **%[1]** |
| *DAS 3 months (n=265)* | | | | | | | | | | |
| Anxiety (T0) | **0.043** | **0.005** | **0.013 – 0.073** | 0.037 | 0.050 | -0.000 – 0.075 | **0.037** | **0.015** | **0.007 – 0.067** | 65.3 |
| Depression (T0) | **0.034** | **0.037** | **0.002 – 0.066** | -0.001 | 0.963 | -0.044 – 0.042 | | | | 11.4 |
| Fatigue (T0) | 0.015 | 0.070 | -0.001 – 0.031 | 0.001 | 0.935 | -0.189 – 0.020 | | | | 7.8 |
| Coping with pain (T0) | **0.028** | **0.012** | **0.006 – 0.051** | 0.024 | 0.051 | -0.000 – 0.048 | **0.024** | **0.036** | **0.002 – 0.046** | 56.7 |
| *DAS 9 months (n=251)* | | | | | | | | | | |
| Anxiety (T6) | 0.017 | 0.217 | -0.010 – 0.044 | 0.004 | 0.822 | -0.034 – 0.043 | | | | 12.3 |
| Depression (T6) | 0.023 | 0.115 | -0.006 – 0.052 | 0.001 | 0.975 | -0.046 – 0.048 | | | | 12.6 |
| Fatigue (T6) | 0.014 | 0.060 | -0.001 – 0.028 | 0.006 | 0.602 | -0.015 – 0.026 | | | | 20.4 |
| Coping with pain (T6) | **0.025** | **0.016** | **0.005 – 0.045** | 0.021 | 0.081 | -0.003 – 0.044 | **0.025** | **0.016** | **0.005 – 0.045** | 59.2 |
| *DAS 15 months (n=162)* | | | | | | | | | | |
| Anxiety (T12) | 0.012 | 0.459 | -0.020 – 0.043 | -0.013 | 0.525 | -0.055 – 0.028 | | | | 11.6 |
| Depression (T12) | 0.028 | 0.095 | -0.005 – 0.060 | 0.011 | 0.669 | -0.040 – 0.062 | | | | 18.2 |
| Fatigue (T12) | **0.019** | **0.020** | **0.003 – 0.035** | 0.017 | 0.179 | -0.008 – 0.041 | **0.019** | **0.020** | **0.003 – 0.035** | 51.5 |
| Coping with pain (T12) | 0.019 | 0.102 | -0.004 – 0.041 | 0.007 | 0.619 | -0.019 – 0.033 | | | | 13.4 |

[1] Selection rate of psychosocial factors after applying backward elimination in bootstrap samples

Abbreviations:

ACPA: Anti-Citrullinated Protein Antibodies

DAS: Disease Activity Score

**Table 3.** Association of psychosocial factors at baseline, 6 and 12 months on DAS components at 3, 9 and 15 months respectively by zero-inflated negative binomial regression or linear regression. All analyses are corrected for age, sex, RF, ACPA, initial treatment group, medication change at previous visit and DAS at previous visit.

| | SJC44[1] | | ln ESR[2] | | RAI[1] | | GH[2] | |
|---|---|---|---|---|---|---|---|---|
| | **beta** | **P** | **beta** | **P** | **beta** | **P** | **beta[2]** | **p** |
| *DAS 3 months (n=252)* | | | | | | | | |
| Anxiety (T0) | 0.006 | 0.723 | -0.005 | 0.752 | 0.033 | 0.031 | 1.728 | <0.001 |
| Depression (T0) | -0.002 | 0.895 | 0.016 | 0.353 | 0.008 | 0.631 | 1.687 | <0.001 |
| Fatigue (T0) | 0.014 | 0.129 | -0.004 | 0.648 | 0.008 | 0.361 | 0.726 | 0.001 |
| Coping with pain (T0) | 0.046 | <0.001 | 0.030 | 0.008 | 0.021 | 0.055 | 0.121 | 0.677 |
| *DAS 9 months (n=214)* | | | | | | | | |
| Anxiety (T6) | 0.004 | 0.859 | -0.014 | 0.469 | 0.012 | 0.508 | 1.689 | <0.001 |
| Depression (T6) | -0.020 | 0.371 | -0.024 | 0.226 | 0.026 | 0.159 | 2.199 | <0.001 |
| Fatigue (T6) | -0.002 | 0.821 | -0.024 | 0.011 | 0.025 | 0.003 | 1.045 | <0.001 |
| Coping with pain (T6) | -0.015 | 0.379 | -0.015 | 0.275 | 0.029 | 0.025 | 0.900 | 0.008 |
| *DAS 15 months (n=141)* | | | | | | | | |
| Anxiety (T12) | 0.008 | 0.817 | -0.010 | 0.636 | 0.020 | 0.458 | 0.499 | 0.334 |
| Depression (T12) | -0.041 | 0.247 | 0.013 | 0.547 | 0.041 | 0.078 | 0.717 | 0.172 |
| Fatigue (T12) | 0.001 | 0.952 | -0.008 | 0.494 | 0.039 | 0.002 | 0.478 | 0.083 |
| Coping with pain (T12) | 0.017 | 0.462 | -0.011 | 0.514 | 0.063 | <0.001 | -0.158 | 0.686 |

[1] Zero-inflated negative binomial regression

[2] Linear regression

Abbreviations:

ACPA: Anti-Citrullinated Protein Antibodies
DAS: Disease Activity Score
ESR: Erythrocyte Sedimentation Rate
GH: Global Health
ln: natural logarithm
RAI: Ritchie Articular Index
RF: Rheumatoid Factor
SJC44: 44 Swollen Joint Count

## Association after 15 months of treatment

Per factor analysis showed that only fatigue was significantly associated with DAS at 15 months when correcting for age, sex, RF, ACPA and DAS at 12 months. This was also the case in the backward elimination model. Sensitivity analyses on bootstrap samples, fatigue was selected in 51.5% of instances, whereas other psychosocial factors were selected in <20% of samples.

### Correlation between psychosocial factors

Pearson correlations between psychosocial factors for each time point are shown (Supplemental Table 2). Especially anxiety, depression and fatigue are highly correlated to each other with correlation coefficients around 50-70%. Coping with pain shows moderate correlations to the other factors with correlation coefficients around 25-50%.

### Course over time of psychosocial factors

To gain further insight, development over time of psychosocial factors was investigated (Supplemental Figure 1). All scores showed significant decreases at 6 and 12 months with respect to baseline scores, except for coping with pain at 6 months.

### Associations between psychosocial factors and DAS components

To evaluate which DAS components are associated with psychosocial factors at the previous visit, linear and zero-inflated negative binomial regression models were performed (Table 3). Most significant associations are observed for the subjective components Ritchie Articular Index (RAI) and Global Health (GH). Some significant associations for objective components are observed as well: Higher levels of baseline coping with pain was associated with both a higher 44 swollen joint count (SJC44) and erythrocyte sedimentation rate (ESR) at 3 months, while higher levels of fatigue at 6 months were associated with lower levels of ESR at 9 months (Table 3).

## DISCUSSION

In this longitudinal study of rheumatoid arthritis patients starting with DMARD therapy, we found that psychosocial factors were independently associated with DAS at the next 3-monthly visit during the first year of follow-up. The psychosocial factors associated with DAS changed over time: Coping with pain and anxiety influenced the disease activity in the first at 3 months, but anxiety did not appear to play a role anymore after 9 months of treatment. In the phase where disease activity is low only fatigue played a role. Although speculative, the change observed might indicate a change in the relative importance of psychosocial factors over the course of disease in newly diagnosed patients with RA. In the first months after diagnose, when disease is still active and optimal treatment effects has not yet been achieved, it is imaginable that anxiety and coping with pain play a more pronounced role, especially by affecting the more subjective components of DAS RAI and GH. Later on, when disease is under control and patients have adapted to living with the disease, fatigue could be more on the foreground. However, it should be noted that the psychosocial factors we investigated are highly correlated, which is in line with previous studies that found that symptoms of anxiety and depression often co-occur in

RA patients (20). Therefore, care should be taken in drawing definite conclusions with respect to the importance of one factor over the other and no definite conclusions of a change in relative importance should be drawn based on the results of this study alone. However, overall, our results do suggest that psychosocial factors in general appear to play an additional role in explaining response to treatment during the entire first year of follow-up.

Several previous studies have investigated the effects of psychosocial factors on DAS at subsequent visits. In a secondary analysis of a clinical trial in early RA, Matcham et al. found that both baseline and persistent symptoms of depression/anxiety symptoms, measured on a combined scale of the EQ5D, were associated with increased DAS28 scores over the first two years of follow-up. This is in part in agreement of our findings, in which we found both baseline anxiety and depression scores to be associated with higher DAS at 3 months of follow-up, but not at later moments (12). Differences may, at least in part, be explained by the use of a different instrument to measure depression/anxiety symptoms and differences in analysis approach (linear mixed model averaging outcome over time) (12).

Previous studies have also looked into which components of the DAS are associated with psychosocial distress. In the COMET trial, significant associations between depression and both subjective (i.e. tender joint count and general health) and objective (i.e. swollen joint count and ESR) components of DAS were observed (10), whereas Matcham et al. only found associations for subjective components of DAS (11, 12). Regarding our own results, most associations are observed for the subjective components (Table 3). In patients with high levels of psychosocial distress, this might lead to overtreatment and higher costs if rheumatologists perform DAS-steered treatment without recognizing that the increased DAS is based on subjective components rather than inflammation. We therefore recommend that rheumatologists be aware of psychosocial distress and its impact on DAS when adjusting therapy.

Several strengths and limitations should be noted. Strong points include the fact that data were used from a prospective randomized clinical trial on early RA patients that were treated to target according to current guidelines (2, 3). Although not powered for this analysis, the sample size appears to be adequate for the scope of this analysis. The number of missing values in predictor variables was small at baseline, but increased at follow-up visits (Supplemental Table 1). To increase power and avoid bias in the analysis, we used multiple imputation to complete missing covariates for those patients having an outcome DAS available at the subsequent visit. Nonetheless, the complete case analysis for patients without missing covariates showed similar results (Supplemental Table 3). Few studies have assessed the additional effect of psychosocial factors on DAS and to our knowledge no previous studies have assessed them at specific time points after baseline.

Several limitations should be mentioned as well. By the multiple imputation procedure, we completed missing covariates for those patients having an outcome DAS available at the subsequent visit. However, this does not take into account potential selection bias by patients completely dropping out from the study over time. Although selective drop-out cannot be ruled out, patients with complete and incomplete follow-up were similar with respect to most baseline characteristics (Table 1).

Data were used from a randomized clinical trial that was not designed for the purpose of these analyses. As the clinical trial setting differs from clinical practice, it cannot be ruled out that by selection bias different effects would have been observed if a similar study were performed in a clinical practice setting. Another potential limitation is the issue of multiple testing. Because of the explorative nature of the study and commonly available solutions like the Bonferroni method tend to be highly conservative, no formal methods were applied to account for this. Although under the null-hypothesis, it is still highly unlikely to obtain 5 out of 12 significant associations (multivariable per factor analysis, Table 2) by chance alone, it cannot be ruled out that some of these were due to chance.

## CONCLUSION

In conclusion, we found that psychosocial factors effect subsequent DAS during the first year of follow-up in patients newly diagnosed with RA. A change in pattern was observed from anxiety and coping with pain being associated with subsequent DAS at baseline towards fatigue being associated with subsequent DAS at 12 months of follow-up. Due to correlation of psychosocial factors and the explorative nature of this study, more research is needed to confirm this pattern.

**Supplement 1.** Multiple Imputation models

t0_das: regress t0_das dur_complaints t0_SHS t3_das Dutch t0_anxiety t0_depression t0_cop_lim t0_cop_pain t0_haq t0_fat_vas t0_fat_fas t0_PCS t0_MCS t6_das t9_das t12_das t6_fat_vas t6_haq t6_fat_fas t12_haq t6_PCS t6_MCS t12_fat_vas t12_fat_fas t6_anxiety t6_depression t12_anxiety t12_depression t6_cop_pain t6_cop_lim t12_PCS t12_MCS t12_cop_lim t12_cop_pain t15_das age sex inital_MTX rf_pos acpa_pos

dur_complaints: regress dur_complaints t0_das t0_SHS t3_das Dutch t0_anxiety t0_depression t0_cop_lim t0_cop_pain t0_haq t0_fat_vas t0_fat_fas t0_PCS t0_MCS t6_das t9_das t12_das t6_fat_vas t6_haq t6_fat_fas t12_haq t6_PCS t6_MCS t12_fat_vas t12_fat_fas t6_anxiety t6_depression t12_anxiety t12_depression t6_cop_pain t6_cop_lim t12_PCS t12_MCS t12_cop_lim t12_cop_pain t15_das age sex inital_MTX rf_pos acpa_pos

t6_med_i: mlogit t6_med_i t0_das dur_complaints t0_SHS t3_das Dutch t0_anxiety t0_depression t0_cop_lim t0_cop_pain t0_haq t0_fat_vas t0_fat_fas t0_PCS t0_MCS t6_das t9_das t12_das t6_fat_vas t6_haq t6_fat_fas t12_haq t6_PCS t6_MCS t12_fat_vas t12_fat_fas t6_anxiety t6_depression t12_anxiety t12_depression t6_cop_pain t6_cop_lim t12_PCS t12_MCS t12_cop_lim t12_cop_pain t15_das age sex inital_MTX rf_pos acpa_pos, augment

t9_med_i: mlogit t9_med_i t0_das dur_complaints t0_SHS t3_das Dutch t0_anxiety t0_depression t0_cop_lim t0_cop_pain t0_haq t0_fat_vas t0_fat_fas t0_PCS t0_MCS t6_das t9_das t12_das t6_fat_vas t6_haq t6_fat_fas t12_haq t6_PCS t6_MCS t12_fat_vas t12_fat_fas t6_anxiety t6_depression t12_anxiety t12_depression t6_cop_pain t6_cop_lim t12_PCS t12_MCS t12_cop_lim t12_cop_pain t15_das age sex inital_MTX rf_pos acpa_pos, augment

t12_med_i: mlogit t12_med_i t0_das dur_complaints t0_SHS t3_das Dutch t0_anxiety t0_depression t0_cop_lim t0_cop_pain t0_haq t0_fat_vas t0_fat_fas t0_PCS t0_MCS t6_das t9_das t12_das t6_fat_vas t6_haq t6_fat_fas t12_haq t6_PCS t6_MCS t12_fat_vas t12_fat_fas t6_anxiety t6_depression t12_anxiety t12_depression t6_cop_pain t6_cop_lim t12_PCS t12_MCS t12_cop_lim t12_cop_pain t15_das age sex inital_MTX rf_pos acpa_pos, augment

t0_SHS: regress t0_SHS t0_das dur_complaints t3_das Dutch t0_anxiety t0_depression t0_cop_lim t0_cop_pain t0_haq t0_fat_vas t0_fat_fas t0_PCS t0_MCS t6_das t9_das t12_das t6_fat_vas t6_haq t6_fat_fas t12_haq t6_PCS t6_MCS t12_fat_vas t12_fat_fas t6_anxiety t6_depression t12_anxiety t12_depression t6_cop_pain t6_cop_lim t12_PCS t12_MCS t12_cop_lim t12_cop_pain t15_das age sex inital_MTX rf_pos acpa_pos

t3_das: regress t3_das t0_das dur_complaints t0_SHS Dutch t0_anxiety t0_depression t0_cop_lim t0_cop_pain t0_haq t0_fat_vas t0_fat_fas t0_PCS t0_MCS t6_das t9_das t12_das t6_fat_vas t6_haq t6_fat_fas t12_haq t6_PCS t6_MCS t12_fat_vas t12_fat_fas t6_anxiety t6_depression t12_anxiety t12_depression t6_cop_pain t6_cop_lim t12_PCS t12_MCS t12_cop_lim t12_cop_pain t15_das age sex inital_MTX rf_pos acpa_pos

Dutch: logit Dutch t0_das dur_complaints t0_SHS t3_das t0_anxiety t0_depression t0_cop_lim t0_cop_pain t0_haq t0_fat_vas t0_fat_fas t0_PCS t0_MCS t6_das t9_das t12_das t6_fat_vas t6_haq t6_fat_fas t12_haq t6_PCS t6_MCS t12_fat_vas t12_fat_fas t6_anxiety t6_depression t12_anxiety t12_depression t6_cop_pain t6_cop_lim t12_PCS t12_MCS t12_cop_lim t12_cop_pain t15_das age sex inital_MTX rf_pos acpa_pos, augment

t0_anxiety: regress t0_anxiety t0_das dur_complaints t0_SHS t3_das Dutch t0_depression t0_cop_lim t0_cop_pain t0_haq t0_fat_vas t0_fat_fas t0_PCS t0_MCS t6_das t9_das t12_das t6_fat_vas t6_haq t6_fat_fas t12_haq t6_PCS t6_MCS t12_fat_vas t12_fat_fas t6_anxiety t6_depression t12_anxiety t12_depression t6_cop_pain t6_cop_lim t12_PCS t12_MCS t12_cop_lim t12_cop_pain t15_das age sex inital_MTX rf_pos acpa_pos

t0_depression: regress t0_depression t0_das dur_complaints t0_SHS t3_das Dutch t0_anxiety t0_cop_lim t0_cop_pain t0_haq t0_fat_vas t0_fat_fas t0_PCS t0_MCS t6_das t9_das t12_das t6_fat_vas t6_haq t6_fat_fas t12_haq t6_PCS t6_MCS t12_fat_vas t12_fat_fas t6_anxiety t6_depression t12_anxiety t12_depression t6_cop_pain t6_cop_lim t12_PCS t12_MCS t12_cop_lim t12_cop_pain t15_das age sex inital_MTX rf_pos acpa_pos

t0_cop_lim: regress t0_cop_lim t0_das dur_complaints t0_SHS t3_das Dutch t0_anxiety t0_depression t0_cop_pain t0_haq t0_fat_vas t0_fat_fas t0_PCS t0_MCS t6_das t9_das t12_das t6_fat_vas t6_haq t6_fat_fas t12_haq t6_PCS t6_MCS t12_fat_vas t12_fat_fas t6_anxiety t6_depression t12_anxiety t12_depression t6_cop_pain t6_cop_lim t12_PCS t12_MCS t12_cop_lim t12_cop_pain t15_das age sex inital_MTX rf_pos acpa_pos

t0_cop_pain: regress t0_cop_pain t0_das dur_complaints t0_SHS t3_das Dutch t0_anxiety t0_depression t0_cop_lim t0_haq t0_fat_vas t0_fat_fas t0_PCS t0_MCS t6_das t9_das t12_das t6_fat_vas t6_haq t6_fat_fas t12_haq t6_PCS t6_MCS t12_fat_vas t12_fat_fas t6_anxiety t6_depression t12_anxiety t12_depression t6_cop_pain t6_cop_lim t12_PCS t12_MCS t12_cop_lim t12_cop_pain t15_das age sex inital_MTX rf_pos acpa_pos

t0_haq: regress t0_haq t0_das dur_complaints t0_SHS t3_das Dutch t0_anxiety t0_depression t0_cop_lim t0_cop_pain t0_fat_vas t0_fat_fas t0_PCS t0_MCS t6_das t9_das t12_das t6_fat_vas t6_haq t6_fat_fas t12_haq t6_PCS t6_MCS t12_fat_vas t12_fat_fas t6_anxiety t6_depression t12_anxiety t12_depression t6_cop_pain t6_cop_lim t12_PCS t12_MCS t12_cop_lim t12_cop_pain t15_das age sex inital_MTX rf_pos acpa_pos

t0_fat_vas: regress t0_fat_vas t0_das dur_complaints t0_SHS t3_das Dutch t0_anxiety t0_depression t0_cop_lim t0_cop_pain t0_haq t0_fat_fas t0_PCS t0_MCS t6_das t9_das t12_das t6_fat_vas t6_haq t6_fat_fas t12_haq t6_PCS t6_MCS t12_fat_vas t12_fat_fas t6_anxiety t6_depression t12_anxiety t12_depression t6_cop_pain t6_cop_lim t12_PCS t12_MCS t12_cop_lim t12_cop_pain t15_das age sex inital_MTX rf_pos acpa_pos

t0_fat_fas: regress t0_fat_fas t0_das dur_complaints t0_SHS t3_das Dutch t0_anxiety t0_depression t0_cop_lim t0_cop_pain t0_haq t0_fat_vas t0_PCS t0_MCS t6_das t9_das t12_das t6_fat_vas t6_haq t6_fat_fas t12_haq t6_PCS t6_MCS t12_fat_vas t12_fat_fas t6_anxiety t6_depression t12_anxiety t12_depression t6_cop_pain t6_cop_lim t12_PCS t12_MCS t12_cop_lim t12_cop_pain t15_das age sex inital_MTX rf_pos acpa_pos

t0_PCS: regress t0_PCS t0_das dur_complaints t0_SHS t3_das Dutch t0_anxiety t0_depression t0_cop_lim t0_cop_pain t0_haq t0_fat_vas t0_fat_fas t0_MCS t6_das t9_das t12_das t6_fat_vas t6_haq t6_fat_fas t12_haq t6_PCS t6_MCS t12_fat_vas t12_fat_fas t6_anxiety t6_depression t12_anxiety t12_depression t6_cop_pain t6_cop_lim t12_PCS t12_MCS t12_cop_lim t12_cop_pain t15_das age sex inital_MTX rf_pos acpa_pos

t0_MCS: regress t0_MCS t0_das dur_complaints t0_SHS t3_das Dutch t0_anxiety t0_depression t0_cop_lim t0_cop_pain t0_haq t0_fat_vas t0_fat_fas t0_PCS t6_das t9_das t12_das t6_fat_vas t6_haq t6_fat_fas t12_haq t6_PCS t6_MCS t12_fat_vas t12_fat_fas t6_anxiety t6_depression t12_anxiety t12_depression t6_cop_pain t6_cop_lim t12_PCS t12_MCS t12_cop_lim t12_cop_pain t15_das age sex inital_MTX rf_pos acpa_pos

t6_das: regress t6_das i.t3_med_i t0_das dur_complaints t0_SHS t3_das Dutch t0_anxiety t0_depression t0_cop_lim t0_cop_pain t0_haq t0_fat_vas t0_fat_fas t0_PCS t0_MCS t9_das t12_das t6_fat_vas t6_haq t6_fat_fas t12_haq t6_PCS t6_MCS t12_fat_vas t12_fat_fas t6_anxiety t6_depression t12_anxiety t12_depression t6_cop_pain t6_cop_lim t12_PCS t12_MCS t12_cop_lim t12_cop_pain t15_das age sex inital_MTX rf_pos acpa_pos

t9_das: regress t9_das t0_das dur_complaints i.t6_med_i t0_SHS t3_das Dutch t0_anxiety t0_depression t0_cop_lim t0_cop_pain t0_haq t0_fat_vas t0_fat_fas t0_PCS t0_MCS t6_das t12_das t6_fat_vas t6_haq t6_fat_fas t12_haq t6_PCS t6_MCS t12_fat_vas t12_fat_fas t6_anxiety t6_depression t12_anxiety t12_depression t6_cop_pain t6_cop_lim t12_PCS t12_MCS t12_cop_lim t12_cop_pain t15_das age sex inital_MTX rf_pos acpa_pos

t12_das: regress t12_das t0_das dur_complaints i.t9_med_i t0_SHS t3_das Dutch t0_anxiety t0_depression t0_cop_lim t0_cop_pain t0_haq t0_fat_vas t0_fat_fas t0_PCS t0_MCS t6_das t9_das t6_fat_vas t6_haq t6_fat_fas t12_haq t6_PCS t6_MCS t12_fat_vas t12_fat_fas t6_anxiety t6_depression t12_anxiety t12_depression t6_cop_pain t6_cop_lim t12_PCS t12_MCS t12_cop_lim t12_cop_pain t15_das age sex inital_MTX rf_pos acpa_pos

t15_med_i: mlogit t15_med_i t0_das dur_complaints t0_SHS t3_das Dutch t0_anxiety t0_depression t0_cop_lim t0_cop_pain t0_haq t0_fat_vas t0_fat_fas t0_PCS t0_MCS t6_das t9_das t12_das t6_fat_vas t6_haq t6_fat_fas t12_haq t6_PCS t6_MCS t12_fat_vas t12_fat_fas t6_anxiety t6_depression t12_anxiety t12_depression t6_cop_pain t6_cop_lim t12_PCS t12_MCS t12_cop_lim t12_cop_pain t15_das age sex inital_MTX rf_pos acpa_pos , augment

t6_fat_vas: regress t6_fat_vas t0_das dur_complaints t0_SHS t3_das Dutch t0_anxiety t0_depression t0_cop_lim t0_cop_pain t0_haq t0_fat_vas t0_fat_fas t0_PCS t0_MCS t6_das t9_das t12_das t6_haq t6_fat_fas t12_haq t6_PCS t6_MCS t12_fat_vas t12_fat_fas t6_anxiety t6_depression t12_anxiety t12_depression t6_cop_pain t6_cop_lim t12_PCS t12_MCS t12_cop_lim t12_cop_pain t15_das age sex inital_MTX rf_pos acpa_pos

t6_haq: regress t6_haq i.t3_med_i t0_das dur_complaints t0_SHS t3_das Dutch t0_anxiety t0_depression t0_cop_lim t0_cop_pain t0_haq t0_fat_vas t0_fat_fas t0_PCS t0_MCS t6_das t9_das t12_das t6_fat_vas t6_fat_fas t12_haq t6_PCS t6_MCS t12_fat_vas t12_fat_fas t6_anxiety t6_depression t12_anxiety t12_depression t6_cop_pain t6_cop_lim t12_PCS t12_MCS t12_cop_lim t12_cop_pain t15_das age sex inital_MTX rf_pos acpa_pos

t6_fat_fas: regress t6_fat_fas t0_das dur_complaints t0_SHS t3_das Dutch t0_anxiety t0_depression t0_cop_lim t0_cop_pain t0_haq t0_fat_vas t0_fat_fas t0_PCS t0_MCS t6_das t9_das t12_das t6_fat_vas t6_haq t12_haq t6_PCS t6_MCS t12_fat_vas t12_fat_fas t6_anxiety t6_depression t12_anxiety t12_depression t6_cop_pain t6_cop_lim t12_PCS t12_MCS t12_cop_lim t12_cop_pain t15_das age sex inital_MTX rf_pos acpa_pos

t12_haq: regress t12_haq t0_das dur_complaints i.t9_med_i t0_SHS t3_das Dutch t0_anxiety t0_depression t0_cop_lim t0_cop_pain t0_haq t0_fat_vas t0_fat_fas t0_PCS t0_MCS t6_das t9_das t12_das t6_fat_vas t6_haq t6_fat_fas t6_

PCS t6_MCS t12_fat_vas t12_fat_fas t6_anxiety t6_depression t12_anxiety t12_depression t6_cop_pain t6_cop_lim t12_PCS t12_MCS t12_cop_lim t12_cop_pain t15_das age sex inital_MTX rf_pos acpa_pos

t6_PCS: regress t6_PCS t0_das dur_complaints t0_SHS t3_das Dutch t0_anxiety t0_depression t0_cop_lim t0_cop_pain t0_haq t0_fat_vas t0_fat_fas t0_PCS t0_MCS t6_das t9_das t12_das t6_fat_vas t6_haq t6_fat_fas t12_haq t6_MCS t12_fat_vas t12_fat_fas t6_anxiety t6_depression t12_anxiety t12_depression t6_cop_pain t6_cop_lim t12_PCS t12_MCS t12_cop_lim t12_cop_pain t15_das age sex inital_MTX rf_pos acpa_pos

t6_MCS: regress t6_MCS t0_das dur_complaints t0_SHS t3_das Dutch t0_anxiety t0_depression t0_cop_lim t0_cop_pain t0_haq t0_fat_vas t0_fat_fas t0_PCS t0_MCS t6_das t9_das t12_das t6_fat_vas t6_haq t6_fat_fas t12_haq t6_PCS t12_fat_vas t12_fat_fas t6_anxiety t6_depression t12_anxiety t12_depression t6_cop_pain t6_cop_lim t12_PCS t12_MCS t12_cop_lim t12_cop_pain t15_das age sex inital_MTX rf_pos acpa_pos

t12_fat_vas: regress t12_fat_vas t0_das dur_complaints t0_SHS t3_das Dutch t0_anxiety t0_depression t0_cop_lim t0_cop_pain t0_haq t0_fat_vas t0_fat_fas t0_PCS t0_MCS t6_das t9_das t12_das t6_fat_vas t6_haq t6_fat_fas t12_haq t6_PCS t6_MCS t12_fat_fas t6_anxiety t6_depression t12_anxiety t12_depression t6_cop_pain t6_cop_lim t12_PCS t12_MCS t12_cop_lim t12_cop_pain t15_das age sex inital_MTX rf_pos acpa_pos

t12_fat_fas: regress t12_fat_fas t0_das dur_complaints t0_SHS t3_das Dutch t0_anxiety t0_depression t0_cop_lim t0_cop_pain t0_haq t0_fat_vas t0_fat_fas t0_PCS t0_MCS t6_das t9_das t12_das t6_fat_vas t6_haq t6_fat_fas t12_haq t6_PCS t6_MCS t12_fat_vas t6_anxiety t6_depression t12_anxiety t12_depression t6_cop_pain t6_cop_lim t12_PCS t12_MCS t12_cop_lim t12_cop_pain t15_das age sex inital_MTX rf_pos acpa_pos

t6_anxiety: regress t6_anxiety t0_das dur_complaints t0_SHS t3_das Dutch t0_anxiety t0_depression t0_cop_lim t0_cop_pain t0_haq t0_fat_vas t0_fat_fas t0_PCS t0_MCS t6_das t9_das t12_das t6_fat_vas t6_haq t6_fat_fas t12_haq t6_PCS t6_MCS t12_fat_vas t12_fat_fas t6_depression t12_anxiety t12_depression t6_cop_pain t6_cop_lim t12_PCS t12_MCS t12_cop_lim t12_cop_pain t15_das age sex inital_MTX rf_pos acpa_pos

t6_depression: regress t6_depression t0_das dur_complaints t0_SHS t3_das Dutch t0_anxiety t0_depression t0_cop_lim t0_cop_pain t0_haq t0_fat_vas t0_fat_fas t0_PCS t0_MCS t6_das t9_das t12_das t6_fat_vas t6_haq t6_fat_fas t12_haq t6_PCS t6_MCS t12_fat_vas t12_fat_fas t6_anxiety t12_anxiety t12_depression t6_cop_pain t6_cop_lim t12_PCS t12_MCS t12_cop_lim t12_cop_pain t15_das age sex inital_MTX rf_pos acpa_pos

t12_anxiety: regress t12_anxiety t0_das dur_complaints t0_SHS t3_das Dutch t0_anxiety t0_depression t0_cop_lim t0_cop_pain t0_haq t0_fat_vas t0_fat_fas t0_PCS t0_MCS t6_das t9_das t12_das t6_fat_vas t6_haq t6_fat_fas t12_haq t6_PCS t6_MCS t12_fat_vas t12_fat_fas t6_anxiety t6_depression t12_depression t6_cop_pain t6_cop_lim t12_PCS t12_MCS t12_cop_lim t12_cop_pain t15_das age sex inital_MTX rf_pos acpa_pos

t12_depression: regress t12_depression t0_das dur_complaints t0_SHS t3_das Dutch t0_anxiety t0_depression t0_cop_lim t0_cop_pain t0_haq t0_fat_vas t0_fat_fas t0_PCS t0_MCS t6_das t9_das t12_das t6_fat_vas t6_haq t6_fat_fas t12_haq t6_PCS t6_MCS t12_fat_vas t12_fat_fas t6_anxiety t6_depression t12_anxiety t6_cop_pain t6_cop_lim t12_PCS t12_MCS t12_cop_lim t12_cop_pain t15_das age sex inital_MTX rf_pos acpa_pos

t6_cop_pain: regress t6_cop_pain t0_das dur_complaints t0_SHS t3_das Dutch t0_anxiety t0_depression t0_cop_lim t0_cop_pain t0_haq t0_fat_vas t0_fat_fas t0_PCS t0_MCS t6_das t9_das t12_das t6_fat_vas t6_haq t6_fat_fas t12_haq t6_PCS t6_MCS t12_fat_vas t12_fat_fas t6_anxiety t6_depression t12_anxiety t12_depression t6_cop_lim t12_PCS t12_MCS t12_cop_lim t12_cop_pain t15_das age sex inital_MTX rf_pos acpa_pos

t6_cop_lim: regress t6_cop_lim t0_das dur_complaints t0_SHS t3_das Dutch t0_anxiety t0_depression t0_cop_lim t0_cop_pain t0_haq t0_fat_vas t0_fat_fas t0_PCS t0_MCS t6_das t9_das t12_das t6_fat_vas t6_haq t6_fat_fas t12_haq t6_PCS t6_MCS t12_fat_vas t12_fat_fas t6_anxiety t6_depression t12_anxiety t12_depression t6_cop_pain t12_PCS t12_MCS t12_cop_lim t12_cop_pain t15_das age sex inital_MTX rf_pos acpa_pos

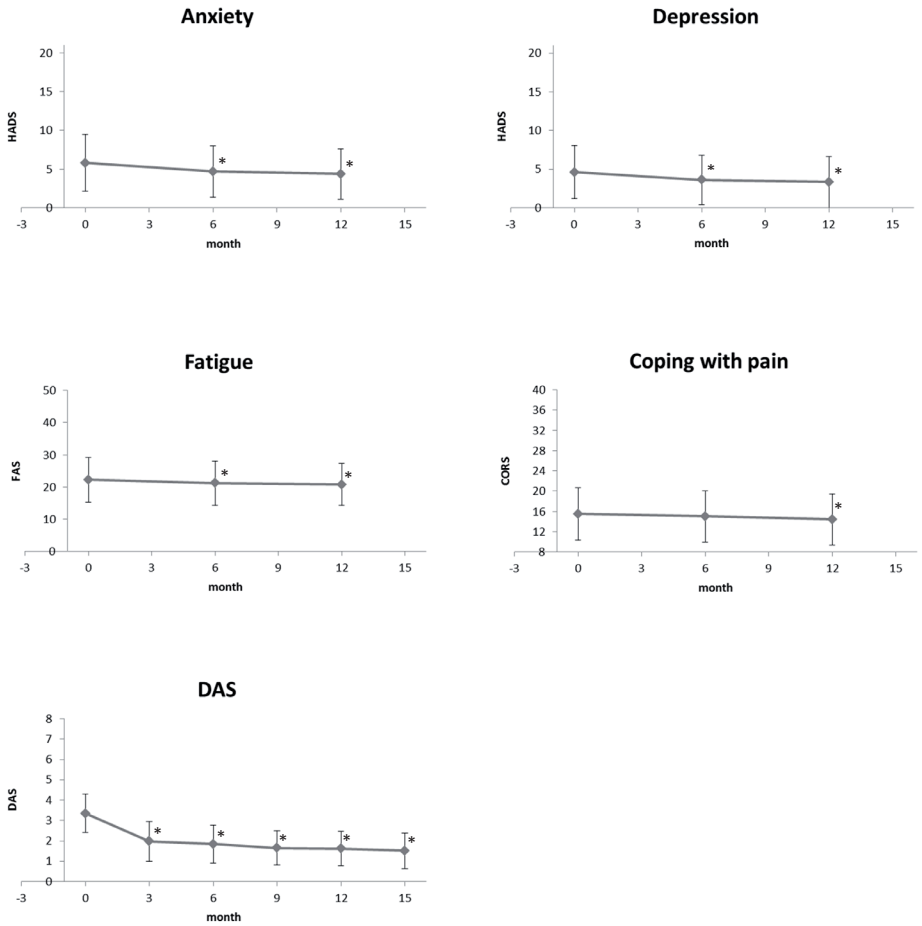
t12_PCS: regress t12_PCS t0_das dur_complaints t0_SHS t3_das Dutch t0_anxiety t0_depression t0_cop_lim t0_cop_pain t0_haq t0_fat_vas t0_fat_fas t0_PCS t0_MCS t6_das t9_das t12_das t6_fat_vas t6_haq t6_fat_fas t12_haq t6_PCS t6_MCS t12_fat_vas t12_fat_fas t6_anxiety t6_depression t12_anxiety t12_depression t6_cop_pain t6_cop_lim t12_MCS t12_cop_lim t12_cop_pain t15_das age sex inital_MTX rf_pos acpa_pos

t12_MCS: regress t12_MCS t0_das dur_complaints t0_SHS t3_das Dutch t0_anxiety t0_depression t0_cop_lim t0_cop_pain t0_haq t0_fat_vas t0_fat_fas t0_PCS t0_MCS t6_das t9_das t12_das t6_fat_vas t6_haq t6_fat_fas t12_haq t6_PCS t6_MCS t12_fat_vas t12_fat_fas t6_anxiety t6_depression t12_anxiety t12_depression t6_cop_pain t6_cop_lim t12_PCS t12_cop_lim t12_cop_pain t15_das age sex inital_MTX rf_pos acpa_pos

t12_cop_lim: regress t12_cop_lim t0_das dur_complaints t0_SHS t3_das Dutch t0_anxiety t0_depression t0_cop_lim t0_cop_pain t0_haq t0_fat_vas t0_fat_fas t0_PCS t0_MCS t6_das t9_das t12_das t6_fat_vas t6_haq t6_fat_fas t12_haq t6_PCS t6_MCS t12_fat_vas t12_fat_fas t6_anxiety t6_depression t12_anxiety t12_depression t6_cop_pain t6_cop_lim t12_PCS t12_MCS t12_cop_pain t15_das age sex inital_MTX rf_pos acpa_pos

t12_cop_pain: regress t12_cop_pain t0_das dur_complaints t0_SHS t3_das Dutch t0_anxiety t0_depression t0_cop_lim t0_cop_pain t0_haq t0_fat_vas t0_fat_fas t0_PCS t0_MCS t6_das t9_das t12_das t6_fat_vas t6_haq t6_fat_fas t12_haq t6_PCS t6_MCS t12_fat_vas t12_fat_fas t6_anxiety t6_depression t12_anxiety t12_depression t6_cop_pain t6_cop_lim t12_PCS t12_MCS t12_cop_lim t15_das age sex inital_MTX rf_pos acpa_pos

t15_das: regress t15_das t0_das dur_complaints i.t12_med_i t0_SHS t3_das Dutch t0_anxiety t0_depression t0_cop_lim t0_cop_pain t0_haq t0_fat_vas t0_fat_fas t0_PCS t0_MCS t6_das t9_das t12_das t6_fat_vas t6_haq t6_fat_fas t12_haq t6_PCS t6_MCS t12_fat_vas t12_fat_fas t6_anxiety t6_depression t12_anxiety t12_depression t6_cop_pain t6_cop_lim t12_PCS t12_MCS t12_cop_lim t12_cop_pain age sex inital_MTX rf_pos acpa_pos




**Supplemental Figure 1.** Mean levels of anxiety, depression, fatigue, coping with pain over time. Error bars indicate standard deviations. Psychosocial factors are plotted at the range of their respective scales.

**Supplemental Table 1.** Missing values.

| | DAS 3 months n=265/281 (94.3%) | DAS 9 months n=251/281 (89.3%) | DAS 15 months n=162/281 (57.7%) |
|---|---|---|---|
| age | 281/281 (100%) | 281/281 (100%) | 281/281 (100%) |
| sex | 281/281 (100%) | 281/281 (100%) | 281/281 (100%) |
| RF | 281/281 (100%) | 281/281 (100%) | 281/281 (100%) |
| ACPA | 281/281 (100%) | 281/281 (100%) | 281/281 (100%) |
| initial treatment | 281/281 (100%) | 281/281 (100%) | 281/281 (100%) |
| medication change | - | 279/281 (99.3%) | 274/281 (97.5%) |
| anxiety | 263/281 (93.6%) | 221/281 (78.6%) | 220/281 (78.3%) |
| depression | 263/281 (93.6%) | 221/281 (78.6%) | 220/281 (78.3%) |
| fatigue | 256/281 (91.1%) | 234/281 (83.3%) | 226/281 (80.4%) |
| coping | 262/281 (93.2%) | 217/281 (77.2%) | 215/281 (76.5%) |

Abbreviations:
ACPA: Anti-Citrullinated Protein Antibodies
DAS: Disease Activity Score
RF: Rheumatoid Factor

**Supplemental Table 2.** Pearson correlation coefficients of psychosocical factors at baseline, 6 months and 12 months of follow-up.

| **Baseline** | *Anxiety* | *Depression* | *Fatigue* | *Coping with pain* |
|---|---|---|---|---|
| *Anxiety* | - | 0.61 | 0.51 | 0.25 |
| *Depression* | 0.61 | - | 0.54 | 0.39 |
| *Fatigue* | 0.51 | 0.54 | - | 0.40 |
| *Coping with pain* | 0.25 | 0.39 | 0.40 | - |

| **6 months** | *Anxiety* | *Depression* | *Fatigue* | *Coping with pain* |
|---|---|---|---|---|
| *Anxiety* | - | 0.69 | 0.59 | 0.32 |
| *Depression* | 0.69 | - | 0.72 | 0.47 |
| *Fatigue* | 0.59 | 0.72 | - | 0.52 |
| *Coping with pain* | 0.32 | 0.47 | 0.52 | - |

| **12 months** | *Anxiety* | *Depression* | *Fatigue* | *Coping with pain* |
|---|---|---|---|---|
| *Anxiety* | - | 0.71 | 0.58 | 0.26 |
| *Depression* | 0.71 | - | 0.69 | 0.32 |
| *Fatigue* | 0.58 | 0.69 | - | 0.46 |
| *Coping with pain* | 0.26 | 0.32 | 0.46 | - |

**Supplemental Table 3.** Multivariable linear regression analysis of psychosocial factors at baseline, 6 and 12 months on DAS at 3, 9 and 15 months respectively. All analyses are corrected for age, sex, RF, ACPA, initial treatment group, medication change at previous visit and DAS at previous visit – complete case analysis.

| | Multivariable, per factor | | Multivariable, full | | Multivariable, after backward elimination | |
|---|---|---|---|---|---|---|
| | **beta** | **P** | **beta** | **P** | **beta** | **P** |
| *DAS 3 months (n=242)* | | | | | | |
| Anxiety (T0) | **0.041** | **0.010** | **0.045** | **0.025** | **0.041** | **0.010** |
| Depression (T0) | **0.036** | **0.035** | -0.004 | 0.848 | | |
| Fatigue (T0) | 0.013 | 0.132 | -0.003 | 0.763 | | |
| Coping with pain (T0) | **0.027** | **0.019** | 0.023 | 0.063 | | |
| *DAS 9 months (n=204)* | | | | | | |
| Anxiety (T6) | 0.027 | 0.062 | 0.019 | 0.367 | | |
| Depression (T6) | **0.032** | **0.040** | 0.003 | 0.919 | | |
| Fatigue (T6) | 0.012 | 0.100 | 0.003 | 0.817 | | |
| Coping with pain (T6) | **0.023** | **0.032** | 0.017 | 0.145 | **0.023** | **0.032** |
| *DAS 15 months (n=146)* | | | | | | |
| Anxiety (T12) | 0.011 | 0.489 | -0.009 | 0.681 | | |
| Depression (T12) | 0.027 | 0.104 | 0.011 | 0.689 | | |
| Fatigue (T12) | **0.020** | **0.022** | 0.016 | 0.228 | **0.020** | **0.022** |
| Coping with pain (T12) | 0.018 | 0.137 | 0.006 | 0.653 | | |

[1] Selection rate of psychosocial factors after applying backward elimination in bootstrap samples

Abbreviations:

ACPA: Anti-Citrullinated Protein Antibodies

DAS: Disease Activity Score

**Supplemental Table 4.** Analysis of multicollinearity: Variance inflation factors for each covariate in the full models, as presented in Table 2.

| | Multivariable, full | | | |
|---|---|---|---|---|
| | **beta** | **P** | **95% CI** | **VIF** |
| *DAS 3 months (n=265)* | | | | |
| Anxiety (T0) | 0.037 | 0.050 | -0.000 – 0.075 | 1.75 |
| Depression (T0) | -0.001 | 0.963 | -0.044 – 0.042 | 1.99 |
| Fatigue (T0) | 0.001 | 0.935 | -0.189 – 0.020 | 1.70 |
| Coping with pain (T0) | 0.024 | 0.051 | -0.000 – 0.048 | 1.41 |
| *DAS 9 months (n=251)* | | | | |
| Anxiety (T6) | 0.004 | 0.822 | -0.034 – 0.043 | 2.04 |
| Depression (T6) | 0.001 | 0.975 | -0.046 – 0.048 | 2.98 |
| Fatigue (T6) | 0.006 | 0.602 | -0.015 – 0.026 | 2.54 |
| Coping with pain (T6) | 0.021 | 0.081 | -0.003 – 0.044 | 1.62 |
| *DAS 15 months (n=162)* | | | | |
| Anxiety (T12) | -0.013 | 0.525 | -0.055 – 0.028 | 2.04 |
| Depression (T12) | 0.011 | 0.669 | -0.040 – 0.062 | 2.53 |
| Fatigue (T12) | 0.017 | 0.179 | -0.008 – 0.041 | 2.45 |
| Coping with pain (T12) | 0.007 | 0.619 | -0.019 – 0.033 | 1.46 |

Abbreviations:
ACPA: Anti-Citrullinated Protein Antibodies
DAS: Disease Activity Score

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# Chapter 4

## Fatigue in early, intensively treated and tight controlled RA patients is frequent, fluctuating and multi-dimensional.

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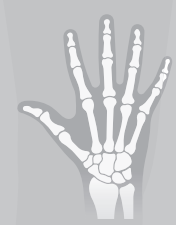


## ABSTRACT

### Objective

Fatigue has a large impact on quality of life, and it is still unmanageable in many patients. The study aims were to i) describe the prevalence and pattern of fatigue over time in patients with early RA ii) identify predictive factors for worsening and recovering of fatigue over time.

### Methods

Data on disease activity from the tREACH study were used. Patients completed patient reported outcomes on fatigue, quality of life and coping and were clinically assessed every 3 months. Descriptive techniques were used to describe fatigue and its associations with covariates. We assessed the evolution of fatigue over time in relation to the covariates using logistic regression.

### Results

Almost half of all patients had high fatigue levels at baseline which decreased slightly over time from 45% at baseline to 43% after 1 year. However, at individual level patients showed fluctuating patterns after 1 year of follow-up. Of the initial fatigue patients, 23% showed a lower level of fatigue whereas in 15% of the low fatigued patients the fatigue level increased. Univariable analyses revealed tender joints, VAS global, DAS score, anxiety and depression and the Mental Component summary of the SF-36 to be associated with developing fatigue, of which depression and coping remained in the multivariable analyses.

### Conclusion

Despite strict treat-to-target strategy, fatigue remained an overall problem during the first year of treatment, however this fluctuated for the individual patient. Signaling signs of depression and coping may be important in managing fatigue.

## INTRODUCTION

Fatigue is known to be a common symptom in patients suffering from rheumatoid arthritis (RA) (1, 2). Whether it is directly related to the disease itself, as a consequence of the disease or its treatment, a pre-existing feature unrelated to the disease or a combination is unknown. Despite its unclear mechanism, fatigue affects the lives of 40-80% of the RA patients depending on what fatigue instrument is used (1, 3, 4). Fatigue had a high impact on patient by influencing the social environment; the impact of fatigue permeates through every aspect of their lives limiting work participation (5), family activities or social activities (6), sports and simply enjoying life as it is. Furthermore, the nature of fatigue, its variable and unpredictable nature requests unplanned anticipation which is for part of the patients difficult to (self-) manage (7).

Factors that might interact with fatigue in early rheumatoid arthritis suggest a possible role for disease related factors like disease activity (pain, functional ability and sleep), cognitive behavioral factors such as mental health and general health and personal factors like age, gender (8-12). Evolvement of fatigue over time on individual level is less well studied in both early and established RA. An 8 year study from the Netherlands suggested little change of fatigue levels over time on group level, while individual levels fluctuated over time (11). In contrast, a study in early RA revealed an improvement in fatigue for 40% of the patients, while another 24% worsened in their fatigue levels (9). Both these studies has been performed in cohort studies where treatment was not protocolled and therefore could have biased the results. Therefore, the objective of the present study was i) to describe the prevalence and pattern of the fatigue over time in patients with early RA under a treat-to-target strategy ii) identify predictive factors for worsening and recovering of fatigue over time.

## METHODS

### Study participants

Patients fulfilling the ACR-EULAR 2010 criteria for RA participating in the tREACH study (treatment in the Rotterdam Early Arthritis Cohort, 2007-2013) were used for this analysis. This multi-centered trial compared different initial treatment strategies in early RA patients. Inclusion criteria for the tREACH were: age ≥18 years, arthritis in one or more joint(s) and symptom duration <1 year. Patients were recruited from the outpatient clinics of all participating centres between July 2007 and April 2011. Initial treatment arms consisted of either: I methotrexate, sulphasalazine, HCQ +GCs intramuscularly; II methotrexate, sulphasalazine (SASP), hydroxychloroquine HCQ+ oral GC tapering scheme; III MTX+ oral GC. Treatment was escalated to biologicals if DAS44 >2.4. Details can be found

in Claessen et al. (13). Medical ethics committees at each participating center approved the study protocol and all patients gave written informed consent before inclusion.

## Data collection

Demographic, clinical characteristics and frequency of erosions of each patient were recorded at baseline. Disease activity measures and its correlated treatment strategy took place every three months. Fatigue, coping strategies used to deal with pain and physical limitations, health related quality of life, symptoms of anxiety and depression were assessed every 6 months.

*Clinical evaluation of disease activity*

The disease activity was assessed by the DAS score, which may range from 0 to10 and is a composite score containing swollen joints, tender joints, VAS global and ESR, where a higher score indicates a higher disease activity (14).

*Fatigue*

Levels of fatigue were measured by Visual Analogue Scale (VAS) and the Fatigue Assessment Scale (FAS). The VAS (100 mm) fatigue involves the severity of the fatigue over the past week with the anchors: no fatigue (0 mm) and extremely fatigued (100 mm). The scale is sensitive to change, valid and reliable, but no cut point has been determined (15, 16). Fatigue Assessment Scale (FAS) is a 10-item fatigue scale with a good internal consistency reliability and validity (17, 18). Five questions reflect physical fatigue and five questions reflect mental fatigue. The instruction is directed at how a person usually feels. Each item is scored on a 5-point rating scale ranging from 1 'never' to 5 'always'. Scores on the FAS range from 10 to 50 and can be divided into 10-21 low fatigue; ≥ 22-34 tired, ≥ 35-50 extremely fatigued as suggested by the developers (19, 20).

*Patient reported outcome measures*

*Disease-related*

The RADAI (Rheumatoid Arthritis Disease Activity Index) measures self-reported disease activity (21). It contains 5 items, global disease activity during the last month, today's disease activity in terms of swollen and tender joints, today's amount of arthritis pain and stiffness and self-assessed tender joints. It uses a scale ranging from 0 to 10, where higher scores indicate more disease activity (22).

*General health*

The health related quality of life (HRQOL) was scored with the SF-36 (range score 0-100). A higher score indicates a better HRQOL. It assesses eight health concepts: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due

to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions which are summarized in a physical component summary (PCS) and mental component summary (MCS) score (23).

*Psychosocial*

Coping was measured via the Coping with Rheumatoid Stressors (CORS) scale. The subscales dealing with pain, decreasing activities (range 8-32) and limitations (range10-40) were included in tREACH. A higher sum score indicates more frequent use of the coping strategy. Both scales have good internal consistency and high test-retest reliability (24, 25).

Depression and anxiety were measured by the HADS. Two subscales with each 7 items are calculated with higher scores indicating more severe symptoms of anxiety or depression (26). Categorical scores are available. Scores between 0 and 7 represent 'no case'; 8 to 10 indicate 'possible case' and 11 to 21 suggest a 'probable case of anxiety or depression' (26, 27).



## Statistical analysis

Simple descriptive techniques were used to describe fatigue and its associations with other covariates at baseline. Fatigue evolution over time was plotted. Mean and SD or percentages were described, as appropriate.

As longitudinal fatigue evolvement was diverse we stratified the analysis into two clinically relevant patient samples: Those with low fatigue (FAS values 10-21) and those fatigued (FAS values 22-50) at baseline. This stratification allows for practical advice for rheumatologist on what to expect of the evolution of fatigue. The cut off value of 21 was chosen as recommended by the developers of the FAS questionnaire (18, 19). Logistic regression was used for the description of the differences between high and low fatigue at baseline on demographics, disease related variables and psychosocial variables. To investigate variables that are important for change of fatigue over time logistic regression analyses predicting fatigue status at 12 months by baseline covariates were performed for each stratum. First, univariable analyses were performed. Thereafter, starting with full models, backward elimination was performed until all remaining variables reached a significance level of $p<0.10$. Age and gender were forced into the models regardless of their levels of significance. Missing values were imputed by multiple imputation with chained equations using m=100 imputation datasets. P-values <0.05 were considered statistically significant.

## RESULTS

A total of 270 individuals, of whom 220 patients had complete data of all variables were available at baseline, 178 at 6 months and 176 patients after 12 months of follow-up. The excluded 50 patients were older (p=0.02) and worked less often (p=0.02) but did not differ with respect to DAS score, the presence of erosions or in which treatment arm they were randomized (data not shown). The early RA population had a mean age of 53 years (SD 14.3 years) and 67% were females (see Table 1). The presence of rheumatoid factor and anti-CCP antibodies at baseline were 73% and 77% respectively. Erosions were present in 18% of patients (Table 1).

**Table 1.** Baseline characteristics, total and high fatigue and low fatigue, mean (SD).

| | **All patients (n=246)** | **Fatigued patients (n=113; FAS >21)** | **Low fatigued patients (n=133; FAS ≤ 21)** | **P-value** |
|---|---|---|---|---|
| Age, in years* | 53.3 (14.30) | 51.3 (14.09) | 55.0 (14.3) | 0.04 |
| Sex, female, (%) | 68% | 75% | 62% | 0.03 |
| Working status (%) | 55% | 52% | 60% | 0.21 |
| Native, Dutch (%) | 83% | 81% | 85% | 0.35 |
| Symptom duration(days) median, IQR | 147.5 (91-213) | 149 (92-236) | 145.5 (88-198) | 0.16 |
| RF pos, % | 73% | 76% | 69% | 0.01 |
| Anti CCP, % | 77% | 76% | 80% | 0.12 |
| Das28 (range 0-10) | 4.8 (1.2) | 5.1 (1.2) | 4.6 (1.2) | 0.001 |
| Tender joints (range 0-44) | 11 (7.9) | 13 (8.6) | 9 (7.0) | 0.002 |
| Swollen joints (range 0-44) | 9 (6.5) | 10 (7.5) | 8 (5.3) | 0.02 |
| ESR(median, IQR) | 29 (21.0) | 30 (21.7) | 30 (20.4) | 0.93 |
| VAS global (range 0-100) | 52 (22) | 60 (19) | 46 (23) | <0.001 |
| VAS fatigue (range 0-100) | 51 (26) | 67 (18) | 38 (24) | <0.001 |
| FAS (range 10-50) | 22 (7) | 28 (5) | 17 (3) | <0.001 |
| RADAI (range 0-10) | 4.0 (1.7) | 4.6 (1.7) | 3.6 (1.6) | <0.001 |
| Coping with pain (range 8–32) | 15.5 (5.2) | 17.4 (5.1) | 13.9 (4.7) | <0.001 |
| Coping with limitations (range 8–40) | 22.9 (7.4) | 24.9 (7.3) | 21.3 (7.0) | <0.001 |
| HADS anxiety (range 0–21) | 5.6 (3.7) | 7.3 (3.5) | 4.6 (3.3) | <0.001 |
| HADS depression (range 0–21) | 4.6 (3.5) | 6.2 (3.5) | 3.2 (2.8) | <0.001 |
| Possible case depression (HADS-D≥ 8, n / %) | 49 (19.9%) | 37 (32.7%) | 12 (9%) | <0.001 |
| SF-36 PCS (range 0-100) | 39.98 (6.52) | 37.81 (6.62) | 41.90 (5.80) | <0.001 |
| SF-36 MCS (range 0-100) | 45.42 (6.78) | 43.08 (6.82) | 47.51 (6.04) | <0.001 |
| SF-36 vitality (range 0-100) | 54.86 (20.19) | 40.97 (13.82) | 66.93 (16.84) | <0.001 |

P-value presented for parametric or non-parametric test as appropriate

At baseline the mean score of the fatigue was VAS (0-100): 51 (sd 26) and FAS (10-50): 22 (sd 7) and 45% of the patients were categorized as fatigued (FAS > 21).

Table 1 summarizes the baseline results for the two strata of fatigue; 113 fatigued and the 133 low fatigued patients. Younger females were most fatigued. The two groups differed in disease related and every patient reported outcomes (PROs) (Table 1). A significant trend was observed for the different categories of the HADS depression; in the fatigued patients 32% reached the clinical relevant levels for possible case for depressions (Table 1).



## Evolution of fatigue

Over time, on average FAS fatigue decreased slightly for all patients with 1.4 points, with 3.8 points for the fatigued patients and with 0.8 points increase for the low fatigued patients (Figure 1a, 1b). After 12 months 43% of all patients were still fatigued. Individual patient profiles showed varying patterns.

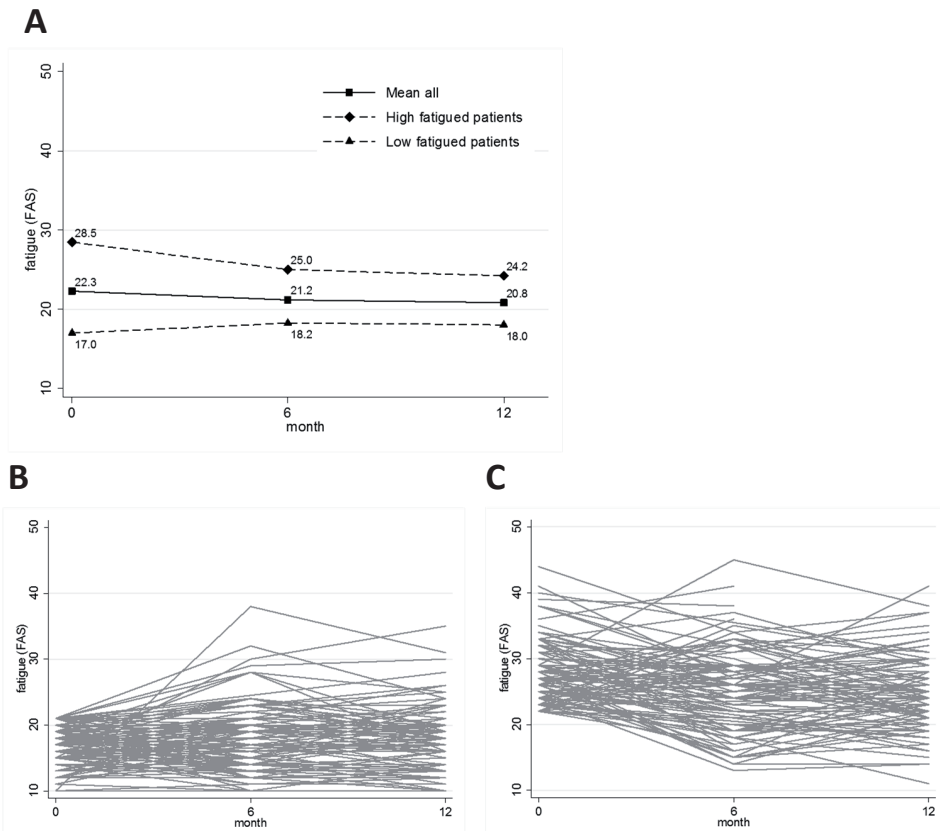


**Figure 1.** Evolution of fatigue over time: Average for all, high fatigued and low fatigued patients (panel A) and individual profile plots for initially low fatigued (panel B) and high fatigued (panel C) patients.

Of all fatigued patients (n=113) at baseline only 23% decreased to below the level of low fatigue and 15% of the low fatigued patients (n=133) became fatigued.

## Factors associated with the strata of fatigue at 12 months

*Low fatigued patients*

In the univariable analysis significant higher levels of fatigue over time were found for more tender joints, higher VAS global, higher DAS score, HADS anxiety and depression, Mental Component summary of the SF-36 (Table 2). In the multivariable analysis the HADS depression and limitation in coping were associated with developing fatigue over time.

*High fatigued patients*

No associated factors were found for the recovering of fatigue in the univariate analysis. Only a role for not having a Dutch nationality lead to a decrease of fatigue in the multivariable analysis (Table 2).

**Table 2.** Univariable and multivariable analysis for developing fatigue after 12 month for low fatigued and fatigued patients.

| | Univariable Odds ratio (CI95%) | | Multivariable Odds ratio (CI95%) | |
|---|---|---|---|---|
| | **Fatigue (≤21)** | **FAS (>21)** | **Fatigue (≤21)** | **FAS (>21)** |
| Sex, female | 2.60 (0.83-8.09) | 1.28 (0.48-3.40) | 3.01 (0.84-10.73) | 1.83 (0.65-5.01) |
| Age, per year | 0.98 (.095-1.02) | 1.00 (0.97-1.04) | 0.97 (0.93-1.01) | 1.00 (0.97-1.04) |
| Education | 1.01 (-0.03-2.07) | -0.03 (-1.08-1.01) | | |
| Working status (Y/N) | 1.89 (0.67-5.30) | 1.28 (0.53-3.06) | | |
| Nationality Natively/Dutch | 1.33 (0.29-6.01) | 2.98 (0.89-9.95) | 7.45 (0.74-74.83) | 3.43 (0.99-11.82)* |
| DAS | 1.96 (1.07-3.59) * | 1.45 (0.93-2.25) | | |
| ESR | 1.007 (0.98-1.02) | 1.00 (0.98-1.02) | | |
| Tender joints (0-44) | 1.12 (1.01-1.23)** | 1.03 (0.96-1.10) | | |
| Swollen joints (0-44) | 1.03 (0.95-1.12) | 1.02 (0.96-1.08) | | |
| VAS global (0-100) | 1.02 (1.00-1.05)** | 1.01 (0.99-1.04) | | |
| Radai (0-10) | 1.19 (0.88-1.61) | 0.97 (0.75-1.25) | | |
| Hads depression (0-21) | 1.20 (1.03-1.40)** | 1.04 ( 0.91-1.19) | 1.33 (1.08-1.62)** | |
| Hads anxiety (0-21) | 1.15 (1.01-1.32)* | 0.98 (0.86-1.12) | | |
| Coping limitations (8-40) | 1.06 (0.99-1.14) | 0.98 (0.92-1.04) | 1.09 (1.00-1.18)* | |
| Coping pain (8-32) | 1.08 (0.98-1.19) | 0.96 (0.87-1.05) | | |
| Physical health (SF36, 0-100) | 0.94 (0.86-1.02) | 1.00 (0.94-1.07) | | |
| Mental health (SF 36, 0-100) | 0.87 (0.80-0.96)** | 0.98 (0.92-1.05) | | |

Level of significance *p=0.05/**p=0.01/***p=0.001 Cut point for FAS≤21 low fatigue/>21 fatigued
Multivariable analysis corrected for sex and age

## DISCUSSION

In this RCT where patient were treated by an early, intensive and tight controlled strategy, almost half of the early rheumatoid arthritis patients were fatigue over the first year after diagnosis. At group level fatigue only decreased slightly, while at the individual level fatigue fluctuated. In the low fatigue group 15% of the patients converted to fatigued, while in the fatigued group most of the patients (77%) remained fatigued despite improvement in disease activity. Literature on the course of fatigue in early RA has been conflicting. Some cohort studies in early RA observe recovery of fatigue over time (9). This was more often observed in studies evaluating biological treatment with patients having much longer RA (28, 29). But other cohort studies showed persistent fatigue over time with almost no change since diagnosis (11). Moreover, a recent meta-analysis found that, although statistically significant, treatment with biologicals only lead to a small improvement in levels fatigue (30). Since our RCT that was performed in early RA with induction of conventional DMARDs, it is interesting to see that a similar pattern was observed, where levels of fatigue decreased with 6%. This might indicate that fatigue stays an important burden of the disease irrespective of disease duration or therapy.

In line with other studies, our analysis showed an association between fatigue and depression. At baseline fatigued patients reported significant higher levels of depressive symptoms which almost reached levels indicative for clinical depression (26, 27). In addition, depression was also an independent predictor for developing fatigue after 1 year of diagnoses. This bidirectional relationship, thus is depression induced by fatigue or fatigue induced by depression, is under debate, both directions seemed to be possible (9,31). A dynamic conceptual model of RA fatigue showed the bi-directional relation for depression and fatigue (31). Irrespectively of the direction, we feel that the high levels of depression at baseline warrant monitoring over time and further examination by a psychologist if symptoms persist.

Another factor associated in the model with the evolution of fatigue was coping with limitations. Results from RA studies suggest that some coping strategies may be useful for patients to better manage the disease, while other are not (32). Maladaptive coping appears to be a risk factor for psychological comorbidity (33). Lower levels of active coping strategies were related to higher levels of depression (33). Thus, it might be that both coping and depression act upon fatigue. Whether they have the same affect or additional upon each other is not clear.

Several aspects of this study need further discussion. The Fatigue Assessment Scale and the VAS fatigue were both included to measure fatigue. This choice was made in 2003 with not much specific RA fatigue instruments available. The Fatigue Assessment Scale (FAS) has a good internal consistency reliability and validity (19, 20). Although the

VAS fatigue was also included, the lack of a standardized VAS cut point for high and low fatigue prohibited a clear message about the VAS fatigue scores.

We were able to analyse a substantial number of covariates influencing fatigue, but some were not available such as sleep quality or the presence of symptoms of fibromyalgia. Strength of this study include its longitudinal design and control for medication and tight-controlled treatment due to the trial design. This allowed us to study the longitudinal evolvement of fatigue and the development of fatigue among those patients with initial low fatigue levels at baseline and recovery of fatigue among those with initial high levels of fatigue, where medication had no effect on the decrease of fatigue in both groups (data not shown).

Given the observed fatigue levels in this early RA RCT and other cohorts, it may be valid to quantify fatigue, depression and coping in daily care. Early identification and intervention may prevent acute fatigue from becoming chronic, but also development of fatigue over time. The results suggest that fatigue does not devolve by itself. Although there are no intervention studies published we suggest that this may be achieved by interventions such as teaching specific coping strategies and identification and follow-up of depression at baseline. Furthermore, it is important to provide patients with knowledge and insight in the course of symptoms of the disease. This may result in more self-management behaviour. Screening on fatigue at baseline and follow up and taking a positive approach to the (self-) management of fatigue may lead to benefits for the patient, feeling their fatigue is acknowledged, and may also improve patient satisfaction and treatment outcomes.

## CONCLUSION

Irrespective of a strict treat to target strategy in patients with early RA, fatigue remains a problem for many patients. A part of the low fatigue patients developed fatigue later, while only a few fatigued patients improved. Higher levels depression and coping were associated with developing fatigue in initially low fatigued patients. Monitoring fatigue and depression at baseline and follow-up might be important to intervene in amenable factors.

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# Chapter 5

## Psychosocial factors are important predictors for meeting criteria of DAS remission in early RA: Results from the tREACH trial

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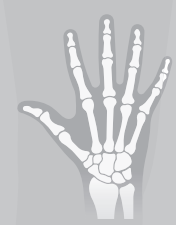


## ABSTRACT

### Objectives

Early disease control leads to better long term outcomes in RA. Identifying factors responsible for an adequate treatment response might pave the way to a more personalized treatment of RA patients. Aim was to identify predictors of early remission on DMARD induction therapy.

### Methods

Nine months follow-up data were used from patients included in tREACH; an RCT comparing initial triple DMARD therapy (iTDT) to methotrexate monotherapy (iMM) with GC bridging in both groups. Patients were treated in a treat-to-target fashion. Early remission was defined as DAS<1.6 at 6 months of follow-up and sustained remission as DAS<1.6 at 6 and 9 months. Demographic, disease-related and psychosocial factors were considered as candidate predictors, analysed by univariable and multivariable logistic regression.

### Results

Data from 281 patients were available. At 6 months 135/281 (48%) patients were in DAS remission. Younger age, male sex, lower baseline DAS, HAQ and lower levels of psychosocial factors anxiety, depression and fatigue were associated with remission within 6 months. Of these, age, sex, baseline DAS and anxiety were identified as independent predictors. Sustained remission at 9 months was independently predicted by age, sex, ACPA-negativity and fatigue.

### Conclusions

In addition to the known demographic (age, sex) and disease related factors (DAS, HAQ), also psychosocial factors (anxiety, depression and fatigue) were identified as predictors for attaining early remission. Results may pave the way for personalized medicine by identifying patients who may benefit from interventions on psychosocial items.

## INTRODUCTION

Current guidelines for the treatment of rheumatoid arthritis recommend treatment should be steered towards remission, or at least low disease activity (LDA), within 6 months using a treat-to-target strategy (1, 2). Adherence to this treat-to-target concept has been shown to lead to lower radiographic damage and better functional outcomes (3). Previous studies like tREACH showed that treatment goals were achieved more quickly and with fewer biological use in patients with initial triple disease modifying anti-rheumatic drug (DMARD) therapy versus methotrexate alone (4). On the other hand, 40% of patients in the initial methotrexate group were in remission within 6 months. Similar findings have been reported in studies comparing induction with methotrexate alone to expensive biologicals (5).



Hence, identification of factors responsible for an adequate response to treatment might pave the way to a more personalized treatment of RA patients. Although several studies have been performed to identify predictors for remission in early RA (6-8), most have focused on disease-related, treatment and / or genetic factors. Associations between psychosocial factors such as anxiety and depression and remission beyond the first year of treatment have been reported as well (9, 10). We therefore hypothesize that psychosocial characteristics may be of predictive value for attaining early remission as well. The primary aim of this study was to identify predictors associated with achieving remission (DAS<1.6) within 6 months of follow-up. To evaluate which patients remained in remission, secondary aim was to identify predictors associated with sustained remission (2xDAS<1.6 at 2 consecutive visits) at 9 months of follow-up.

## METHODS

### Study population

Nine months follow-up data were used from the tREACH cohort, for which a detailed description of the inclusion criteria and protocol can be found in the original tREACH paper (4). In short, patients with early arthritis (duration of complaints < 1 year) and a high risk of developing persistent arthritis (score >6 points on Visser model (11)) were eligible. Of the included patients, 97% fulfilled the ACR/EULAR 2010 criteria for RA (4, 12). Patients were randomized to the following induction treatment strategies: Triple DMARD therapy (iTDT; methotrexate (MTX) 25 mg/week, sulphasalazine 2000 mg/day and hydroxychloroquine 400 mg/day or MTX monotherapy 25 mg/week (iMM). Both groups received bridging therapy with glucocorticoids (triamcinolone acetonide 80 mg or methylprednisolone 120 mg once by intramuscular injection or oral prednisone 15 mg for 4 weeks, thereafter tapered by 5 mg/week). Patients were evaluated every 3

months. In case DAS was >2.4, patients were switched to a TNF-blocker combined with MTX 25 mg/week. If sustained remission (DAS<1.6 at 2 consecutive visits) was achieved, medication was tapered according to protocol. Detailed information on the medication scheme can be found in the original tREACH paper (4). This study was approved by the Erasmus MC medical ethics committee, Rotterdam (NL-14580.078.06). All patients gave written informed consent before inclusion.

### Outcome

Primary outcome was remission (DAS<1.6) within 6 months of follow-up.

Secondary outcome was sustained remission (2x DAS<1.6 at 2 consecutive visits) at 9 months of follow-up.

### Candidate predictors

Demographic, disease-related and psychosocial factors were included as candidate predictors into the model. Demographic characteristics included age, sex, ethnicity and having paid work at baseline. Disease-related factors included initial treatment strategy (initial triple DMARD therapy or MTX monotherapy), baseline disease activity (DAS), functional ability (Health Assessment Questionnaire, HAQ), radiographic damage (Sharp-van der Heijde Score), Rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA) status, duration of complaints and physical functioning (SF36 physical component score (PCS)). Psychosocial factors included mental functioning (SF36 mental component scale), internal, external and chance locus of control (multidimensional health locus of control (MHLC), anxiety and depression (hospital anxiety and depression score (HADS)), fatigue (Visual Analogue Scale (VAS)) and coping with pain (Coping with Rheumatic Stressors). The demographic and disease related assessments are described in the original tREACH paper (4). Psychosocial questionnaires are explained in more detail below.

Locus of control: The locus of control was determined by the Multidimensional Health Locus of Control (MHLC) questionnaire, containing 18 questions about health and diseases. The MHLC assesses 3 different loci of control: internal, external and chance (Cronbach's alpha 0.68-0.78). An "internal" locus of control indicates that a patient beliefs he is responsible for his health, whereas someone with an "external" locus of control beliefs that the practitioner is responsible for his health status. The "chance" locus of control reflects that someone beliefs that his health depends on fate or luck. Each domain has a sum score ranging from 6 to 36, higher scores indicating a higher belief in that particular locus of control (13).

Coping style: Coping style was measured by the Coping with Rheumatic Stressors (CORS) questionnaire. The list contains 8 questions about coping with pain (Cronbach's alpha 0.88) and 10 questions about coping with limitations (Cronbach's alpha 0.91).

Scores for coping with pain range from 8-40 and for coping with limitations between 10-40. Higher scores indicate more passive coping (14).

Depression and anxiety: The Hospital Anxiety and Depression Scale (HADS) was used to measure depression and anxiety. The scores for depression and anxiety range between 0 to 21, higher scores indicating symptoms related to more anxiety or depression (15).

Fatigue: Fatigue was assessed using a visual analog scale ranging from 0-100, higher scores indicating higher levels of fatigue.

### Statistical analyses

Missing values in baseline covariates (<10% missing, see Supplemental Table 1) were completed using multiple imputation with chained equations (mi impute chained procedure in STATA) with m=50 imputation models. Univariable logistic regression analyses were performed for all candidate predictors to assess their association with outcomes remission within 6 months and sustained remission at 9 months respectively. Candidate predictors with p<0.20 were entered into the multivariable models, after which backward selection was applied until significance was reached for all remaining predictors. Statistical analyses were performed using STATA 14.1 (StataCorp, 4905 Lakeway Drive College Station, Texas, USA). P-values <0.05 were considered statistically significant.



## RESULTS

Data from 281 patients participating in tREACH were available for analysis. Overall, 68% of patients were female and mean age was 53.3 years. Mean baseline DAS was 3.35 (95%CI 3.24-3.36) (Table 1). A flowchart of follow-up is shown in Figure 1. During 6 months of follow-up, remission was achieved by 135/281 (48%) of patients, while 96/281 (34%) of patients achieved sustained remission at 9 months of follow-up.

### Predictors for remission within 6 months

Univariable analyses revealed older age and female sex were associated with a lower probability to attain remission within 6 months (Table 2). Of disease related factors, higher baseline DAS and HAQ scores resulted in a lower odds for remission, whereas higher scores on SF36 physical component scale (reflecting better physical health, were associated with a higher chance for remission. Of psychosocial factors, higher scores on SF36 mental component scale and internal locus of control were associated with a higher odds for attaining remission. On the contrary, higher levels of anxiety, depression and fatigue were associated with a lower probability to attain remission within 6 months. In the final multivariable model, age, sex, baseline DAS and anxiety remained as independent predictors for remission within 6 months (Table 2).

**Table 1.** Baseline characteristics of all patients and patients by remission status.

| | | Remission within 6 months | |
|---|---|---|---|
| | **All patients (n=281)** | **No (n=146)** | **Yes (n=135)** |
| **Demographic** | | | |
| Age | 53 (14) | 55.0 (13) | 51.3 (15) |
| Sex, female, n (%) | 190 (68) | 108 (74) | 82 (61) |
| **Disease-related** | | | |
| Duration of complaints, days, mean (sd) | 166 (91) | 171 (95) | 162 (88) |
| RF-positive | 228 (81) | 113 (77) | 115 (85) |
| ACPA-positive | 226 (80) | 119 (82) | 107 (79) |
| Fulfilling ACR/EULAR 1987 criteria | 189 (67) | 95 (65) | 94 (70) |
| Fulfilling ACR/EULAR 2010 criteria | 267 (95) | 140 (96) | 127 (94) |
| DAS, mean (sd) | 3.36 (0.96) | 3.66 (0.87) | 3.03 (0.94) |
| HAQ, mean (sd) | 1.00 (0.66) | 1.12 (0.66) | 0.87 (0.64) |
| tSvHs, median (IQR) | 0 (0-0) | 0 (0-0) | 0 (0-0) |

Abbreviations:
- ACPA: Anti-Citrullinated Protein Antibodies
- ACR: American College of Rheumatology
- DAS: Disease Activity Score
- EULAR: European League against Rheumatism
- HAQ: Health Assessment Questionnaire
- IQR: Interquartile range
- RF: Rheumatoid Factor
- sd: standard deviation
- tSVHS: total Sharp van der Heijde Score

## Predictors for sustained remission at 9 months (in remission at 6 and 9 months)

When considering patients in remission at both 6 and 9 months, univariable analyses revealed female sex to be associated with a lower probability to attain sustained remission. Of disease related factors, higher baseline DAS scores and HAQ scores resulted in a lower odds for remission, whereas higher scores on SF36 physical component scale was associated with a higher chance for remission. Of psychosocial factors, higher scores on internal locus of control were associated with a higher odds for attaining remission. On the contrary, higher levels of anxiety, depression, fatigue and passive coping with pain were associated with a lower probability to attain remission within 6 months. In the final multivariable model age, sex, ACPA positivity and fatigue remained as independent predictors for sustained remission at 9 months (Table 2).

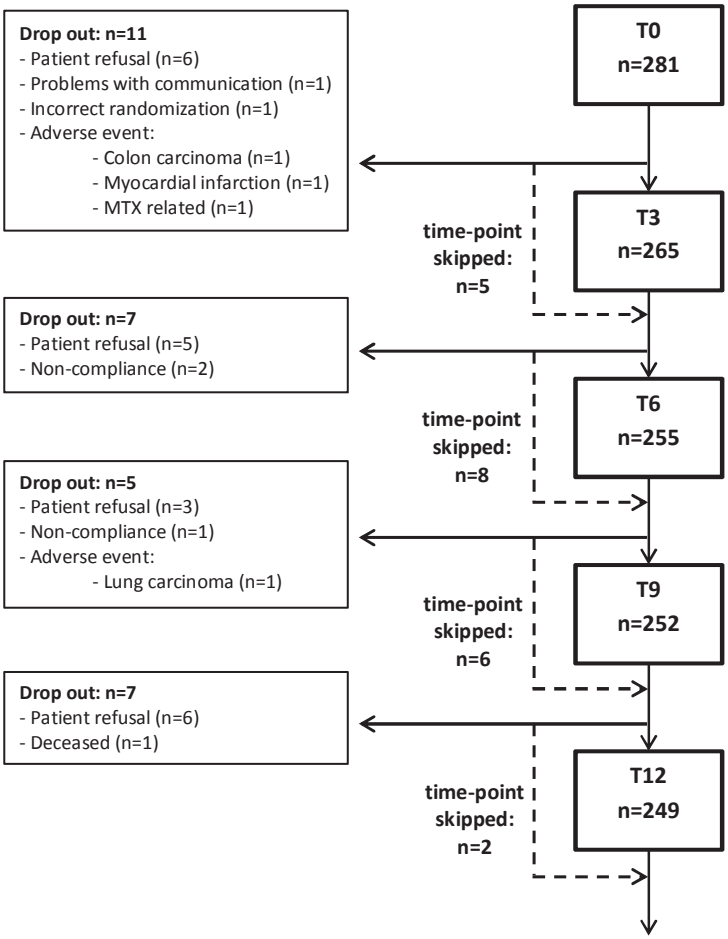


**Figure 1.** Flow-chart of follow-up.

**Table 2.** Predictors for attaining remission (DAS<1.6) within 6 months and sustained remission (DAS<1.6 at 2 consecutive visits) at 9 months by logistic regression.

| | Remission within 6 months (n=135 cases) | | | | Sustained remission at 9 months (n=83 cases) | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariable | | Multivariable* | | Univariable | | Multivariable* | |
| | OR | P | OR | P | OR | P | OR | P |
| **Demographics** | | | | | | | | |
| Age (years) | **0.982** | **0.032** | **0.978** | **0.026** | 0.988 | 0.183 | **0.965** | **0.002** |
| Sex (female) | **0.544** | **0.018** | **0.538** | **0.033** | **0.373** | **<0.001** | **0.372** | **0.001** |
| Dutch ethnicity | 1.128 | 0.707 | | | 1.294 | 0.488 | | |
| Paid work | 1.198 | 0.465 | | | 1.529 | 0.125 | | |
| **Disease** | | | | | | | | |
| MTX monotherapy | 0.657 | 0.098 | | | 0.642 | 0.122 | | |
| DAS (baseline) (0-10) | **0.447** | **<0.001** | **0.495** | **<0.001** | **0.582** | **0.001** | | |
| HAQ (baseline) (0-3) | **0.565** | **0.003** | | | **0.549** | **0.006** | | |
| tSvHS (baseline) | 0.939 | 0.241 | | | 0.940 | 0.339 | | |
| RF positive | 1.679 | 0.098 | | | 1.762 | 0.123 | | |
| ACPA positive | 0.867 | 0.635 | | | 0.612 | 0.119 | **0.441** | **0.018** |
| Duration of complaints (days) | 0.999 | 0.421 | | | 0.999 | 0.324 | | |
| Physical functioning (SF36 PCS) (0-100) | **1.055** | **0.007** | | | **1.068** | **0.004** | | |
| **Psychosocial** | | | | | | | | |
| Mental functioning (SF36 MCS) (0-100) | **1.038** | **0.045** | | | 1.032 | 0.128 | | |
| Internal locus of control (MHLC) (6-36) | 1.054 | 0.056 | | | **1.088** | **0.006** | | |
| External locus of control (MHLC) (6-36) | 1.010 | 0.726 | | | 0.992 | 0.788 | | |
| Chance locus of control (MHLC) (6-36) | 1.005 | 0.842 | | | 0.994 | 0.814 | | |
| Anxiety (HADS) (0-21) | **0.886** | **0.001** | 0.907 | 0.015 | **0.886** | **0.004** | | |
| Depression (HADS) (0-21) | **0.882** | **0.001** | | | **0.881** | **0.005** | | |
| Fatigue (VAS) (0-100) | **0.983** | **0.001** | | | **0.978** | **<0.001** | **0.973** | **<0.001** |
| Coping with pain (CORS) (8-40) | 0.960 | 0.093 | | | **0.945** | **0.040** | | |

* Backward selection, variables with p<0.20 in univariable analysis were entered

Abbreviations:

- ACPA: Anti-Citrullinated Protein Antibodies
- ACR: American College of Rheumatology
- CORS: Coping with Rheumatic Stressors
- DAS: Disease Activity Score
- EULAR: European League against Rheumatism
- FAS: Fatigue Assessment Scale
- HADS: Hospital Anxiety and Depression Scale
- HAQ: Health Assessment Questionnaire
- IQR: Interquartile range
- MCS: Mental Component Scale
- MHLC: Multidimensional Health Locus of Control
- MTX: Methotrexate
- OR: Odds Ratio
- PCS: Physical Component Scale
- RF: Rheumatoid Factor
- sd: standard deviation
- SF36: Short Form 36
- tSVHS: total Sharp van der Heijde Score
- VAS: Visual Analog Scale

## DISCUSSION

In our analyses of predictors for attaining remission within 6 months after starting DMARD therapy in early RA patients, we found that besides the known factors age, sex and disease related factors (baseline DAS and HAQ), also physical functioning and several psychosocial factors (mental functioning, internal locus of control, anxiety, depression and fatigue) were associated. We found similar results for sustained remission at 9 months.

Several recently published studies on predictors for attaining remission focused on specific treatment regimens or used different definitions of remission, both of which have been shown to influence the identification of predictors (16, 17). Furthermore, these studies were performed in patients with established rather than early RA. Although this heterogeneity makes direct comparison difficult, we identified several recent (> the year 2010) studies in early RA patients on predictors for remission initiating treatment with conventional DMARDs that we will discuss shortly (8-10, 18-21). In line with our findings, five studies reported that males respond better to treatment (8, 18-21). Men have been reported to have both lower levels of ESR (22) and pain scores (16) compared to women, which may explain why achieving remission is more difficult for women. Younger age was found to be a predictor for remission in two studies as well (8, 20), but 4 studies reported insignificant associations (9, 10, 19, 21). Therefore, whether age is truly a predictor for remission remains unclear. Baseline DAS (21) or its components tender joint count (8, 20), swollen joint (20) count or CRP (10) have been reported as predictors, as well as baseline HAQ (8). Treatment with combination DMARD therapy compared to MTX alone was identified as a predictor by Kuriya et al. (19) ACPA status was evaluated in 3 studies (8, 10, 21), none of which found a significant association. Although few studies assessed psychosocial factors, lower depression scores were identified as independent predictors for remission both in the EUPA cohort (10) and the COMET trial (9). The latter study also found an association between baseline anxiety and remission, which is in line with our findings (9).

In addition to the factors just mentioned, genetic factors have been associated with attaining remission as well. Fransen et al. proposed a prediction rule for attaining DAS<2.4 within 6 months of follow-up with methotrexate alone based on clinical and genetic factors (6). This model was able to correctly classify 75% of patients as (non-)responders in its own sample (6).

Comparing predictors for attaining point remission within 6 months to the more stringent criterion of attaining sustained remission (remission at both 6 and 9 months), we observe that baseline DAS is an independent predictor for remission within 6 months, whereas ACPA-negativity is an independent predictor for being in sustained remission at 9 months. Likely, the impact of baseline DAS on disease activity diminishes over

time by the treat-to-target regimen, whereas ACPA-positive status reflects a tendency for a higher DAS that remains present. We also observe that anxiety was identified as an independent predictor for point remission and fatigue as an independent predictor for sustained remission within 6 months. This finding does not necessarily implicate a real difference. As measures anxiety, fatigue and depression are correlated to each other (Pearson correlation coefficients: anxiety-depression 0.59, anxiety-fatigue 0.43, depression-fatigue 0.46), they likely measure, at least in part, a common domain that is reflected by patient well-being.

Several strengths and limitations should be noted. Strong points include the fact that data were used from a prospective randomized clinical trial on early RA patients that were treated to target according to current guidelines (1, 2). Although not powered for this analysis, the sample size appears to be adequate as for many candidate predictors significant results were obtained. The number of missing values in predictor variables were small <10%. Nonetheless, we used multiple imputation to increase power of the analysis. Nonetheless, the complete case analysis showed similar results (Supplemental Table 1). Few studies have assessed the predictive value of psychosocial factors and to our knowledge no previous studies have assessed them as predictors for attaining early remission.

Limitations can be noted as well. Data were used from a randomized clinical trial that was not designed for the purpose of these analyses. As the clinical trial setting differs from clinical practice, it cannot be ruled out that by selection bias different predictors would be identified if a similar study were performed in a clinical practice setting. Treatment in tREACH was steered to low disease activity (DAS<2.4) rather than remission (DAS<1.6) as used in our analysis. It is possible that, if treatment were steered towards remission rather than LDA, more patients would have achieved sustained remission and different factors would have been identified. On the other hand, treatment in clinical practice is often steered on DAS28 remission, which is a less stringent criterion than DAS remission. Therefore steering on DAS LDA may better reflect clinical practice and make our results more generalizable to this setting.

In this analysis, we specifically looked at predictors for remission within 6 months, as this is the recommend treatment goal (1, 2). However, this does not mean that patients achieving remission at a later point in time do not still have a better prognosis than patients not achieving remission at all. The course of disease for all patients achieving sustained remission within the first 2 years in tREACH has been published before (23).

Results from our study suggest that psychosocial factors like anxiety, depression and fatigue are associated with a decreased probability of meeting DAS criteria for remission. Whereas age and sex may be regarded as predictors that cannot be modified, interventions aimed to increase the efficiency of drug therapy or to relieve symptoms of anxiety, depression and fatigue may be feasible. Therefore we suggest these factors might be used

for personalized treatment strategy. A systematic review on the effects of interventions aimed at self-regulation in RA found that psychological interventions utilizing more self-regulation techniques reduced depressive symptoms and anxiety significantly more than interventions utilizing fewer such techniques, especially in those with early disease. Also person-centered physical therapy in RA patients was found to give significant improvements in fatigue and anxiety (24). Whether such personalized interventions, in addition to a treat-to-target regimen, lead to improvements in remission rates as well should be further investigated. At last, results of our study may guide development of a prediction model as well. Addition of psychosocial factors to existing models based on clinical and genetic factors (6, 20) may improve the predictive ability. However, as the psychosocial factors likely act mostly through the subjective components of DAS (25), addition may not be warranted if the model is used for the purpose of identifying patients who need more intensive DMARD therapy.



## CONCLUSION

In conclusion, we identified male sex, younger age, lower baseline DAS and less symptoms of anxiety as independent predictors for attaining remission within 6 months. Results suggest that features of fatigue, anxiety and depression may prevent patients from attaining remission despite treatment according to a tight control and treat-to-target strategy. Future studies may be addressed at evaluating the (cost-)effectiveness of early personalized treatment and psychological interventions in early RA patients starting DMARD therapy.

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**Supplemental Table 1.** Number of patients with missing values in covariates of 281 patients included in the analysis.

| | Missing, n (%) | Regression method for imputation |
|---|---|---|
| **Demographics** | | |
| Age | 0 (0) | - |
| Sex (female) | 0 (0) | - |
| Dutch ethnicity | 16 (6) | logistic |
| Paid work | 24 (9) | logistic |
| **Disease** | | |
| MTX monotherapy | 0 (0) | - |
| DAS (baseline) | 1 (0.4) | truncated |
| HAQ (baseline) | 19 (7) | truncated |
| tSvHS (baseline) | 14 (5) | ordered logistic |
| RF positive | 0 (0) | - |
| ACPA positive | 0 (0) | - |
| Duration of complaints | 2 (0.7) | truncated |
| Physical functioning (SF36 PCS) | 26 (9) | truncated |
| **Psychosocial** | | |
| Mental functioning (SF36 MCS) | 26 (9) | truncated |
| Internal locus of control (MHLC) | 22 (8) | truncated |
| External locus of control (MHLC) | 22 (8) | truncated |
| Chance locus of control (MHLC) | 23 (8) | truncated |
| Anxiety (HADS) | 18 (6) | truncated |
| Depression (HADS) | 18 (6) | truncated |
| Fatigue (VAS) | 21 (7) | truncated |
| Coping with pain (CORS) | 19 (7) | truncated |

Abbreviations:
ACPA: Anti-Citrullinated Protein Antibodies
CORS: Coping with Rheumatic Stressors
DAS: Disease Activity Score
HADS: Hospital Anxiety and Depression Score
HAQ: Health Assessment Questionnaire
MCS: Mental Component Scale
MHLC: Multidimensional Health Locus of Control
MTX: Methotrexate
PCS: Physical Component Scale
RF: Rheumatoid Factore
tSvHS: total Sharp-van der Heijde Score
VAS: Visual Analog Scale

**Supplemental Table 2.** Complete case analysis of predictors for attaining remission (DAS<1.6) within 6 months and sustained remission (DAS<1.6 at 2 consecutive visits) at 9 months by logistic regression.

| | Remission within 6 months (n=135 cases) | | | | Sustained remission at 9 months, (n=83 cases) | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariable | | Multivariable* | | Univariable | | Multivariable* | |
| | OR | P | OR | P | OR | P | OR | P |
| **Demographics** | | | | | | | | |
| Age (years) | **0.982** | **0.032** | **0.978** | **0.027** | 0.988 | 0.183 | **0.969** | **0.006** |
| Sex (female) | **0.544** | **0.018** | **0.512** | **0.025** | **0.373** | **<0.001** | **0.362** | **0.001** |
| Dutch ethnicity | 1.193 | 0.584 | | | 1.421 | 0.348 | | |
| Paid work | 1.220 | 0.432 | | | 1.400 | 0.230 | | |
| **Disease** | | | | | | | | |
| MTX monotherapy | 0.657 | 0.098 | | | **0.642** | **0.122** | | |
| DAS (baseline) (0-10) | **0.447** | **<0.001** | **0.518** | **<0.001** | **0.583** | **0.001** | | |
| HAQ (baseline) (0-3) | **0.550** | **0.002** | | | **0.545** | **0.006** | | |
| SvH (baseline) | 0.935 | 0.216 | | | 0.943 | 0.354 | | |
| RF positive | 1.679 | 0.098 | | | 1.762 | 0.123 | | |
| ACPA positive | 0.867 | 0.635 | | | 0.612 | 0.119 | **0.451** | **0.025** |
| Duration of complaints (days) | 0.999 | 0.414 | | | 0.998 | 0.302 | | |
| Physical functioning (SF36 PCS) (0-100) | **1.054** | **0.008** | | | **1.075** | **0.002** | | |
| **Psychosocial** | | | | | | | | |
| Mental functioning (SF36 MCS) (0-100) | **1.042** | **0.029** | | | 1.037 | 0.087 | | |
| Internal locus of control (MHLC) (6-36) | **1.056** | **0.049** | | | **1.094** | **0.004** | | |
| External locus of control (MHLC) (6-36) | 1.012 | 0.674 | | | 0.997 | 0.935 | | |
| Chance locus of control (MHLC) (6-36) | 1.004 | 0.855 | | | 0.996 | 0.872 | | |
| Anxiety (HADS) (0-21) | **0.886** | **0.001** | **0.908** | **0.015** | **0.881** | **0.002** | | |
| Depression (HADS) (0-21) | **0.881** | **0.001** | | | **0.877** | **0.004** | | |
| Fatigue (VAS) (0-100) | **0.982** | **0.001** | | | **0.977** | **<0.001** | **0.973** | **<0.001** |
| Coping with pain (CORS) (8-40) | 0.964 | 0.128 | | | **0.946** | **0.050** | | |

* Backward selection, variables with p<0.20 in univariable analysis were entered

Abbreviations:

- ACPA: Anti-Citrullinated Protein Antibodies
- ACR: American College of Rheumatology
- CORS: Coping with Rheumatic Stressors
- DAS: Disease Activity Score
- EULAR: European League against Rheumatism
- FAS: Fatigue Assessment Scale
- HADS: Hospital Anxiety and Depression Scale
- HAQ: Health Assessment Questionnaire
- IQR: Interquartile range
- MCS: Mental Component Scale
- MHLC: Multidimensional Health Locus of Control
- MTX: Methotrexate
- OR: Odds Ratio
- PCS: Physical Component Scale
- RF: Rheumatoid Factor
- sd: standard deviation
- SF36: Short Form 36
- tSVHS: total Sharp van der Heijde Score
- VAS: Visual Analog Scale

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# Chapter 6

## Tapering conventional synthetic DMARDs in early arthritis patients in sustained remission: 2 year follow-up of the tREACH trial

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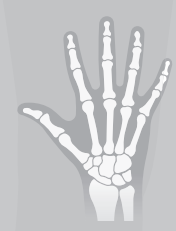


## ABSTRACT

### Objectives

With early and intensive treatment many early RA patients attain remission. Aims were to investigate 1) the frequency and time to sustained remission and subsequent tapering in patients initially treated with conventional synthetic (cs)DMARD strategies and 2) the frequency and time to flare and regained remission in patients tapering csDMARDs and biologic (b)DMARDs during 2 years of follow-up.

### Methods

Two year follow-up data from the tREACH cohort were used. Patients were randomized to initial treatment with triple DMARD therapy (iTDT) with glucocorticoid (GC) bridging or methotrexate monotherapy (iMM) with GC bridging. Patients were evaluated every 3 months. In case Disease Acitivity Score (DAS) was >2.4 treatment was switched to a TNF-blocker. In case DAS<1.6 at 2 consecutive time points, tapering was initiated according to protocol. Outcomes were rates of sustained remission (DAS<1.6 at 2 consecutive time points), flare (medication increase after tapering) and remission after flare (DAS<1.6). Data were analyzed using Kaplan-Meier analyses.

### Results

During 2 years of follow-up, sustained remission was achieved at least once by 159 (57%) of patients, of whom 118 and 23 patients initiated tapering of csDMARDs and bDMARDs respectively. Thirty-four patients achieved drug-free remission. Flare rates were 41% and 37% and within 1 year respectively. After flare, 65% of patients tapering csDMARDs re-achieved remission within 6 months after treatment intensification.

### Conclusions

Regardless of initial treatment strategy, 56% of patients achieved sustained remission during 2 years of follow-up. Flare rates were 41% and 37% within 12 months in patients tapering csDMARDs and bDMARDs respectively.

## INTRODUCTION

Several studies (1-3), among which the tREACH study (1), have shown that by early and intensive treatment remission can be achieved in many early RA patients. Current evidence suggests that once remission has been achieved, treatment de-escalation may be considered (4, 5), but most recent studies have focused on de-escalation of biological (b)DMARDs only (4).

In this follow-up study of tREACH (1), we investigated the frequency and time to remission and subsequent tapering of conventional synthetic (cs)DMARDs and bDMARDs and the frequency and time to flare and regained remission in patients tapering csDMARDs and bDMARDs.



## METHODS

Data were used from the tREACH cohort, a detailed description of the inclusion criteria and protocol can be found in the original tREACH paper (1). In short, patients with early arthritis (duration of complaints < 1 year) and a high risk of developing persistent arthritis (score >6 points on Visser model (6)) were eligible. Of included patients, 97% fulfilled the ACR/EULAR 2010 criteria for RA (1, 7). Patients were randomized for induction treatment strategies with triple DMARD therapy (iTDT; methotrexate (MTX) 25 mg/week, sulphasalazine 2000 mg/day and hydroxychloroquine 400 mg/day or MTX monotherapy 25 mg/week (iMM). Both groups received bridging therapy with glucocorticoids (triamcinolone acetonide 80 mg or methylprednisolone 120 mg once by intramuscular injection or oral prednisone 15 mg for 4 weeks, thereafter tapered by 5 mg/week). For this analysis, the 2 groups receiving iTDT with oral or intramuscular glucocorticoids were combined (n=184). Patients were evaluated every 3 months and treated in a treat-to-target fashion. If DAS was >2.4 on initial treatment, patients were switched to a TNF-blocker combined with MTX 25 mg/week. If sustained remission (DAS<1.6 at 2 consecutive visits) was achieved, medication was tapered according to protocol (expert opinion of project group) while remission remained: (1) iTDT: Sulphasalazine stop, half dose MTX, quarter dose MTX, stop MTX, stop hydroxychloroquine; iMM: half dose MTX, quarter dose MTX, stop MTX; Combination of MTX and TNF-blocker: Randomization to taper MTX first (aforementioned regimen) or TNF-blocker first: doubling of interval, then half dose, then stop. In case MTX or TNF-blocker had been completely tapered, the remaining agent was tapered according aforementioned scheme (also see Supplement 1). Flare was defined as an increase in medication after initiation of tapering. Initially, duration of follow-up was 12 months, which was soon extended to ≥24 months after the trial had started. For this reason 76 (27%) of patients missed one or more visits during the second year of follow-up. Groups

were compared using simple descriptive statistics. Sustained low disease activity (LDA) was defined as DAS<2.4 at 2 consecutive visits. Drug-free remission was defined as DAS<1.6 without using DMARDs. Rates of sustained remission, flares and time to regain remission between groups were analysed using Kaplan-Meier analyses. Baseline predictors for drug-free remission were evaluated using logistic regression. Statistical analyses were performed using STATA 14.1 (StataCorp, 4905 Lakeway Drive College Station, Texas, USA). P-values <0.05 were considered statistically significant.

## RESULTS

Data from 281 patients participating in tREACH were available for analysis. Overall, 68% of patients were female and mean age was 53.3 years. Mean baseline DAS was 3.35 (95%CI 3.24-3.36). At baseline, groups were similar with respect to demographic and disease-related characteristics (Table 1). A flowchart of follow-up is shown in Figure 1. During two years of follow-up, sustained remission was achieved in the iTDT and iMM groups in 108 (59%) and 51 (53%) of patients and sustained low disease activity (LDA) in 148 (80%) and 76 (78%) of patients respectively. Remission was achieved with a biological in 12 (11%) and 13 (26%) patients in the iTDT and iMM groups respectively. After sustained remission had been achieved, 94 (87%) and 47 (92%) initiated tapering in the iTDT and iMM groups respectively. Tapering involved a conventional DMARD in 84% (n=118) and a biological DMARD in 16% (n=23) of cases.

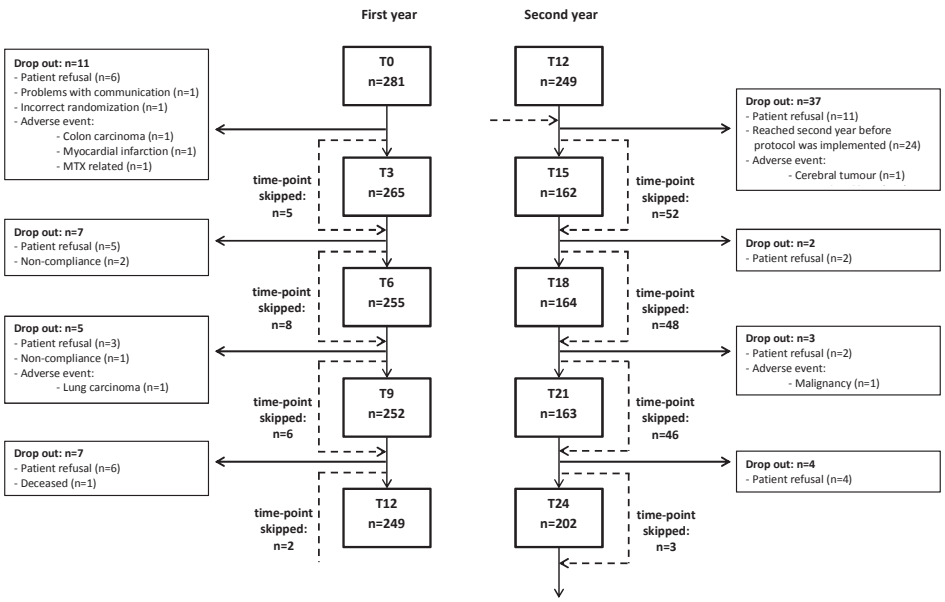


**Figure 1.** Flow-chart of follow-up.

**Table 1.** Baseline characteristics of all patients initiating with csDMARD therapy and the subset of patients tapering DMARDs (synthetic and/or biologic).

| | All patients (n=281) | Tapering DMARDs (n=141) |
|---|---|---|
| *Demographic* | | |
| Age, mean (sd) | 53 (14) | 52 (15) |
| Sex, female, n(%) | 190 (68) | 79 (56) |
| | | |
| *Disease-related* | | |
| Duration of complaints, days, mean (sd) | 166 (91) | 167 (88) |
| RF-positive, n(%) | 228 (81) | 17 (83) |
| ACPA-positive, n(%) | 226 (80) | 108 (77) |
| Fulfilling ACR/EULAR 1987 criteria, n(%) | 189 (67) | 96 (68) |
| Fulfilling ACR/EULAR 2010 criteria, n(%) | 267 (95) | 134 (95) |
| DAS, mean (sd) | 3.36 (0.96) | 3.18 (1.03) |
| SJC44, median (IQR) | 7 (4-12) | 8 (4-12) |
| ESR , median (IQR) | 24 (14-42) | 22 (12-39) |
| CRP, median (IQR) | 9 (4-23) | 10 (5-26) |
| TJC44, median (IQR) | 9 (4-14) | 7 (3-13) |
| Global Health, median (IQR) | 53 (33-69) | 50 (28-67) |
| HAQ, mean (sd) | 1.00 (0.66) | 0.88 (0.62) |
| tSvHs, median (IQR) | 0 (0-0) | 0 (0-0) |
| | | |
| Complete follow-up at 2 years, n(%) | 248 (88) | 133 (94) |

Abbreviations:
ACPA: Anti-Citrillunated Protein Antibody
CRP: C-Reactive Protein
DAS: Disease Activity Score
ESR: Erythrocyte Sedimentation Rate
HAQ: Health Assessment Questionaire
RF: Rheumatoid Factor
SJC44: 44 Swollen Joint Count
TJC44: 44 Tender Joint Count
tSvHs: total Sharp – van der Heijde Score

## Time to remission

Of patients achieving sustained remission, 56 (52%) and 19 (37%) achieved this within 6 months (p=0.09) and 91 (84%) and 39 (76%) within 1 year (p=0.27) in the iTDT and iMM groups respectively. Therefore, a trend for higher frequency of sustained remission and subsequent tapering was observed in the iTDT group compared to the iMM group, but this trend became less prominent over time (Figure 2A). Kaplan-Meier analysis over two years also revealed no significant difference between groups (Figure 2A).

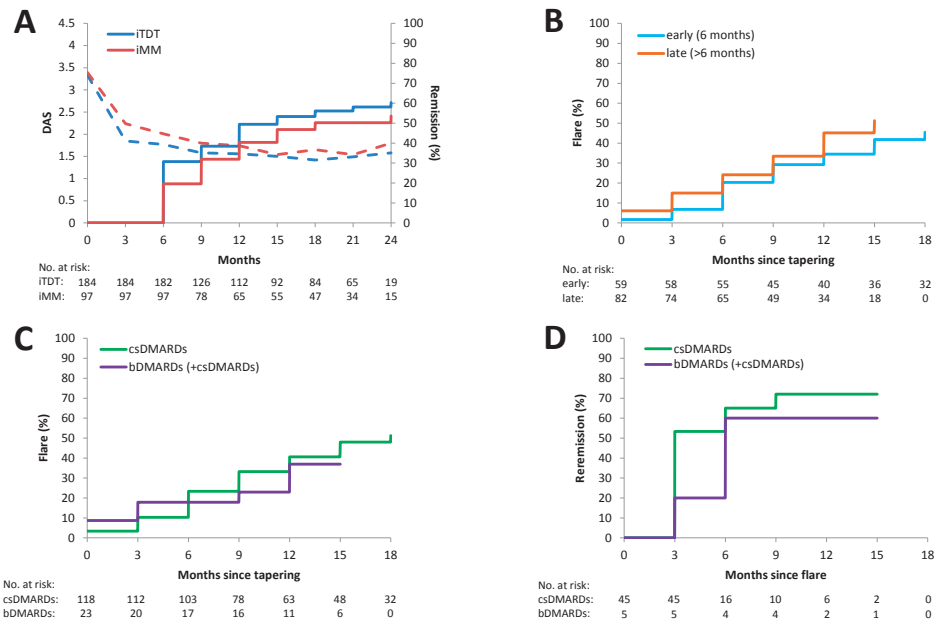


**Figure 2.** Survival analysis of patients initiating with triple DMARD therapy (iTDT, blue line) versus patients initiating with MTX monotherapy (iMM, red line) with respect to sustained remission (panel A), of patients achieving early remission (light blue line) versus late remission (orange line) with respect to occurence of flare (panel C), of patients tapering csDMARDs (green line) or bDMARDs (+csDMARDs) (purple line) with respect to occurrence of flare (panel C), and time to regain remission after flare of patients tapering csDMARDs (green line) or bDMARDs (+csDMARDs) (purple line) (panel D).

## Remission duration

Sustained remission at ≥3 consecutive visits was achieved by 123 patients (3 visits: n=27, 4: n=40, 5: n=22, 6: n=11, 7: n=7, 8: n=16). After tapering DMARDs 34 patients achieved drug-free remission, of whom 11 and 7 remained in drug-free remission for at least 3 and 6 months respectively. Nine and 7 patients failed drug-free remission or were censored after 3 months respectively. Baseline predictors male sex, lower DAS and HAQ and not having paid work were associated with achieving drug-free remission (Supplemental Table 1).

## Flare

For all 141 patients tapering any DMARD, no difference in flare rate was observed for patients achieving remission early (≤6 months) or thereafter (figure 2B). Of 118 patients tapering csDMARDs, 52 (44%) experienced a flare during the 2-year follow-up period. Kaplan-Meier analysis revealed a flare rate of 41% (95%CI 32%-50%) within 1 year and

51% (95%CI 42%-62%) within 18 months after initiation of tapering (figure 2C). Of 23 patients tapering bDMARDs, 7 (30%) experienced a flare during 2 years of follow-up. Kaplan-Meier analysis revealed a flare rate of 37% (95%CI 19%-64%) within 1 year after initiation of tapering (figure 2C). Upon medication increase after a flare, Kaplan-Meier analysis revealed that 53% (95%CI 40%-68%) of patients tapering csDMARDs regained DAS-remission within 3 months and 65% (95CI 50%-79%) within 6 months (figure 2D). Of five patients tapering bDMARDs , three regained DAS-remission within 6 months after flare.

## DISCUSSION



In this study of early rheumatoid arthritis, a trend for a higher frequency of achieving sustained remission, with less use of biologicals, was observed in patients with initial triple DMARD therapy compared to initial methotrexate monotherapy. We found that 57% of patients reached sustained remission and 78% sustained LDA at least once during 2 years of follow-up. This is in line with findings by others. Previous studies found sustained remission rates of 50% during 2 years of follow-up in patients initiating with MTX monotherapy (8) and an LDA rate of 78% at 2 years of follow-up in early RA patients initiating with combination csDMARD therapy with tapered high dose prednisone (9). Although in recent years, many clinical trials and observational studies on tapering DMARDs have emerged (4), most deal with the de-escalation of biologic DMARDs (4, 10-12) or report mixed results for groups in which both bDMARDs and csDMARDs were tapered (13, 14). A recent publication on data from a Dutch registry study found that de-escalation of MTX in patients using concomitant TNFi did not influence average DAS and drug survival (15). However, studies that specifically focus on de-escalation of conventional DMARDs generally date from the nineties or before and were performed in patients with established RA (4). Results from this study on the tapering of conventional DMARDS may therefore provide additional value to current literature. The 1-year flare rates after tapering csDMARDS (41% (95% CI 32%- 50%)) and bDMARDS (37% (95%CI 19%- 64%)) appear to be comparable to the pooled flare rate found for studies de-escalating TNF-blockers of 33% (95%CI 23%- 45%) (4). Also in line with the findings of the systematic review, we found that the majority of patients (65% (95%CI 50-79%) regained a state of remission within 6 months after treatment intensification.

This study has several strengths and limitations. Strong points of this study include the fact that we performed an analysis in a large clinical trial population of early RA patients treated in a treat-to-target fashion. Some limitations in the analysis should be noted as

well. First of all, follow-up with respect to the outcome measures used in this analysis was not complete. Especially during the second year of follow-up we had a substantial amount of missing observations. This had to do with the fact that initially the trial was set up to have a follow-up duration of 12 months. Only after the trial had started, the follow-up was extended to 36 months. Hence, part of the patients have only been followed for 1 year. This problem was addressed by using Kaplan-Meier estimates, which allowed to correctly analyse censored data. The tapering of medication was performed largely according to protocol, however this protocol was not always exactly followed by the rheumatologists in practice. Reasons may vary from unfamiliarity with the protocol to deviation on purpose because the disease status as indicated by the DAS did not agree with the rheumatologists' opinion. Although this may be seen as a limitation, it may also be a strong point as our results are likely to better reflect the way in which tapering is performed in clinical practice. Another potential limitation is that the flare rates in this study may depend on the tapering scheme used. We used stepwise tapering as long as sustained remission was maintained. It is possible that more patients would have remained in sustained remission if only dose reduction of csDMARDs were applied, which has already been shown for TNF-inhibitors. (16, 17) Considering the DMARDs patients received at the moment flare occurred (Supplement 1), we observe that 15/32 of patients having a flare while tapering combination DMARD therapy experienced the flare during the first 2 steps (tapering sulphasalazine and methotrexate, arguably cutting dose in half) and 6/15 patients when tapering MTX to half dose. Possibly, dose reduction is more difficult to achieve in patients receiving csDMARDs only than in patients treated with bDMARDs. It should be noted that after flare, the majority of patients regained remission within 6 months which is similar to re-remission rates observed in studies de-escalating biological DMARDs (4). At last it should be noted that data are from an early RA population with relatively mild disease. Results may not be generalizable to populations with established RA for which rates of remission and successful tapering may be lower.

In conclusion, we found a trend for earlier achievement of sustained remission, with less use of biologicals, in early RA patients initiating with triple DMARD therapy compared to MTX monotherapy. Regardless of initial treatment strategy, 56% of patients achieved sustained remission during 2 years of follow-up. Of patients tapering csDMARDs, 41% experienced a disease flare within 12 months. After flare, 65% of patients tapering csDMARDs regained a state of remission within 6 months after treatment intensification.

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**Supplement 1.** Treatment de-escalation steps for patients in sustained remission. Numbers in boxes indicate the number of flares on each respective step.

Flare after tapering combination DMARD therapy (MTX25 mg/week, Sulphasalazine 2000 mg/day, Hydroxychloroquine (HCQ) 200 mg/day), n=32/84[§]

| Step 1<br>MTX 25 mg/week<br>HCQ 200 mg/day | Step 2<br>MTX 12.5 mg/week<br>HCQ 200 mg/day | Step 3<br>MTX 7.5 mg/week<br>HCQ 200 mg/day | Step 4<br>HCQ 200 mg/day | Step 5<br>No DMARDs |
|---|---|---|---|---|
| n=8 | n=7 | n=6 | n=8 | n=3 |

Flare after tapering MTX25 mg/week, n=15/29[§]

| Step 1<br>MTX 12.5 mg/week | Step 2<br>MTX 7.5 mg/week | Step 3<br>No DMARDs |
|---|---|---|
| n=6 | n=6 | n=3 |

Flare after tapering Enbrel 50 mg/week and MTX 25 mg /week, Enbrel first, n=6/12[§]

| Step 1<br>Enbrel 50mg/2weeks<br>MTX 25 mg/week | Step 2<br>Enbrel 25mg/2weeks<br>MTX 25 mg/week | Step 3<br>MTX 25 mg/week | Step 4<br>MTX 12,5 mg/week | Step 5<br>MTX 7.5 mg/week | Step 6<br>No DMARDs |
|---|---|---|---|---|---|
| n=3 | - | n=2 | n=1 | - | - |

Flare after tapering Enbrel 50 mg/week and MTX 25 mg /week, MTX first, n=1/7[§]

| Step 1<br>Enbrel 50mg/week<br>MTX 12.5 mg/week | Step 2<br>Enbrel 50mg/week<br>MTX 7.5 mg/week | Step 3<br>Enbrel 50 mg/week | Step 4<br>Enbrel 50mg/2weeks | Step 5<br>Enbrel 25mg/2weeks | Step 6<br>No DMARDs |
|---|---|---|---|---|---|
| n=1 | - | - | - | - | - |

Flare after tapering other medication/dosages: n=5/9[§]

[§] Note: Due to right-censored nature of data ratios should be interpreted with caution

**Supplemental Table 1.** Predictors for attaining drug-free remission.

| | Drug-free remission (logistic regression) | | | |
|---|---|---|---|---|
| | Univariable | | Multivariable* | |
| | OR | P | OR | P |
| *Demographics* | | | | |
| Age | 0.995 | 0.709 | | |
| Sex (female) | **0.373** | **0.008** | **0.352** | **0.010** |
| Dutch ethnicity | 3.316 | 0.110 | | |
| Paid work | **0.438** | **0.037** | **0.404** | **0.030** |
| *Disease* | | | | |
| MTX monotherapy | 1.589 | 0.212 | | |
| DAS (baseline) | **0.590** | **0.014** | **0.587** | **0.022** |
| HAQ (baseline) | **0.515** | **0.038** | | |
| SvH (baseline) | 0.993 | 0.870 | | |
| RF positive | 1.399 | 0.511 | | |
| ACPA positive | 0.636 | 0.283 | | |
| Duration of complaints | 1.001 | 0.801 | | |
| Physical functioning (SF36 PCS) | 1.056 | 0.085 | | |

* Backward selection, variables with p<0.20 in univariate analysis were entered.

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# Chapter 7

## Flare rate in patients with rheumatoid arthritis in low disease activity or remission tapering or stopping synthetic or biologic DMARDs: A systematic review

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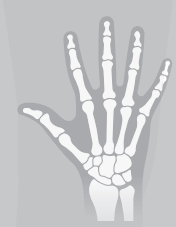



## ABSTRACT

### Objective

To evaluate the risk of having a disease flare in rheumatoid arthritis patients with low disease activity or remission, when de-escalating (tapering or stopping) DMARD therapy.

### Methods

A search in medical databases including publications from January 1950 to February 2015 was performed. Included were trials and observational studies in adults with rheumatoid arthritis with low disease activity or remission, evaluating ≥20 patients tapering or stopping DMARDs. Flare rates had to have been reported. A meta-analysis was performed on studies de-escalating TNF-blockers.

### Results

Four studies evaluated synthetic DMARDs. Flare rates ranged from 8% at 24 weeks to 63% at 4 months after de-escalation. Fifteen studies reported on TNF-blockers. Estimated flare rates by meta-analysis on studies tapering or stopping TNF-blockers were 0.26 (95% CI 0.17-0.39) and 0.49 (95% CI 0.27-0.73) for good and moderate quality studies, respectively. Flare rates in three studies stopping tocilizumab and three studies de-escalating abatacept ranged from 41% at 9 months - 87% at 1 year and 34% at 1 year - 75% at 6 months, respectively. Five studies evaluating radiographic progression in patients de-escalating treatment all found limited to no progression.

### Conclusion

Results suggest that more than one third of patients with RA in low disease activity or remission may taper or stop DMARD treatment without experiencing a disease flare within the first year.

Dose reduction of TNF-blockers results in lower flare rates than stopping and may be non-inferior to continuing full dose. Radiological progression after treatment de-escalation remains low, but may increase slightly.

## INTRODUCTION

The treatment of rheumatoid arthritis (RA) has advanced greatly. Combination therapy with disease modifying anti-rheumatic drugs (DMARDs), early, tight controlled treatment, and biologic agents improve outcomes in patients (1). Increasing numbers of patients reach and maintain a state of low disease activity or remission. The issue rises whether then DMARD therapy should be continued unchanged (infinitely) to keep the disease under control. De-escalation (tapering or stopping) of one or more anti-rheumatic agents could yield several benefits, such as less drug toxicity, less adverse reactions and less medical costs. However, it would then be important to know the risk of flare, radiographic progression and whether disease control can be easily regained after flare.

Objective of this review was to assess the course of disease after tapering or stopping synthetic DMARD (sDMARD) or biologic DMARD (bDMARD) therapy in patients with rheumatoid arthritis in remission or low disease activity. To do this, we set out the following goals:

1. To assess the risk of having a disease flare after tapering or stopping DMARDs.
2. To evaluate the mean or median time to flare (time-to-flare) after tapering or stopping DMARDs.
3. To evaluate the rate of radiographic progression after tapering or stopping DMARDs.
4. To assess how much time is needed to regain a state of low disease activity or remission (time-to-remission) after a disease flare has occurred.



## MATERIALS AND METHODS

### Search strategy and selection criteria

This systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines (2).

The search strategy developed and performed in collaboration with two medical librarians, was performed in the digital databases of Ovid-SP, Embase, PubMed and the Cochrane library for articles published up to February 2015. Keywords included terms and synonyms for rheumatoid arthritis, specific types of disease modifying anti-rheumatic drugs (e.g. methotrexate, etanercept) and stopping/tapering. One investigator (TMK) manually searched through cited references of published reviews of de-escalation of DMARDs in rheumatoid arthritis. The complete search strategy can be found in Supplement 1.

We included both clinical trials and observational studies on adult patients with rheumatoid arthritis in low disease activity or remission (as defined by any available criteria or on clinical grounds), tapering down or stopping DMARDs, reporting a flare rate at ≤ 1 year of follow-up. A minimum sample size of 20 patients de-escalating DMARDs was

required to be included. Patients needed to have equal lengths of follow-up in studies that reported flare rates as percentage or alternatively reported flares per person years in case patients had unequal length of follow-up. Studies were excluded if published only in the form of congress abstracts and studies reporting only combined flare rates for DMARDs with different modes of action (e.g. TNF-inhibitors and tocilizumab) were excluded. As most disease flares would be expected to occur within the first 3-6 months after treatment de-escalation, we believe a follow-up time of up to 1 year to be adequate.

### Data extraction

One investigator (TMK) reviewed titles and abstracts and selected potential manuscripts for retrieval. After retrieval of potential manuscripts, the same investigator established study eligibility applying the selection criteria specified above. In case of he was doubt, the study was discussed with the co-investigators (FBGL, JWGJ, JMWH) until consensus was reached. We used a standardized data collection form to extract the following information: Type of study, patient definition, number of patients tapering down or stopping medication, the DMARD that was tapered down or stopped, co-medication, definition of low disease activity / remission used, manner in which medication was tapered down or stopped, definition of flare, number of flares per follow-up time, mean/median time to flare, radiological progression and time to regain disease control after a flare.

### Risk of bias assessment

We used a modification of Black's list to perform a quality assessment on observational studies (3). The original list contains 27 items, distributed over five subscales: reporting, external validity, bias, confounding and power. Some minor modifications were made to the original list to suit it better use on treatment de-escalation studies: Items 6, 10, 16 and 25 from the original list were omitted, while item 17 was extended with two sub-items addressing the adequateness of follow-up for the outcomes flare rate and radiographic progression. Item 27 was modified to: "Was the sample size used to calculate the flare rate larger than n=100?", ensuring an adequate precision (95%-CI < 0.2). The modified list is available (Supplement 2). Two investigators (FBGL and JJL) independently rated each study. Disagreements were resolved by consensus. A table with item scores for each study was generated (Supplement 3), so that readers can easily identify design flaws introducing a potential for bias among studies.

### Pooling of data

Because of small numbers and differences in study design, meta-analysis was deemed inappropriate for studies on abatacept, tocilizumab and sDMARDs. A meta-analysis was performed on studies de-escalating TNF-blockers, reporting a flare rate at 1 year of follow-up.

The software Comprehensive Meta-Analysis version 2.2 (Biostat Inc., 14 North Dean

Street, Englewood, USA) was used. A random effects model was chosen based on the assumption that there are 2 sources of variability in effects observed in the various studies, i.e. sampling error and variability introduced by doing studies in different populations. Subgroup analyses by study quality were performed using a moderator variable. First, a quality score was generated using the items scores from the quality assessment as follows: Quality score = (#items "yes" + 0.5* #items "partly") / total #items. Then, based on the median score of the studies selected for meta-analysis, a dichotomous moderator variable was created to compare the results of studies according their quality. In case one or more studies had exactly the median score these studies were classified as having good quality.

## RESULTS

The search in electronic databases yielded 8147 publications, of which 7909 articles were excluded based on title and abstract (Figure 1). After full text assessment of the remaining 238 publications, 25 studies remained that were eligible for inclusion (Figure 1).



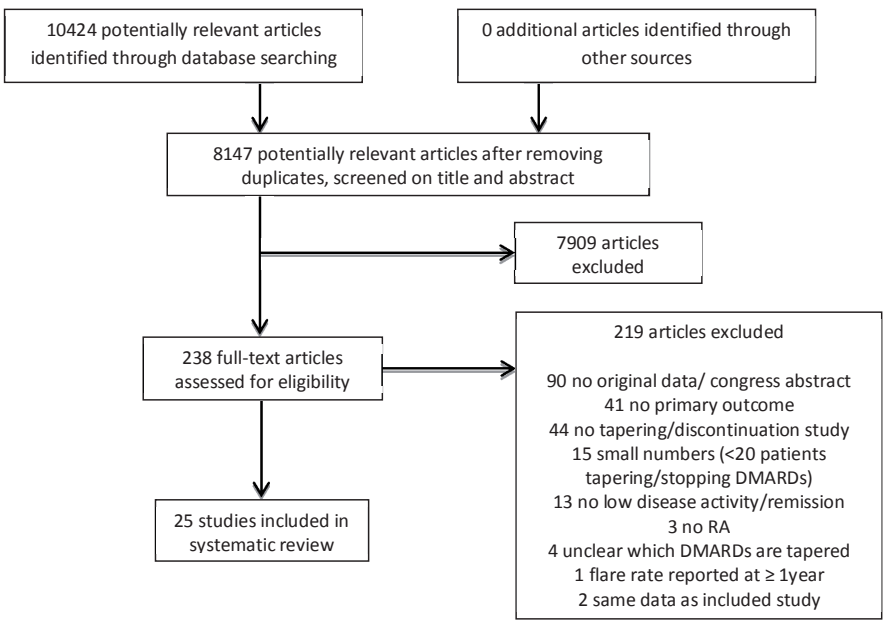



**Figure 1.** Flow diagram of study selection.

Included studies showed a large heterogeneity in the specific DMARDs, the concomitant treatment with other DMARDs, the remission criteria used to initiate tapering and follow-up time (Table 1). Sample sizes were relatively small (median 65, range 22-717).

**Table 1.** Overview of included studies.

| First Author, year of publication | Study design | Disease duration | Patients | Criteria used to initiate tapering / discontinuation | Medication tapered/ stopped | Co-medication |
|---|---|---|---|---|---|---|
| **Biological DMARDs: TNF inhibitors** | | | | | | |
| Smolen, 2013 (PRESERVE) (17) | RCT | mean 6.9 years | RA, 18-70 years old; etn+MTX 36 weeks | DAS28≤3.2 for 24 weeks | etn 50 mg / week + MTX, randomized 1:1:1 to A) etn 50 mg/ week +MTX, B) etn 25 mg/ week +MTX C) pbo + MTX | MTX ± gcs |
| van der Maas, 2012 (21) | single-arm trial | median 12 years | RA, 1987 ACR | DAS28<3.2 for 6 months | ifx, down-titration 3 mg/ kg every 8-12 weeks | ± sDMARDs |
| Heimans, 2013 (IMPROVED) (5) | single-arm trial | 8 months | early RA (ACR 2010) or undifferentiated arthritis | DAS44<1.6 for 4 months | ada 40 mg/ 2 weeks, MTX 25 mg/week, tapered† to MTX monotherapy | MTX |
| Maneiro, 2013 (13) | retrospective observational study | median 10.6 years | early and established RA (≤ and > 2 years of diagnosis respectively) | early RA: sustained‡ DAS28<2.6; established RA: sustained‡ DAS28<3.2 | ifx 5 to 3 mg/ kg and/or 6 to 8 weeks etn 7 to 10 days ada 2 to 3 weeks ctz 2 to 3 weeks | ± sDMARDs ± gcs |
| Tanaka, 2010 (RRR) (22) | single-arm trial | mean 5.9 years | RA, 1987 ACR | DAS28<3.2 for >24 weeks; prednisolone < 5 mg/day | ifx, stop | MTX |

| # patients tapered/ stopped | Flare definition | Flare % (n) / follow-up | Median / mean time to flare | Time to remission after flare | Radiological progression | Study limitations (items)[#] |
|---|---|---|---|---|---|---|
| 202 (full dose etn), 202 (half dose etn), 200 (pbo) | DAS28>3.2 at 52 weeks | 50 mg: 17.4% (35) 25 mg: 20.9% (42) placebo: 57.4% (113) / 1 year | - | - | group A:-0.06 u/year, B: 0.05 u/year, C: 0.60 u/year; A vs C was significant | 9, 11, 12,26; partly: 1 |
| 51 | reversed EULAR response criteria¶ | 54% (28) / 1 year | 200 days (median) | - | - | 9, 12,15,19, 26 |
| 26 | DAS44>1.6 | 35% (9) / 4 months | - | - | - | 9, 12, 14, 19, 27 |
| 54 (ada 9, ctz 7, etn 28, ifx 10) | DAS28 increase >20% *OR* increase in dose or frequency of bDMARDs, sDMARDs or gcs | all 19,1% (ada 30,8% ctz 50,0% etn 11,1% ifx 25,0%) / 1 year | ada 19 m etn 15,5 m ifx 16,5 m ctz not reported | - | - | 1, 5, 11-15, 19, 27 |
| 114 | ifx restarted within 1 year; DAS28≥3.2 at year 1 | 40% (46) / 1 year | 6.4 months (mean) | majority within 24 weeks | - | 11, 12, 19, 26; partly: 3, 9, 15 |

**Table 1.** Continued

| First Author, year of publication | Study design | Disease duration | Patients | Criteria used to initiate tapering / discontinuation | Medication tapered/ stopped | Co-medication |
|---|---|---|---|---|---|---|
| Van den Broek, 2011 (BeSt) (20) | single-arm trial | median 23 months | RA, 1987 ACR | DAS44<2.4 for 6 months | ifx, stop | MTX |
| Brocq, 2009 (8) | single-arm trial | mean 11.3 years | Inflammatory joint disease; 304/442 fulfilling 1987 ACR criteria | DAS28<2.6 for 6 months; DMARDs stable for 6 months; no NSAIDs; prednisolone < 5 mg | TNF-blocker (ifx, etn, ada), stop | sDMARDs |
| Harigai, 2012 (BRIGHT) (10) | retrospective cohort study | mean 10.3 years | RA | DAS28-CRP≤2.7 | ada, stop | MTX ± gcs |
| Tanaka, 2015 (HONOR) (19) | observational cohort (with control group) | mean 7.5 years (sd 10.2 years) | RA, 1987 ACR Inadequate response to MTX and/or sDMARDs | DAS28<2.6 for 6 months; Stable MTX dose ≥ 12 weeks; no gcs; no NSAIDs | ada 40 mg/ 2 weeks, stop | MTX |
| Smolen, 2014 (OPTIMA) (16) | RCT | < 1 year | early RA, 1987 ACR | DAS28-CRP<3.2 at week 22 and 26 | ada 40 mg / 2 weeks<br>A) stop<br>B) continue | MTX 20 mg/week<br>±NSAIDs<br>±gcs |

| | # patients tapered/ stopped | Flare definition | Flare % (n) / follow-up | Median / mean time to flare | Time to remission after flare | Radiological progression | Study limitations (items)[#] |
|---|---|---|---|---|---|---|---|
| | 104 | DAS44>2.4 | 20% (21) / 1 year | 17 months (median) | - | - | 9, 12,15,19, 26; partly: 1 |
| | 24 | DAS28>3.2 | 63% (15) / 1 year | 14.7 weeks (mean) | 5.6 weeks (mean) | - | 9, 12, 15, 19, 26, 27; partly: 11 |
| | 22 | DAS28-CRP >2.7 or restart of bDMARDs | 54% (12) / 1 year | - | - | - | 8, 9, 12, 15, 19, 23, 26, 27; partly: 5 |
| | A) 52<br>B) 23 (control) | DAS28≥3.2 | A) 40% (21)<br>B) 9% (2)<br>/ 1 year | - | Restart ada ± mtx:<br>90% LDA within 6 months;<br>100% LDA within 9 months | - | 9,14, 15, 19, 23, 27 |
| | A) 102<br>B) 105 | DAS28-CRP≥3.2 | A) 19% (19)<br>B) 9% (9)<br>/ 1 year | - | - | radiographic non-progression (ΔTSS≤0.05) from baseline to week 78:<br>A) 81%<br>B) 89%<br>(p=0.06) | 9, 12, 19 |

**Table 1.** Continued

| First Author, year of publication | Study design | Disease duration | Patients | Criteria used to initiate tapering / discontinuation | Medication tapered/ stopped | Co-medication |
|---|---|---|---|---|---|---|
| Iwamoto, 2014 (11) | observational cohort | 8.2 years | RA, 1987 ACR OR 2010 ACR/ EULAR | DAS28<2.6 | TNFi (ifx, etn, ada, gol, ctz), stop | ±MTX ±gcs |
| Emery, 2014 (9) | RCT | 6.8 months | early active disease; RA, 1987 ACR; MTX + biological naïve; etn + MTX for 52 weeks | DAS≤3.2 at week 39 AND DAS<2.6 at week 52 | etn 50 mg / week + MTX 10 -25 mg / week, randomized to: A) etn 25 mg / week + MTX B) MTX + pbo C) pbo + pbo for 39 weeks. Thereafter if DAS28≤3.2 all treatment was withdrawn. | ±gcs |
| Marks, 2015 (14) | prospective cohort | 129.5 months | RA, 2010 ACR/ EULAR; TNFi >1 year | DAS28≤2.6 + PDUS=0 > 6 months; no oral gcs | TNFi, tapered 1/3 (increased interval) | ±sDMARD |
| Raffeiner, 2014 (15) | RCT | 14.3 years | RA, 1987 ACR; failure traditional DMARDs; etn 25 mg 2x/week | DAS28<2.6 for ≥ 12 weeks | A) etn 25 mg / week B) etn 25 mg 2x / week | ±sDMARD ±NSAIDs ±gcs |

| | # patients tapered/ stopped | Flare definition | Flare % (n) / follow-up | Median / mean time to flare | Time to remission after flare | Radiological progression | Study limitations (items)[#] |
|---|---|---|---|---|---|---|---|
| | 32 | DAS28>3.2 & escalation of anti-rheumatic treatment | 38% (12) / 6 months | mean 14.8 weeks | - | - | 9, 11, 12, 14, 19, 26, 27; partly: 5, 15 |
| | A) 63<br>B) 65<br>C) 65 | DAS28≥2.6 | A) 21% (13)<br>B) 46% (30)<br>C) 62% (40)<br>/ 39 weeks | - | - | ΔmTSS (mean ±SE):<br>A) 0.1 ±0.1<br>B)-0.0 ±0.2<br>C) 0.4 ±0.2<br>/ 39 weeks<br>(p A vs B = 0.79<br>p A vs C = 0.48<br>p B vs C = 0.34) | 9, 17c, 19 |
| | 69 | DAS28≥2.6 OR PDUS≥1 OR according to patient | 63% (43) / 9 months | median 6 – 9 months | - | - | 9, 12, 14, 15, 17a, 18, 19, 26, 27; partly: 3 |
| | A) 159<br>B) 164 | DAS28>2.6 | A) 11% (18)<br>B) (not reported)<br>/ 1 year | - | - | ΔTSS= 0; >0 ;≥5<br>1 year:<br>A) 82%; 18%; 1%<br>B) 82%; 18%; 1%<br>2 years:<br>A) 85%; 16%; 1%<br>B) 80%; 20%; 1% | 9, 12, 15, 19, 24, 26 |

**Table 1.** Continued

| First Author, year of publication | Study design | Disease duration | Patients | Criteria used to initiate tapering / discontinuation | Medication tapered/ stopped | Co-medication |
|---|---|---|---|---|---|---|
| Kavanaugh, 2014 (12) | observational cohort | median 8 years | RA, discontinued first TNFi, no other previous bDMARD | CDAI≤10 | TNFi, stop | ±sDMARDs ±gcs |
| **Biological DMARDs: tocilizumab** | | | | | | |
| Nishimoto, 2013 (DREAM/ RESTORE) (24, 26) | Single-arm trial | median 7.8 years | RA, 1987 ACR; ≥20 years old | DAS28≤3.2 at 2-3 consecutive time points | tcz | ±NSAIDs ± oral gcs |
| Aguilar, 2013 (23) | prospective cohort | mean 13.7 years | RA, MTX + tcz for 5 years | DAS28<2.6 & SJC=0 | tcz 8mg/kg/4 weeks, stop | MTX |
| Van Herwaarden, 2014 (25) | retrospective cohort | median 10 years | RA, 1987 ACR OR 2010 ACR/ EULAR OR clinical diagnosis | DAS28<3.2 OR judgement rheumatologist | tcz 8 mg/kg/4 weeks to 4 mg/ kg/4 weeks | ±MTX ±sDMARD ±gcs |

| # patients tapered/ stopped | Flare definition | Flare % (n) / follow-up | Median / mean time to flare | Time to remission after flare | Radiological progression | Study limitations (items)[#] |
|---|---|---|---|---|---|---|
| 717 | CDAI>10 OR bDMARD initiation OR sDMARD initiation / dose escalation OR gcs initiaton / dose escalation | 26.6% (191) / 1 year | ≥ 20 months (median) | - | - | 8, 9, 15, 19, 26 |
| 187 | DAS28>3.2 at 2 consecutive observations | 86.6 % (162) / 1 year | - | 139 of 157 (88.5%) retreated with TCZ achieved DAS28<2.6 within 12 weeks | - | 12-15, 19 |
| 45 | SJC≥1 | 55% (25) / 1 year | 3 months (median) | - | - | 9, 12-15, 26, 27; partly: 3, 5 |
| 22 | DAS28>3.2 OR judgement rheumatologist | 41% (9) / 6 months | 7/9 (78%) within first 16 weeks | after dose-escalation 8/9 achieved LDA (clinical judgement) within 6 months; 1/9 LDA after 6 months | | 9, 12, 15, 26, 27 |

**Table 1.** Continued

| First Author, year of publication | Study design | Disease duration | Patients | Criteria used to initiate tapering / discontinuation | Medication tapered/ stopped | Co-medication |
|---|---|---|---|---|---|---|
| **Biological DMARDs: abatacept** | | | | | | |
| Emery, 2015 (AVERT) (27) | single-arm trial | ≤ 2years (symptoms) | clinical synovitis ≥ 2 joints for ≥ 8 weeks; ACPA positive; MTX naïve; ≥ 18 years | DAS28-CRP<3.2 at month 12 | A) aba 125 mg/ week + MTX 15-20 mg/ week<br>B) aba 125 mg/ week<br>C) MTX 15 – 20 mg/ week<br>Aba stopped immediately, MTX + steroids tapered over 1 month | ± gcs |
| Westhovens, 2014 (AGREE) (28) | RCT | ≤ 2years | early RA, seropositive, erosive | DAS28-ESR<2.6 at 1 year | aba 10 mg / kg i.v.<br>A) 5 mg / kg i.v.<br>B) 10 mg / kg i.v. | ±sDMARDs<br>±gcs |
| Takeuchi, 2014 (18) | prospective cohort with control | 9.6 years (A); 15.3 years (B) | RA, 1987 ACR; age ≥ 20 years; aba > 2 years | DAS28-CRP<2.3 | aba 10 mg/kg/ 4 weeks:<br>A) stop<br>B) continue | ±sDMARDs<br>±NSAIDs<br>±gcs |

| # patients tapered/ stopped | Flare definition | Flare % (n) / follow-up | Median / mean time to flare | Time to remission after flare | Radiological progression | Study limitations (items)[#] |
|---|---|---|---|---|---|---|
| A) 84<br>B) 66<br>C) 73 | DAS28-CRP≥3.2 | A) 75% (55)<br>B) 72% (36)<br>C) 83% (44)<br>/ 6 months | - | - | - | 9, 12, 14, 15, 17c, 19, 23, 26, 27; partly: 5, 8 |
| A) 50<br>B) 58 | DAS28-CRP≥3.2 at 2 visits OR additional DMARD required OR aba 10 mg required OR ≥2 courses of gcs | A) 34% (17)<br>B) 31% (18)<br>/ 1 year | - | restart aba 10 mg / kg: 3/4 remission within 1 year | - | 9, 27 |
| A) 34<br>B) 17 | DAS28-CRP>2.7 | A) 41% (14)<br>B) 6% (1)<br>/ 1 year | - | - | ΔmTSS:<br>A) 0.80 / year<br>B) 0.32 / year<br>(p=0.37) | 9, 12, 14, 15, 23, 27 |

**Table 1.** Continued

| First Author, year of publication | Study design | Disease duration | Patients | Criteria used to initiate tapering / discontinuation | Medication tapered/ stopped | Co-medication | |
|---|---|---|---|---|---|---|---|
| **Synthetic DMARDs** | | | | | | | |
| Fleischmann, 2005 (iRAMT) (4) | single-arm trial | mean 10.4 years | RA,1987 ACR | 40% reduction in TJC + SJC | MTX, tapering 5 mg/8 weeks to minimum of 5 mg/week | ifx ± gcs | |
| Heimans, 2013 (IMPROVED) (5) | single-arm trial | 8 months | early RA (ACR 2010) or undifferentiated arthritis | DAS44<1.6 for 4 months | prednisone 7.5 mg/day, ssz 2000 mg/day, hcq 400 mg/day, MTX 25 mg/ week; tapered in above order to MTX monotherapy | MTX | |
| Luis, 1999 (6) | RCT | mean 2.8 years | RA, 1987 ACR; functional class I or II; disease duration < 15 years | Clinical remission ACR criteria ≥ 6 months; stable dose weekly MTX ≥9 months | MTX, weekly-> 2-weekly | ±hcq ± gcs | |
| Ten Wolde, 1996 (7) | RCT | median 9 years | RA, 1987 ACR; age 18-85 years | Good therapeutic response ARA criteria (5/6); stable disease for 1 year; RX second-line drugs for 2 years; no previous unsuccessful attempt to discontinue second line drugs | sDMARDs (chl, hcq, pg, dpen, ssz, aza, MTX), stop | ± NSAIDs | 143 |

¶ DAS28 increase ≥ 1.2 compared to baseline at two consecutive visits with at least two weeks in between or DAS28 increase ≥ 0.6 if DAS28>3.2

† Mode of tapering was not described

‡ Remission duration was not further specified

# Study limitations (also see Supplement 3): reporting: items 1-9; external validity: items 11-13; internal validity/bias: items14-20; internal validity/confounding: items 21-26; power: item 27

| # patients tapered/ stopped | Flare definition | Flare % (n) / follow-up | Median / mean time to flare | Time to remission after flare | Radiological progression | Study limitations (items)[#] |
|---|---|---|---|---|---|---|
| 159 | loss of response (response defined as 40% reduction in TJC + SJC compared to baseline) | 42% (67) / 32 weeks | - | - | - | 9, 12, 15, 19; partly: 1, 5 |
| 30 | DAS44>1.6 | 63% (19) / 4 months | - | - | - | 9, 12, 14, 19, 27 |
| 25 | loss of remission (clinical criteria) | 8% (2) / 24 weeks | - | - | - | 2, 12, 14, 19, 27; partly: 3, 5, 24 |
| SJC≥3 and ≥2 additional criteria; clear clinical recurrence of synovitis | Overall: 37% (53)<br>hcq/chl: 33% (26)<br>pg: 33% (11)<br>ssz: 47% (8)<br>pen: 40% (4)<br>aza: 67% (2)<br>MTX 100% (2)<br>/ 1 year | - | 24/51 ( 47%) patients retreated with same cDMARD achieved ACR20 response within 3 months | - | 12, 19; partly: 3 | |

Abbreviations
aba = abatacept
ada = adalimumab
aza = azathioprine
bDMARDs = biologic disease modifying antirheumatic drugs
CDAI = clinical disease activity index
chl = chloroquine
CRP = C-reactive protein
ctz = certolizumab pegol
DAS = disease activity score
dpen = d-penicillamine
etn= etanercept
gcs = glucocorticoids
hcq = hydroxychloroquine
ifx = infliximab
mTSS = modified Total Sharp Score
MTX = methotrexate
NSAIDS = non-steroidal anti-inflammatory drug
pbo = placebo
PDUS = power doppler ultrasound
pen = penicillamine
pg = parenteral gold
RA = rheumatoid arthritis
RCT = randomized controlled trial
sDMARDs = synthetic disease modifying antirheumatic drugs
SJC = swollen joint count
ssz = sulphasalazine
TJC = tender joint count
TNFi = tumor necrosis factor inhibitor
tcz = tocilizumab
TSS = Total Sharp Score

**Table 2:** Reported flare rates among studies de-escalating TNF-blockers. Pooled estimates were calculated for studies categorized as having good and moderate quality separately and overall. Flare rates for study arms that were not included in the pooled analysis are shown as well.

| Study (arm), year | Medication | Charac-teristics | Follow-up | n | Flare rate (95% CI) | Forest plot |
|---|---|---|---|---|---|---|
| *Good quality* | | | | | | |
| Smolen (half dose), 2013 (17) | etn | r[1], p | 1 year | 202 | 0.21 (0.16-0.27) | |
| Smolen (stop), 2013 (17) | etn | s, p | 1 year | 200 | 0.57 (0.51-0.64) | |
| Tanaka, 2010 (22) | ifx | s, a | 1 year | 114 | 0.45 (0.36-0.54) | |
| van den Broek, 2011 (20) | ifx | s, a, e | 1 year | 104 | 0.20 (0.13-0.29) | |
| Smolen (stop), 2014 (16) | ada | s, a, e | 1 year | 102 | 0.19 (0.12-0.27) | |
| Raffeiner, 2014 (15) | etn | r[2], p | 1 year | 159 | 0.11 (0.07-0.17) | |
| Kavanaugh, 2014 (12) | TNFi | s, p | 1 year | 717 | 0.27 (0.24-0.30) | |
| Tanaka, 2015* (19) | ada | s, a | 1 year | 52 | 0.40 (0.28-0.54) | |
| **Pooled estimate** | | | | **1650** | **0.28 (0.19-0.40)[h1]** | |
| *Moderate quality* | | | | | | |
| van der Maas, 2012 (21) | ifx | r[3], p | 1 year | 51 | 0.55 (0.41-0.68) | |
| Maneiro, 2013 (13) | ada, ctz, etn, ifx | s, p | 1 year | 52 | 0.19 (0.11-0.32) | |
| Brocq, 2009 (8) | ifx, etn, ada | s, a | 1 year | 21 | 0.75 (0.53-0.89) | |
| Harigai, 2012 (10) | ada | s, a | 1 year | 22 | 0.55 (0.34-0.74) | |
| **Pooled estimate** | | | | **146** | **0.49 (0.27-0.73)[h2]** | |
| **Overall** | | | | **1796** | **0.34 (0.25-0.45)[h3]** | |

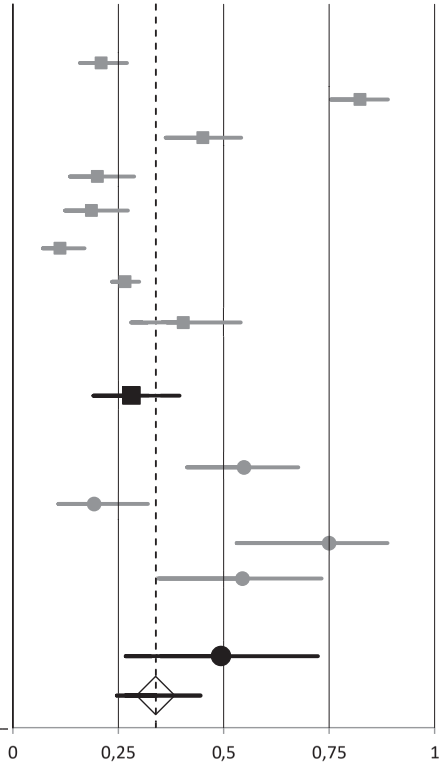
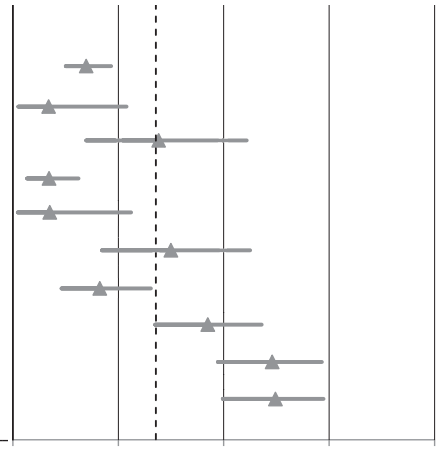


**Table 2:** Reported flare rates among studies de-escalating TNF-blockers. Pooled estimates were calculated for studies categorized as having good and moderate quality separately and overall. Flare rates for study arms that were not included in the pooled analysis are shown as well. (*continued*)

| Study (arm), year | Medication | Charac-teristics | Follow-up | n | Flare rate (95% CI) | Forest plot |
|---|---|---|---|---|---|---|
| *Not included in pooled analysis* | | | | | | |
| Smolen (full dose), 2013 (17) | etn | c, p | 1 year | 202 | 0.17 (0.12-0.23) | |
| Harigai (full dose), 2012 (10) | ada | c, a | 1 year | 24 | 0.08 (0.01-0.27) | |
| Heimans, 2013* (5) | ada | $r^4$, e | 4 months | 26 | 0.35 (0.17-0.56) | |
| Smolen (full dose), 2014 (16) | ada | c, a, e | 1 year | 105 | 0.09 (0.03-0.16) | |
| Tanaka (full dose), 2015 (19) | ada | c, a | 1 year | 23 | 0.09 (0.01-0.28) | |
| Iwamoto, 2014* (11) | TNFi | s, p | 6 months | 32 | 0.38 (0.21-0.56) | |
| Emery (etn half dose), 2014* (9) | etn | $r^1$, a, e | 39 weeks | 63 | 0.21 (0.12-0.33) | |
| Emery (etn stop), 2014* (9) | etn | s, a, e | 39 weeks | 65 | 0.46 (0.34-0.59) | |
| Emery (stop + MTX stop), 2014* (9) | etn | s, a, e | 39 weeks | 65 | 0.62 (0.49-0.73) | |
| Marks, 2015* (14) | TNFi | $r^5$, p | 9 months | 69 | 0.62 (0.50-0.74) | |



* = not pooled because flare rate was not estimated at 1 year
a = co-medication with sDMARDs in all patients
c = continued treatment (control arm)
e = early RA
h = heterogeneity: h1 = $I^2$:94.4; h2 = $I^2$:86.1; h3 = $I^2$: 93.1
n = no co-medication with sDMARDs
p = co-medication with sDMARDs in selected patients
$r^1$ = dose reduction: etn 50 mg/week, dose reduced to etn 25 mg/week
$r^2$ = dose reduction: etn 2x 25mg/week, dose reduced to etn 25mg/week
$r^3$ = dose reduction: ifx 3 mg/kg, tapered down 0.75 mg/kg every 8-12 weeks
$r^4$ = dose reduction: ada 40 mg/2 weeks, tapered down to mtx monotherapy
$r^5$ = dose reduction with 1/3 (by increasing interval *1.5)
s = stop

ada = adalimumab
sDMARDS = synthetic disease modifying anti-rheumatic drugs
ctz = certolizumab
etn = etanercept
ifx = infliximab
MTX = methotrexate
TNFi = tumor necrosis factor inhibitor

## Synthetic DMARDs

*Risk of disease flare*

Four studies (two RCTs, two single-arm trials) evaluated the de-escalation of sDMARDs (Table 1) (4-7). Reported flare rates after tapering methotrexate (MTX) ranged from 8% at 24 weeks (flare defined on clinical criteria) (6) to 42% at 32 weeks (loss of 40% reduction in swollen and tender joint counts compared to baseline) (4). In patients on triple DMARD therapy with prednisone, tapering of subsequent DMARDs (prednisone, sulphasalazine and hydroxychloroquine) to MTX monotherapy was evaluated (5). Sixty-three percent of patients lost response to therapy (defined as DAS>1.6) after 4 months (5). Ten Wolde et al. (7) defined flare as having ≥3 swollen joints while fulfilling ≥2 additional criteria (7) and found an overall flare rate of 37% at 1 year (see Table 1 for flare rates specified by sDMARD).

*Radiographic progression*

None of the included studies evaluated radiographic progression for sDMARDs.

*Time-to-flare*

None of the included studies evaluated time-to-flare for sDMARDs.

*Time-to-remission*

No data on time-to-remission was available. Ten Wolde found that 47% of patients re-treated with the same sDMARD achieved ACR20 response within 3 months (7).

## Biologic DMARDs: TNF inhibitors

*Risk of disease flare*

Fifteen studies (five single-arm trials, two retrospective cohort studies, four prospective cohort studies and four RCTs) evaluated the tapering or stopping of TNF-blockers (Table 1) (5, 8-21), four of which were in early RA (5, 9, 16, 20). A meta-analysis was performed on the 11 studies (10 study arms) de-escalating TNF-blockers reporting a flare rate at 1 year (Table 2). Overall heterogeneity was high ($I^2$: 93.1) with respect to patients (early versus established RA), de-escalation strategy, type of TNF-blocker, co-medication with sDMARDs. Pooled flare rates for the studies with a good (12, 15-17, 19, 20, 22) and moderate (8, 10, 13, 21) quality scores were 0.28 (95% CI 0.19-0.40) and 0.49 (95% CI 0.27-0.73) respectively and the overall flare rate was 0.34 (95% CI 0.25-0.45). Pooling studies on tapering versus stopping of TNF-blockers did not lead to different flare rates (Supplemental Table 1).

*Radiographic progression*

Three studies evaluated radiological progression by directly comparing groups of patients continuing and stopping treatment (16, 17) or de-escalating treatment to various extents (9). The PRESERVE study compared radiological progression between groups of patients continuing full-dose etanercept to patients switching to half-dose or stopping of etanercept (17). ΔmTSS was significantly higher in the group stopping etanercept (0.60 units/year) compared to the group continuing etanercept 50 mg/week (-0.06 units/year, p=0.026)). However, no significant difference was found between the group receiving etanercept 25 mg/week (0.05 units/year) compared to the full-dose or placebo groups (17). In the OPTIMA trial, patients with early RA were randomized to stop or continue adalimumab. After 1 year, there was no significant difference in the percentage of non-progressors (ΔTSS≤0.05) between groups (stop 81%, continue 89%, p=0.06) (16). Emery et al. compared three de-escalation strategies in early RA patients treated with MTX and etanercept: reducing etanercept to half dose, stopping etanercept and stopping both etanercept and MTX (9). After 39 weeks, mean ΔmTSS (±SE) were similar for all groups 0.1 (0.1),-0.0 (0.2) and 0.4 (0.2) respectively.

Three studies (19, 20, 22) evaluated radiographic progression by comparing patients experiencing a flare to those with sustained LDA/remission after stopping infliximab (20, 22) or adalimumab (19). The BeSt study reported a median damage progression of 0 units/year at 1 year in both groups (20), while the RRR study reported similar progression for the flare group (1.6 units/year) and the non-flare group (0.3 units/year, p=0.11) at 28 weeks (22). The HONOR study found that ΔmTSS increased from -0.74 to 0.85 / year in patients with a flare. Those with sustained LDA had equal ΔmTSS regardless of whether adalimumab was continued (19).

*Time-to-flare*

Eight studies de-escalating TNF-blockers (8, 11-14, 20-22)reported on the mean or median time-to-flare. Reported times-to-flare ranged from 14.7 weeks (mean) (8) to ≥20 months (median) (gentle tapering scheme) (12).

*Time-to-remission*

Three studies stopping TNF-blockers evaluated time-to-remission (8, 19, 22). In the RRR study restart of infliximab was effective in 70% of patients, of whom the majority reached DAS28<3.2 within 24 weeks (22). Brocq et al. found that all 15 patients regained remission after restarting the same TNF-blocker, 87% within 2 months (8). In the HONOR study, MTX dose-escalation was not effective in 75% of patients experiencing a flare, but after re-administration of adalimumab those patients regained LDA, 90% within 6 months (19).

## Biologic DMARDs: tocilizumab

*Risk of disease flare*

Three studies reported on the de-escalation of tocilizumab (23-25). The DREAM study reported a flare rate of 87% at 1 year for patients with low disease activity stopping tocilizumab and not using any concurrent DMARDs (24). Aguilar et al. found a flare rate of 55% one year after stopping tocilizumab in patients in remission with combination therapy of tocilizumab and MTX (23). Van Herwaarden et al. reported that after 6 months, 41% of patients lost LDA after dose reduction of tocilizumab from 8 mg/kg to 4 mg/kg every 4 weeks (25).

*Radiographic progression*

None of the included studies evaluated radiographic progression for tocilizumab.

*Time-to-flare*

Two studies de-escalating tocilizumab (23, 25) reported on time to flare. After stopping tocilizumab, 50% of flares occurred within 3 months (23), while in another study 78% of flares occurred within the first 4 months after dose reduction of tocilizumab (25).

*Time-to-remission*

In the DREAM/RESTORE study (88%), achieved DAS28 remission within 12 weeks after re-starting tocilizumab (24, 26). In the dose reduction study by van Herwaarden, all patients who experienced a flare achieved LDA after dose escalation, 89% within 6 months (25).

## Biologic DMARDs: abatacept

*Risk of disease flare*

De-escalation of abatacept was evaluated in 3 studies (18, 27, 28). In the AVERT study early initially active RA patients with LDA at one year entered the treatment withdrawal period in which all treatment was stopped. After 6 months, flare rates were 75% and 72% in the abatacept + MTX and abatacept monotherapy arms respectively (27). Dose reduction of abatacept to half dose in early RA patients was evaluated in the AGREE study (28). At 1 year 34% (half dose) and 31% (full dose) of patients experienced a flare (28). In a cohort of patients with established RA, Takeuchi et al. compared stopping and continuing abatacept (18). Flare rates at 1 year were 41% (stop) versus 6% (continuation) (18).

*Radiographic progression*

Only one study presented radiological data. Takeuchi et al. found no difference in radiographic progression after 1 year between the groups stopping (ΔmTSS = 0.80) and continuing (ΔmTSS = 0.32) abatacept (p=0.37) (18).

*Time-to-flare*

None of the included studies evaluated time-to-flare for abatacept.

*Time-to-remission*

Increasing abatacept from half dose to full dose after flare resulted in 75% of patients regaining remission within 1 year (28).

## DISCUSSION

Despite a large heterogeneity in primary studies, tapering down or stopping synthetic or biologic DMARD therapy without experiencing an immediate flare of disease is possible in more than one third of patients with low disease activity or remission. De-escalation of TNF-blockers suggest even better results with flare rates at 1 year of 0.26 (95% CI 0.17-0.39) for good quality studies and 0.49 (95% CI 0.27-0.73) for moderate quality studies in the pooled analysis. Furthermore, evidence from two well executed RCTs suggests that reducing TNF-inhibitors to half dose results in a lower risk of flare (≈20%) compared to stopping (≈50%) (9, 17) and is possibly non-inferior to full dose continuation (17). Precaution should be taken in the decision to taper medication as evidence on radiographic progression is limited. Only 5 studies presented radiographic data comparing patients continuing and stopping bDMARDs, of which the PRESERVE study found a significantly higher rate of radiographic progression in the stop group versus the continuation group (17). In three other studies (9, 16, 18), a trend for slightly more progression was found for the discontinuation versus the continuation arms, but differences were not significant. However, it should be emphasized that included studies were not powered to detect differences in radiographic progression.

Time needed to regain remission after the occurrence of a flare was evaluated in six studies stopping bDMARDs (8, 19, 22, 24, 25, 28). The majority of patients regained a state of low disease activity within 2-6 months after reinitiating therapy with the same bDMARD. No data were available for sDMARDs. Whether de-escalation of TNF-blockers leads to increased immunogenicity and formation anti-drug antibodies remains unclear and should be subject of further study, as the formation of such antibodies could lead to treatment inefficacy on re-introducing the TNF-blocker after a flare (29).

Two RCTs found a lower risk of flare for dose reduction versus complete stop of etanercept (9, 17) This was less clear when we pooled the flare rates among study arms tapering versus immediately stopping TNF-blockers. Pooling resulted in a small but insignificant difference (flare rate of 0.31 versus 0.38 respectively), but a difference may well have been missed because of heterogeneity among studies. Among included studies in early RA patients, flare rates for bDMARDs (9, 16, 20, 27, 28) are not consistently lower

compared to those in studies in patients with established RA. A discussion on risk factors for flare that were addressed in the primary studies is provided in Supplement 4.

Time to flare was assessed in studies de-escalating bDMARDs only and ranged widely (mean 14.7 weeks – median ≥20 months) across studies (8, 11-14, 20-23, 25). No relation could be observed between use of concomitant DMARDs or de-escalation strategy and time to flare.

A risk of bias assessment was performed (3) (see Supplement 3) to assess the internal validity of the primary studies and to see whether this would influence the observed flare rate. In the meta-analysis of TNF de-escalation, good quality studies showed lower flare rates compared to moderate quality studies. No single quality assessment item discriminated well between good and moderate quality studies, except for sample size, which was consistently larger in good quality studies. Higher study quality was observed in the more recent studies as they were more often randomized controlled trials compared to earlier cohort studies that were using existing data not necessarily collected with the aim to evaluate de-escalation strategies.

Three systematic (30-32) and two narrative (33, 34) reviews have previously been published on the de-escalation of both bDMARDs (30, 32, 34) and sDMARDs (31, 33). While overlap exists between our review and those previously published, we are the first systematic review with quality assessment addressing both sDMARDs and bDMARDs, performing a pooled analysis on TNF-inhibitors. Regarding sDMARDs the authors were reluctant to say that part of the patients could de-escalate treatment given the higher flare rates compared to treatment continuation (31, 33). Considering bDMARDs, in line with our findings, Yoshida (32) reported that studies showed large heterogeneity, Tanaka (34) and Navarro-Millan (30) concluded that discontinuation is possible in RA patients.

This review has several strengths and weaknesses. We synthesized all available data to be able to answer clinically relevant questions regarding de-escalation of DMARDs, despite the underlying heterogeneity in the primary studies. For de-escalation of TNF-blockers data was meta-analyzed, resulting in a different flare rate between good and moderate quality studies. This should be interpreted with caution due to underlying differences in study designs. Relevant publications could have been missed, although we performed an extensive systematic search in various database without the use of language restrictions. Regarding radiographic progression, a major limitation of the primary studies is that they were not powered to detect differences in progression rates among groups. To address this, data from adequately powered cohort studies and RCTs, using uniform definitions for initiation of de-escalation and flare, is needed.

## CONCLUSION

Despite a large heterogeneity between studies, our overall results suggest that more than one third of patients with low disease activity or remission may taper or stop DMARD treatment without experiencing a flare within the first year. Limited radiological data suggests progression after treatment de-escalation remains low, but data is needed from adequately powered cohorts or RCTs.

## ACKNOWLEDGEMENTS

We thank Gerdien de Jonge and Wichor Bramer, librarians at the Erasmus Medical Center, for their assistance performing our search strategy.

**Supplement 1.** Search strategies.

*Embase (including Medline)*

('rheumatoid arthritis'/de OR ((rheuma* NEXT/1 arthrit*) OR (RA AND (rheuma* OR arthrit*))):ab,ti) AND ('disease modifying antirheumatic drug'/exp OR (DMARD* OR (disease NEAR/3 modif*) OR methotrexat* OR metotrex* OR mexate OR amethopterin* OR ametopterin* OR emthexat* OR emtrexat* OR ledertrexat* OR MTX OR novatrex OR rheumatrex OR leflunomide OR Arava OR arabloc OR salazosulfapyridin* OR salicylazosulfapyridin* OR sulfasalazin* OR Azulfidin* OR Sulfazin* OR Salazopyrin* OR sulphasalazin* OR sulphazin* OR chloroquin* OR aralen* OR arthrochin* OR nivaquin* OR hydroxychloroquin* OR hydroxychlorochin* OR HCQ OR plaquenil* OR ercoquin* OR chlorochin* OR quinolin* OR quensyl* OR penicillamin* OR dimethylcystein* OR cuprimin* OR depen* OR gold* OR monogold* OR aurothiomalat* OR myochrysin* OR tauredon* OR organogold* OR azathioprin* OR azothioprin* OR imuran* OR immuran* OR cyclosporin* OR Neoral* OR Gengraf* OR Sandimmun* OR CyA OR etanercept* OR Enbrel* OR ((***TNF* OR factor*) NEAR/3 (***block* OR antagon* OR anti* OR inhibit* OR 'fusion protein'***)) OR TNFis** OR adalimumab* OR Humira* OR Trudexa* OR certolizumab* OR Cimzia* OR CDP870 OR 'CDP 870' OR golimumab* OR Simponi OR infliximab* OR ((Mab OR monoclonal) NEAR/3 cA2) OR Remicade OR Avakine OR Revellex OR abatacept* OR Orencia* OR 'BMS 188667' OR BMS188667 OR CTLA4 OR 'CTLA 4' OR belatacept* OR BMS224818 OR 'BMS 224818' OR Nulojix* OR (('interleukin 1' OR interleukin1 OR 'il 1' OR Il1 OR 'interleukin 6' OR interleukin6 OR 'il 6' OR Il6) NEAR/3 (block* OR antagon* OR anti* OR inhibit*)) OR Antril* OR Kineret* OR Anakinra* OR rituximab* OR Mabthera OR Rituxan OR Reditux* OR CD20 OR 'CD 20' OR tocilizumab* OR Actemra* OR Roactemra* OR Atlizumab* OR biological* OR Tetracyclin* OR Minocyclin* OR Azithromycin* OR Doxycyclin* OR cyclophosphamid* OR Cytoxan* OR Endoxan* OR tacrolimus* OR Prograf):ab,ti,de) AND ('drug dose reduction'/de OR 'drug dose titration'/de OR 'treatment withdrawal'/de OR ((dos* OR treatm* OR therap* OR medic*) NEAR/5 (reduc* OR adjust* OR withdraw* OR withhold* OR withheld* OR stop* OR taper* OR titrat* OR discontin* OR cessat* OR lower* OR retract* OR ceas* OR diminish* OR deescal* OR 'de escalation' OR 'de escalations' OR 'de escalating' OR 'de escalate' OR 'de escalated')):ab,ti)

*OVID-SP (Medline)*

("Arthritis, Rheumatoid"/ OR ((rheuma* ADJ arthrit*) OR (RA AND (rheuma* OR arthrit*))).ab,ti.) AND ((DMARD* OR (disease ADJ3 modif*) OR methotrexat* OR metotrex* OR mexate OR amethopterin* OR ametopterin* OR emthexat* OR emtrexat* OR ledertrexat* OR MTX OR novatrex OR rheumatrex OR leflunomide OR Arava OR arabloc OR salazosulfapyridin* OR salicylazosulfapyridin* OR sulfasalazin* OR Azulfidin* OR Sulfazin* OR Salazopyrin* OR sulphasalazin* OR sulphazin* OR chloroquin* OR aralen* OR arthrochin* OR nivaquin* OR hydroxychloroquin* OR hydroxychlorochin* OR HCQ OR plaquenil* OR ercoquin* OR chlorochin* OR quinolin* OR quensyl* OR penicillamin* OR dimethylcystein* OR cuprimin* OR depen* OR gold* OR aurothiomalat* OR myochrysin* OR tauredon* OR organogold* OR azathioprin* OR azothioprin* OR imuran* OR immuran* OR cyclosporin* OR Neoral* OR Gengraf* OR Sandimmun* OR CyA OR etanercept* OR Enbrel* OR "TNFR-Fc fusion protein" OR ((***TNF* OR factor*) ADJ3 (***block* OR antagon* OR anti* OR inhibit****)) OR TNFis** OR adalimumab* OR Humira* OR Trudexa* OR certolizumab* OR Cimzia* OR CDP870 OR "CDP 870" OR golimumab* OR Simponi OR infliximab* OR ((Mab OR monoclonal) ADJ3 cA2) OR Remicade OR Avakine OR Revellex OR abatacept* OR Orencia* OR "BMS 188667" OR BMS188667 OR CTLA4 OR "CTLA 4" OR belatacept* OR BMS224818 OR "BMS 224818" OR Nulojix* OR (("interleukin 1" OR interleukin1 OR "il 1" OR Il1 OR "interleukin 6" OR interleukin6 OR "il 6" OR Il6) ADJ3 (block* OR antagon* OR anti* OR inhibit*)) OR Antril* OR Kineret* OR Anakinra* OR rituximab* OR Mabthera OR Rituxan OR Reditux* OR CD20 OR "CD 20" OR tocilizumab* OR Actemra* OR Roactemra* OR Atlizumab* OR biological* OR Tetracyclin* OR Minocyclin* OR Azithromycin* OR Doxycyclin* OR cyclophosphamid* OR Cytoxan* OR Endoxan* OR tacrolimus* OR Prograf**)**.mp.) AND ("Dose response relationship, Drug"/ OR **"**Withholding Treatment"/ OR ((dos* OR treatm* OR therap* OR medic*) ADJ5 (reduc* OR adjust* OR withdraw* OR withhold* OR withheld* OR stop* OR taper* OR titrat* OR discontin* OR cessat* OR lower* OR retract* OR ceas* OR diminish* OR (de ADJ escalat*))).ab,ti.)

*Cochrane Central*

(((rheuma* NEXT/1 arthrit*) OR (RA AND (rheuma* OR arthrit*))):ab,ti) AND ((DMARD* OR (disease NEAR/3 modif*) OR methotrexat* OR metotrex* OR mexate OR amethopterin* OR ametopterin* OR emthexat* OR emtrexat* OR ledertrexat* OR MTX OR novatrex OR rheumatrex OR leflunomide OR Arava OR arabloc OR salazosulfapyridin* OR salicylazosulfapyridin* OR sulfasalazin* OR Azulfidin* OR Sulfazin* OR Salazopyrin* OR sulphasalazin* OR sulphazin*

OR chloroquin* OR aralen* OR arthrochin* OR nivaquin* OR hydroxychloroquin* OR hydroxychlorochin* OR HCQ OR plaquenil* OR ercoquin* OR chlorochin* OR quinolin* OR quensyl* OR penicillamin* OR dimethylcystein* OR cuprimin* OR depen* OR gold* OR monogold* OR aurothiomalat* OR myochrysin* OR tauredon* OR organogold* OR azathioprin* OR azothioprin* OR imuran* OR immuran* OR cyclosporin* OR Neoral* OR Gengraf* OR Sandimmun* OR CyA OR etanercept* OR Enbrel* OR ((***TNF* OR factor*) NEAR/3 (***block* OR antagon* OR anti* OR inhibit* OR "fusion protein"***)) OR TNFis**** OR adalimumab* OR Humira* OR Trudexa* OR certolizumab* OR Cimzia* OR CDP870 OR "CDP 870" OR golimumab* OR Simponi OR infliximab* OR ((Mab OR monoclonal) NEAR/3 cA2) OR Remicade OR Avakine OR Revellex OR abatacept* OR Orencia* OR "BMS 188667" OR BMS188667 OR CTLA4 OR "CTLA 4" OR belatacept* OR BMS224818 OR "BMS 224818" OR Nulojix* OR (("interleukin 1" OR interleukin1 OR "il 1" OR Il1 OR "interleukin 6" OR interleukin6 OR "il 6" OR Il6) NEAR/3 (block* OR antagon* OR anti* OR inhibit*)) OR Antril* OR Kineret* OR Anakinra* OR rituximab* OR Mabthera OR Rituxan OR Reditux* OR CD20 OR "CD 20" OR tocilizumab* OR Actemra* OR Roactemra* OR Atlizumab* OR biological* OR Tetracyclin* OR Minocyclin* OR Azithromycin* OR Doxycyclin* OR cyclophosphamid* OR Cytoxan* OR Endoxan* OR tacrolimus* OR Prograf):ab,ti,kw) AND (((dos* OR treatm* OR therap* OR medic*) NEAR/5 (reduc* OR adjust* OR withdraw* OR withhold* OR withheld* OR stop* OR taper* OR titrat* OR discontin* OR cessat* OR lower* OR retract* OR ceas* OR diminish* OR deescal* OR "de escalation" OR "de escalations" OR "de escalating" OR "de escalate" OR "de escalated")):ab,ti)

*PubMed*

(((rheuma*[tiab] AND arthrit*[tiab]) OR (RA[tiab] AND (rheuma*[tiab] OR arthrit*[tiab])))) AND ((DMARD*[tiab] OR (disease[tiab] AND modif*[tiab]) OR methotrexat*[tiab] OR metotrex*[tiab] OR mexate OR amethopterin*[tiab] OR ametopterin*[tiab] OR emthexat*[tiab] OR emtrexat*[tiab] OR ledertrexat*[tiab] OR MTX[tiab] OR novatrex[tiab] OR rheumatrex[tiab] OR leflunomide[tiab] OR Arava[tiab] OR arabloc[tiab] OR salazosulfapyridin*[tiab] OR salicylazosulfapyridin*[tiab] OR sulfasalazin*[tiab] OR Azulfidin*[tiab] OR Sulfazin*[tiab] OR Salazopyrin*[tiab] OR sulphasalazin*[tiab] OR sulphazin*[tiab] OR chloroquin*[tiab] OR aralen*[tiab] OR arthrochin*[tiab] OR nivaquin*[tiab] OR hydroxychloroquin*[tiab] OR hydroxychlorochin*[tiab] OR HCQ OR plaquenil*[tiab] OR ercoquin*[tiab] OR chlorochin*[tiab] OR quinolin*[tiab] OR quensyl*[tiab] OR penicillamin*[tiab] OR dimethylcystein*[tiab] OR cuprimin*[tiab] OR depen*[tiab] OR gold[tiab] OR aurothiomalat*[tiab] OR myochrysin*[tiab] OR tauredon*[tiab] OR organogold*[tiab] OR azathioprin*[tiab] OR azothioprin*[tiab] OR imuran*[tiab] OR immuran*[tiab] OR cyclosporin*[tiab] OR Neoral*[tiab] OR Gengraf*[tiab] OR Sandimmun*[tiab] OR CyA OR etanercept*[tiab] OR Enbrel*[tiab] OR TNFR-Fc fusion protein[tiab] OR ((TNF*[tiab] OR factor*[tiab]) AND (block*[tiab] OR antagon*[tiab] OR anti*[tiab] OR inhibit*[tiab])) OR TNFis*[tiab] OR adalimumab*[tiab] OR Humira*[tiab] OR Trudexa*[tiab] OR certolizumab*[tiab] OR Cimzia*[tiab] OR CDP870 OR CDP 870 OR golimumab*[tiab] OR Simponi[tiab] OR infliximab*[tiab] OR ((Mab[tiab] OR monoclonal[tiab]) AND cA2[tiab]) OR Remicade[tiab] OR Avakine[tiab] OR Revellex[tiab] OR abatacept*[tiab] OR Orencia*[tiab] OR BMS 188667[tiab] OR BMS188667[tiab] OR CTLA4[tiab] OR CTLA 4[tiab] OR belatacept*[tiab] OR BMS224818[tiab] OR BMS 224818[tiab] OR Nulojix*[tiab] OR ((interleukin 1[tiab] OR interleukin1[tiab] OR il 1[tiab] OR Il1[tiab] OR interleukin 6[tiab] OR interleukin6[tiab] OR il 6[tiab] OR Il6[tiab]) AND (block*[tiab] OR antagon*[tiab] OR anti*[tiab] OR inhibit*[tiab])) OR Antril*[tiab] OR Kineret*[tiab] OR Anakinra*[tiab] OR rituximab*[tiab] OR Mabthera[tiab] OR Rituxan[tiab] OR Reditux*[tiab] OR CD20[tiab] OR CD 20[tiab] OR tocilizumab*[tiab] OR Actemra*[tiab] OR Roactemra*[tiab] OR Atlizumab*[tiab] OR biological*[tiab] OR Tetracyclin*[tiab] OR Minocyclin*[tiab] OR Azithromycin*[tiab] OR Doxycyclin*[tiab] OR cyclophosphamid*[tiab] OR Cytoxan*[tiab] OR Endoxan*[tiab] OR tacrolimus*[tiab] OR Prograf)) AND (((dos*[tiab] OR treatm*[tiab] OR therap*[tiab] OR medic*[tiab]) AND (reduc*[tiab] OR adjust*[tiab] OR withdraw*[tiab] OR withhold*[tiab] OR withheld*[tiab] OR stop*[tiab] OR taper*[tiab] OR titrat*[tiab] OR discontin*[tiab] OR cessat*[tiab] OR lower*[tiab] OR retract*[tiab] OR ceas*[tiab] OR diminish*[tiab] OR (de escalat*[tiab])))) AND (publisher[sb] OR 2012/11/20:3000[mhda])

**Supplement 2.** Modification to Downs and Black's list (3) used for quality assessment.

1) Is the hypothesis/aim/objective of the study clearly described?
yes/no/partly/unclear

2) Are the main outcomes to be measured clearly described in the introduction or methods section?
yes/no/partly/unclear

3) Are the characteristics of the patients included in the study clearly described?
yes/no/partly/unclear

4) Are the interventions of interest clearly described?
yes/no/partly/unclear

5) Are the distributions of principal confounders in each group of subjects clearly described?
yes/no/partly/unclear

6) Are the main findings of the study clearly described?
yes/no/partly/unclear

7) [Omitted, not relevant for outcome flare rate]

8) Have all important adverse events that may be a consequence of the intervention been reported?
yes/no/partly/unclear/NA

9) Have the characteristics of patients lost to follow-up been reported?
yes/no/partly/unclear

10) [Omitted, not relevant for outcome flare rate]

11) Were the studies asked to participate in the study representative of the entire population from which they were recruited?
yes/no/partly/unclear

12) Were those subjects who were prepared to participate representative of the entire population from which they were recruited?
yes/no/partly/unclear

13) Were the staff, places and facilities where patients were treated, representative of the treatment the majority of patients receive?
yes/no/partly/unclear

14) Was an attempt made to blind study subjects to the intervention they received?
yes/no/partly/unclear/NA

15) Was an attempt made to blind those measuring the main outcomes of the intervention?
yes/no/partly/unclear

16) [Omitted, not relevant for de-escalation studies]

17) a) In trials and cohort studies, doe the analyses adjust for different lengths of follow-up of patients, (…)?
yes/no/partly/unclear/NA
b) Was the follow-up time with respect to flares adequate?
yes/no/partly/unclear
c) Was the follow-up time with respect to radiological progression adequate?
yes/no/partly/unclear/NA

18) Were the statistical tests used to assess the main outcomes appropriate?
yes/no/partly/unclear

19) Was compliance with the intervention reliable?
yes/no/partly/unclear

20) Were the main outcome measures used accurate (valid and reliable?)
yes/no/partly/unclear

21) Were the patients in different intervention groups (…) recruited from the same population?
yes/no/partly/unclear/NA

22) Were the study subjects in different intervention groups (…) recruited over the same period of time?
yes/no/partly/unclear/NA

23) Were the study subjects randomized to intervention groups?
yes/no/partly/unclear/NA

24) Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?
yes/no/partly/unclear/NA

25) [Omitted, not relevant for de-escalation studies]

26) Were losses of patients to follow-up taken into account?
yes/no/partly/unclear

27) Was the study sample size ≥ 100, so that a flare rate of 0.5 could be estimated with such precision that the size of the 95% confidence interval is less than 0.2?
yes/no/partly/unclear

**Supplement 3.** Quality Assessment.

***sDMARDs***

| | (6) Luis 1999 | (4) Fleischmann 2005 | (5) Heimans 2013 | (7) ten Wolde 1996 |
|---|---|---|---|---|
| Flare rate | 8% | 42% | 35% | 37% |
| Study design | RCT | single-arm | single-arm | RCT |
| DMARD | conventional | conventional | conventional/ TNF-blocker | conventional |
| 1 | yes | Partially | yes | yes |
| 2 | no | Yes | yes | yes |
| 3 | partially | Yes | yes | partially |
| 4 | yes | Yes | yes | yes |
| 5 | partly | Partially | yes | yes |
| 6 | yes | Yes | yes | yes |
| 7 | xxxxxxxxxxxx | xxxxxxxxxxxx | xxxxxxxxxxxx | xxxxxxxxxxxx |
| 8 | yes | Yes | NA | yes |
| 9 | yes | Unclear | no | yes |
| 10 | xxxxxxxxxxxx | xxxxxxxxxxxx | xxxxxxxxxxxx | xxxxxxxxxxxx |
| 11 | yes | Yes | yes | yes |
| 12 | unclear | unclear | unclear | unclear |
| 13 | yes | Yes | yes | yes |
| 14 | no | NA | no | yes |
| 15 | yes | Unclear | yes | yes |
| 16 | xxxxxxxxxxxx | xxxxxxxxxxxx | xxxxxxxxxxxx | xxxxxxxxxxxx |
| 17a | yes | NA | yes | yes |
| 17b | yes | Yes | yes | yes |
| 17c | NA | NA | yes | NA |
| 18 | yes | Yes | yes | yes |
| 19 | unclear | Unclear | unclear | unclear |
| 20 | yes | Yes | yes | yes |
| 21 | yes | NA | yes | yes |
| 22 | yes | NA | yes | yes |
| 23 | yes | NA | yes | yes |
| 24 | partly | NA | yes | Yes |
| 25 | xxxxxxxxxxxx | xxxxxxxxxxxx | xxxxxxxxxxxx | Xxxxxxxxxxxx |
| 26 | yes | Yes | yes | Yes |
| 27 | no | yes | no | Yes |

*TNF-inhibitors - 1*

| | (13) Maneiro 2013 | (10) Harigai 2012 | (21) van der Maas 2012 | (8) Brocq 2009 | (22) Tanaka 2010 | (20) van den Broek 2011 | (17) Smolen 2013 |
|---|---|---|---|---|---|---|---|
| Flare rate | 19.1% | 54% | 54% | 63% | 40% | 20% | 57.4% ; 20.9% |
| Study design | cohort | cohort | single-arm | single-arm | single-arm | single-arm | RCT |
| DMARD | TNF-blocker | TNF-blocker | TNF-blocker | TNF-blocker | TNF-blocker | TNF-blocker | TNF-blocker |
| | moderate | moderate | moderate | moderate | good | good | good |
| 1 | unclear | Yes | Yes | Yes | Yes | Partially | partly |
| 2 | yes | Yes | Yes | Yes | Yes | Yes | yes |
| 3 | yes | Yes | Yes | Yes | Partially | Yes | yes |
| 4 | yes | Yes | Yes | Yes | Yes | Yes | yes |
| 5 | unclear | Partially | Yes | Yes | Yes | Yes | yes |
| 6 | yes | Yes | Yes | Yes | Yes | Yes | yes |
| 7 | xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx |
| 8 | yes | No | Yes | Yes | Yes | Yes | yes |
| 9 | yes | Unclear* | Unclear* | Unclear* | Partially | Unclear* | no |
| 10 | xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx |
| 11 | unclear | Yes | Yes | Partially | Unclear | Yes | unclear |
| 12 | unclear | unclear | unclear | unclear | Unclear | unclear | unclear |
| 13 | unclear | Yes | Yes | Yes | Yes | Yes | yes |
| 14 | no | NA | NA | NA | NA | NA | yes |
| 15 | no | Unclear | Unclear | Unclear | Partially | Unclear | yes |
| 16 | xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx |
| 17a | NA | NA | NA | NA | NA | NA | yes |
| 17b | yes | Yes | Yes | Yes | Yes | Yes | yes |
| 17c | NA | NA | NA | Yes | Yes | Yes | yes |
| 18 | yes | Yes | Yes | Yes | Yes | Yes | yes |
| 19 | unclear | Unclear | Unclear | Unclear | Unclear | Unclear | yes |
| 20 | yes | Yes | Yes | Yes | Yes | Yes | yes |
| 21 | NA | Yes | NA | NA | NA | NA | yes |
| 22 | NA | Yes | NA | NA | NA | NA | yes |
| 23 | NA | No | NA | NA | NA | NA | yes |
| 24 | NA | NA | NA | NA | NA | NA | yes |
| 25 | xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx |
| 26 | yes | Unclear* | Unclear* | Unclear* | Unclear | Unclear* | unclear |
| 27 | no | no | no | no | yes | yes | yes |

| | (16) Smolen 2014 | (12) Kavanaugh 2014 | (15) Raffeiner 2014 |
|---|---|---|---|
| Flare rate | 19% | 26.60% | 11% |
| Study design | RCT | observational | RCT |
| DMARD | TNF-blocker | TNF-blocker | TNF-blocker |
| | good | good | good |
| 1 | Yes | Yes | Yes |
| 2 | Yes | Yes | Yes |
| 3 | Yes | Yes | Yes |
| 4 | Yes | Yes | Yes |
| 5 | Yes | Yes | Yes |
| 6 | Yes | Yes | Yes |
| 7 | xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx |
| 8 | Yes | No | Yes |
| 9 | no | No | No |
| 10 | xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx |
| 11 | yes | yes | Yes |
| 12 | unclear | yes | unclear |
| 13 | Yes | yes | Yes |
| 14 | Yes | Not Applicable | Yes |
| 15 | Yes | No | unclear |
| 16 | xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx |
| 17a | Yes | Yes | Yes |
| 17b | Yes | Yes | Yes |
| 17c | Yes | Not Applicable | Yes |
| 18 | Yes | Yes | Yes |
| 19 | Unclear | No | unclear |
| 20 | Yes | Yes | Yes |
| 21 | Yes | Not Applicable | Yes |
| 22 | Yes | Not Applicable | Yes |
| 23 | Yes | Not Applicable | Yes |
| 24 | Yes | Not Applicable | unclear |
| 25 | xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx |
| 26 | Yes | No | unclear |
| 27 | Yes | yes | Yes |

| (19) Tanaka 2015 | (11) Iwamoto 2014 | (9) Emery 2014 | (14) Marks 2015 |
|---|---|---|---|
| 40% | 38% | 21%; 46%; 64% | 63% |
| cohort | cohort | RCT | cohort |
| TNF-blocker | TNF-blocker | TNF-blocker | TNF-blocker |
| no pooling | no pooling | no pooling | no pooling |
| Yes | Yes | Yes | Yes |
| Yes | Yes | Yes | Yes |
| Yes | Yes | Yes | Partially |
| Yes | Yes | Yes | Yes |
| Yes | Partially | Yes | Yes |
| Yes | Yes | Yes | Yes |
| xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx |
| Yes | yes | Yes | yes |
| unclear | no | unclear | no |
| xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx |
| Yes | unclear | Yes | yes |
| Yes | unclear | Yes | no |
| Yes | yes | Yes | yes |
| No | no | Yes | no |
| No | Partially | Yes | unclear |
| xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx |
| Yes | NA | Yes | unclear |
| Yes | Yes | Yes | yes |
| Yes | NA | no | NA |
| Yes | Yes | Yes | unclear |
| unclear | unclear | unclear | unclear |
| Yes | Yes | Yes | Yes |
| Yes | NA | Yes | Yes |
| Yes | NA | Yes | Yes |
| No | NA | Yes | NA |
| NA | NA | Yes | NA |
| xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx |
| Yes | unclear | Yes | no |
| no | No | Yes | no |

*Tocilizumab*

| | (23) Aguilar 2013 | (24) Nishimoto 2014 | (25) van Herwaarden 2014 |
|---|---|---|---|
| Flare rate | 55% | 86.6% | 41% |
| Study design | cohort | single-arm | cohort |
| DMARD | tocilizumab | tocilizumab | tocilizumab |
| 1 | yes | yes | yes |
| 2 | yes | yes | yes |
| 3 | partially | yes | yes |
| 4 | yes | yes | yes |
| 5 | partly | yes | yes |
| 6 | yes | yes | yes |
| 7 | xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx |
| 8 | yes | yes | yes |
| 9 | no | yes | unclear |
| 10 | xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx |
| 11 | yes | yes | yes |
| 12 | unclear | unclear | unclear |
| 13 | unclear | unclear | yes |
| 14 | no | no | NA |
| 15 | no | no | no |
| 16 | xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx |
| 17a | NA | NA | yes |
| 17b | yes | yes | yes |
| 17c | NA | NA | NA |
| 18 | yes | yes | yes |
| 19 | yes | unclear | yes |
| 20 | yes | yes | yes |
| 21 | NA | NA | NA |
| 22 | NA | NA | NA |
| 23 | NA | NA | NA |
| 24 | NA | NA | NA |
| 25 | xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx |
| 26 | unclear | yes | unclear |
| 27 | no | yes | no |

*Abatacept*

| (27) Emery 2015 | (28) Westhovens 2014 | (18) Takeuchi 2014 |
|---|---|---|
| 75%; 72%; 83% | 34% | 41% |
| single-arm | RCT | cohort |
| abatacept | abatacept | abatacept |
| Yes | yes | yes |
| Yes | yes | yes |
| Yes | yes | yes |
| Yes | yes | yes |
| Partially | yes | yes |
| Yes | yes | yes |
| xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx |
| Partially | yes | yes |
| no | no | no |
| xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx |
| yes | yes | yes |
| unclear | yes | no |
| yes | yes | yes |
| no | yes | no |
| unclear | yes | unclear |
| xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx |
| Yes | Yes | yes |
| Yes | Yes | yes |
| no | NA | yes |
| Yes | Yes | yes |
| unclear | Yes | yes |
| Yes | yes | yes |
| Yes | yes | yes |
| Yes | yes | yes |
| no | yes | no |
| NA | yes | NA |
| xxxxxxxxxxx | xxxxxxxxxxx | xxxxxxxxxxx |
| unclear | yes | yes |
| no | no | no |

*Item Legend*

| Item | Description |
|---|---|
| 1 | Is the hypothesis/aim/objective of the study clearly described? |
| 2 | Are the main outcomes to be measured clearly described in the introduction or methods section? |
| 3 | Are the characteristics of the patients included in the study clearly described? |
| 4 | Are the interventions of interest clearly described? |
| 5 | Are the distributions of principal confounders in each group of subjects clearly described? |
| 6 | Are the main findings of the study clearly described? |
| 7 | Does the study provide estimates of the random variability in the data for the main outcomes? |
| 8 | Have all important adverse events that may be a consequence of the intervention been reported? |
| 9 | Have the characteristics of patients lost to follow-up been reported |
| 10 | Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001 |
| 11 | Were the subjects asked to participate in the study representative of the entire population from which they were recruited? |
| 12 | Were those subjects who were prepared to participate representative of the entire population from which they were recruited? |
| 13 | Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive? |
| 14 | Was an attempt made to blind study subjects to the intervention they received? |
| 15 | Was an attempt made to blind those measuring the main outcomes of the intervention |
| 16 | If any of the results of the study were based on data dredging, was this made clear? |
| 17a | In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, (…)? |
| 17b | Was the follow-up time with respect to flares adequate? |
| 17c | Was the follow-up time with respect to radiological progression adequate? |
| 18 | Were the statistical tests used to assess the main outcomes appropriate? |
| 19 | Was compliance with the intervention reliable? |
| 20 | Were the main outcome measures used accurate (valid and reliable)? |
| 21 | Were the patients in different intervention groups (…) recruited from the same population |
| 22 | Were the study subjects in different intervention groups (…) recruited over the same period of time? |
| 23 | Were the study subjects randomized to intervention groups? |
| 24 | Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable? |
| 25 | Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? |
| 26 | Were losses of patients to follow-up taken into account? |
| 27 | Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%? (n≥100 order to obtain CI smaller than 0.2) |

**Supplement 4.** Risk factors for flare addressed in primary studies.

Several studies looked at risk factors for flare. Six studies evaluated the effect of using concomitant sDMARDs on flare risk after stopping the TNF-blocker, but found no significant association (8, 11, 12, 14, 21, 25). Of three studies (8, 11, 12) one found a lower risk of disease flare for a longer duration of remission (8). Of 12 studies evaluating the effect of disease duration (7, 8, 11, 12, 18-22, 24, 25, 27), 4 found a significant association between a longer disease duration and an increased risk of flare (19, 20, 22, 27) and 8 found no association (7, 8, 11, 12, 18, 21, 24, 25). Eleven studies assessed the effect of disease activity score on flare rate (8, 11, 12, 18-22, 24, 25, 27), five of which found a significant association for a higher disease activity score at moment of de-escalation (12, 18, 19, 24, 27). Other factors that could influence flare rates that were not addressed in the primary studies are taper or stop criterion (e.g. remission or LDA), follow-up time and monitoring frequency of disease activity.

**Supplemental Table 1.** Reported flare rates among studies de-escalating TNF-blockers. Pooled estimates were calculated for studies discontinuing and tapering TNF-blockers.

| Study (arm), year | Medication | Characteristics | Follow-up | n | Flare rate (95% CI) |
|---|---|---|---|---|---|
| *Stop* | | | | | |
| Smolen (stop), 2013 (17) | etn | s, a | 1 year | 200 | 0.57 (0.50-0.64) |
| Tanaka, 2010 (22) | ifx | s, a | 1 year | 114 | 0.45 (0.36-0.54) |
| van den Broek, 2011 (20) | ifx | s, a, e | 1 year | 104 | 0.20 (0.13-0.29) |
| Maneiro, 2013 (13) | ada, ctz, etn, ifx | s, p | 1 year | 52 | 0.19 (0.11-0.32) |
| Brocq, 2009 (6) | ifx, etn, ada | s, a | 1 year | 21 | 0.75 (0.53-0.89) |
| Harigai, 2012 (10) | ada | s, a | 1 year | 22 | 0.55 (0.34-0.74) |
| Smolen, 2014 (17) | ada | s, a, e | 1 year | 102 | 0.19 (0.12-0.27) |
| Kavanaugh, 2014 (12) | TNFi | s, p | 1 year | 717 | 0.27 (0.24-0.30) |
| Tanaka, 2015 (19) | ada | s, a | 24 weeks | 52 | 0.40 (0.28-0.54) |
| Iwamoto, 2014 (11) | TNFi | s, p | 6 months 32 | 32 | 0.38 (0.23-0.55) |
| Emery (etn stop), 2014 (9) | etn | s, a, e | 39 weeks | 65 | 0.46 (0.35-0.58) |
| Emery (etn + MTX stop), 2014 (9) | etn | s, a, e | 39 weeks | 65 | 0.62 (0.49-0.73) |
| **Pooled estimate** | | | | **1546** | **0.38 (0.29-0.48)** |
| *Tapering* | | | | | |
| Smolen (half dose), 2013 (17) | etn | r[1], a | 1 year | 202 | 0.19 (0.14-0.25) |
| Maneiro, 2013 (35) | ada, ctz, etn, ifx | s, p | 1 year | 52 | 0.19 (0.11-0.32) |
| van der Maas, 2012 (21) | ifx | r[2], p | 1 year | 51 | 0.55 (0.41-0.68) |
| Heimans, 2013 (5) | ada | r[3], a | 4 months | 26 | 0.35 (0.19-0.55) |
| Raffeiner, 2014 (15) | etn | r[4], p | 1 year | 159 | 0.11 (0.07-0.17) |
| Emery (etn half dose), 2014 (9) | etn | r[1], a, e | 39 weeks | 63 | 0.21 (0.12-0.32) |
| Marks, 2015 (14) | TNFi | r[5], p | 9 months | 69 | 0.62 (0.50-0.73) |
| **Pooled estimate** | | | | **570** | **0.31 (0.16-0.51)** |

a = co-medication with sDMARDs in all patients
e = early RA
p = co-medication with sDMARDs in selected patients
r1 = dose reduction: etn 50 mg/week, dose reduced to etn 25 mg/week
r2 = dose reduction: ifx 3 mg/kg, tapered down 0.75 mg/kg every 8-12 weeks
r3 = dose reduction: ada 40 mg/2 weeks, tapered down to MTX monotherapy
r4 = dose reduction: etn 2x 25mg/week, dose reduced to etn 25mg/week
r5 = dose reduction with 1/3 (by increasing interval *1.5)
s = stop

ada = adalimumab
ctz = certolizumab pegol
etn = etanercept
ifx = infliximab
MTX = methotrexate
sDMARDs = synthetic disease modifying anti-rheumatic drugs
TNFi = tumor necrosis factor inhibitor

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# Chapter 8

## Doctors' preferences in de-escalating DMARDs in rheumatoid arthritis: A discrete choice experiment

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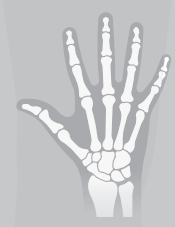


## ABSTRACT

### Background

Current guidelines suggest reduction of DMARDs can be considered in RA patients in remission. Objectives were 1) to estimate the relative importance of patient characteristics rheumatologists consider in their decision to de-escalate 2) to assess whether heterogeneity exists among rheumatologists with respect to de-escalation and 3) to identify the preferred de-escalation strategy.

### Methods

A discrete choice experiment (DCE) was conducted. All rheumatologists and trainees in The Netherlands were invited to participate. A conditional logit model was estimated to assess overall preference for de-escalation and its determinants. Heterogeneity was estimated by latent class analysis.

### Results

The DCE questionnaire was completed by 156 doctors. This questionnaire was constructed using the results of semi-structured interviews with 12 rheumatologists that identified 5 patient characteristics relevant for de-escalation: Number of swollen joints (SJC), presence of DAS remission/low disease activity (LDA), patient history, duration of remission/LDA and patient willingness to de-escalate DMARDs. Overall SJC and patient history were most important. Latent class analysis revealed 5 subgroups of doctors, showing differences regarding willingness to de-escalate and relative importance of patient characteristics. De-escalation of the TNF-inhibitor rather than methotrexate first was the most preferred strategy.

### Conclusion

Rheumatologists are not uniform in their decision in whom to de-escalate. Differences emerged in which characteristics they traded off resulting in 5 subgroups: Those that taper 1) always, 2) in absence of swollen joints, 3) in absence of swollen joints and presence of favorable patient history, 4) in DAS remission and favorable patient history and 5) taking into account all factors.

## BACKGROUND

Treatment of rheumatoid arthritis (RA) has advanced greatly during the past decades. The introduction of combination therapy with disease modifying anti-rheumatic drugs (DMARDs), the recognition of early, tight controlled treatment and the introduction of biologic agents have contributed to improved outcomes for patients suffering from RA (1). With intensive use of (a combination of) DMARDs, a state of low disease activity (LDA) or remission can be achieved by many patients while preventing erosions and functional impairment (2, 3). Although DMARD therapy is essential to obtain disease control, continuous use comes with several disadvantages. Apart from obvious drawbacks such as drug toxicity and side effects, medication use by itself may be perceived as burdensome and unhealthy by patients. Hence many patients view medication use as a necessary burden and wish to minimize its use. Also medication costs, especially for expensive biological treatments, are of increasing concern for governments. From this viewpoint tapering or discontinuation of DMARDs is preferable once disease control has been obtained.



Current guidelines suggest that reduction of biological DMARDs can be considered, especially if this treatment is combined with a conventional synthetic (cs)DMARD, once sustained remission has been achieved and glucocorticoids have been tapered first (4, 5). In addition, guidelines state that a cautious reduction of csDMARDs could be considered, as a shared decision between patient and physician, after glucocorticoids and bDMARDs have been succesfully withdrawn (5). Furthermore, a general recommendation is included that, apart from disease activity, other factors should be taken into account such as progression of structural damage, comorbidities and safety issues (5).

Indeed, evidence from a range of clinical studies suggests that de-escalation of DMARDs is feasible in a large number of patients in LDA or disease remission. (6-8) However, to date there is no standardized way to determine the patient for whom de-escalation of DMARD therapy is appropriate. (8) Also, adherence of rheumatologists to the guidelines that are currently available for de-escalation may not be optimal. (9) Therefore large differences are expected to exist between rheumatologists with respect to whether, when, and in which patients they will de-escalate therapy. Obtaining insight in these differences may assist in future guideline development and guide further research into this topic. In the assessment whether a patient is suitable candidate for treatment de-escalation, rheumatologists weigh several patient characteristics together at the same time. Hence a simple questionnaire in which the importance of patient characteristics are rated separately does not reflect a real-life decision. A discrete choice experiment (DCE) is a method that allows for the analysis of such complex decisions. It does so by presenting a series of "choice tasks" to the participant. Each choice task consists of two hypothetical patients with varying characteristics. The participant must then choose the patient with

the most favorable combination of characteristics. By analyzing the choices participants made based on the characteristics, the relative importance of patient characteristics on the decision to de-escalate treatment can be assessed. A technique very similar to that of a discrete choice experiment was used in the process of the development of the ACR/EULAR 2010 criteria for RA (10).

Objectives of this study were (1) to estimate the relative importance of patient characteristics rheumatologists consider in their decision to de-escalate medication, (2) to quantify how these characteristics influence doctor's preferences for de-escalating DMARDs, (3) to assess whether heterogeneity exists among rheumatologists with respect to their preference for de-escalation and the patient characteristics influencing this decision and (4) to identify the most preferred de-escalation strategy.

## MATERIALS AND METHODS

### DCE

In a DCE it is assumed that the analyzing process leading to a decision to medically intervene, such as de-escalation of medication, can be described by features relevant for making that decision (patient and disease characteristics) (11, 12). In case of a rheumatologist deciding whether to de-escalate DMARDs for a certain patient, these characteristics are likely disease related (e.g. presence of swollen joints indicating active disease). Each characteristic can then be further described by specific variants or levels (e.g. presence of 0, 1 or 2 swollen joints) (11, 12). Another assumption is that an individual's preference for the intervention is determined by the levels of these characteristics (11, 12). By offering a series of choices between two options with different characteristics (patients with different characteristics), the relative importance of the characteristics on the decision can be determined (11).

### Questionnaire design

To identify patient characteristics that determine the decision making for DMARD de-escalation, 12 rheumatologists were randomly selected for interviews stratified by region and type of hospital (university or general). A semi-structured interview schedule (Supplement 1) was designed based on characteristics identified by pilot interviews of rheumatologists and literature (7). During the semi-structured interviews, rheumatologists were questioned by telephone about their personal opinion and attitude with respect to DMARD de-escalation. The number of interviews was deemed sufficient as no new themes were mentioned during the final interviews, and therefore no other rheumatologists were approached. Based on the interviews, five patient characteristics with corresponding levels were developed (Table 1).

**Table 1.** Choice task example. Participants were required to choose the patient they deemed most suitable for de-escalation or neither (opt-out). For each choice task patient characteristics were varied by assigning different levels. Possible levels are indicated in the subscript. All patients were assumed to use the combination of methotrexate 20-25 mg / week and a TNF-blocker.

| | **Patient A** | **Patient B** |
|---|---|---|
| Duration of remission[1] | 6 months | 1 year |
| Patient preference for de-escalation at the start of the consult[2] | Patient is not willing to de-escalate | Patient is willing to de-escalate |
| Number of swollen joints[3] | 1 | 2 |
| DAS28[4] | ≤ 3.2 | < 2.6 |
| Medical history[5] | Difficult to accomplish remission | Easy to accomplish remission |
| | Non-erosive | Erosive |

[1] Levels were "6 months" and "12 months"
[2] Levels were "patient is not willing to de-escalate" and "patient is willing to de-escalate"
[3] Levels were "0", "1" and "2"
[4] Levels were "≤ 3.2" and "< 2.6"
[5] Levels were "difficult to accomplish remission, erosive", "difficult to accomplish remission, non-erosive", "easy to accomplish remission, erosive" and "easy to accomplish remission, non-erosive"



## Study design and questionnaire

A questionnaire containing 16 choice tasks, each consisting of two hypothetical patients, was deemed feasible to complete by rheumatologists attending the annual convention of the Dutch Society of Rheumatology (Nederlandse Vereniging voor Reumatologie, NVR). All hypothetical patients were assumed to use the combination of methotrexate 20-25 mg / week and a TNF-blocker, without additional glucocorticoids. In order to gain as much information as possible (enhancing precision) from a limited number of choice sets and sample size, computer software using experimental design theory (NGENE 1.1.2, 2014 ChoiceMetrics software) was used to generate the most efficient sets of choices given the characteristics as defined previously (optimized for a main effect model with full dummy specification). To further optimize this process, priors were chosen reflecting the expected direction of characteristic levels on preference (Supplemental Table 1) but not imposing any strong assumptions about the weight of each characteristic in the decision that might (dis)favor identification of some effects over others.

Choice sets consisted of two hypothetical patients and an opt-out option (Supplemental Table 2). From each choice set, rheumatologists were asked to choose the patient they deemed most suitable to de-escalate DMARDs. The opt-out option was included in case respondents deemed neither patient suitable for de-escalation, resembling real-life decision-making. Of note, only after rheumatologists chose to de-escalate treatment in either patient they were offered a second question to select the strategy they most preferred. If de-escalation was deemed appropriate, a second choice was given on how

they would de-escalate DMARDs. To make respondents familiar with the concept of DCE, two introductory questions were included. To avoid bias by presentation, the order of choice sets and order of attributes were randomized for each participant (13).

### Study sample

All rheumatologists and rheumatology trainees active in the Netherlands were eligible for participation.

### Invitation of subjects

A list of active rheumatologists was kindly provided by the Dutch Society of Rheumatology (NVR). Doctors were recruited during the annual meeting of the NVR 25 and 26 September 2014. Questionnaires were provided electronically on iPads. Non-attending rheumatologists received an invitation by e-mail to complete the questionnaire at their own computer.

### Statistical analyses

We estimated a conditional logit model to assess overall preference for de-escalation of DMARDs and its determinants (Supplement 2).

To assess whether preferences for de-escalation and relative importance of patient characteristics determining this decision differed among rheumatologists, a subgroup analysis (latent class model) was performed as well (Supplement 2). With this model subgroups of rheumatologists (clusters or classes) can be identified. To determine the optimal number of classes we selected the model with the best fit on the consistent Akaike information criterion (CAIC). This measure deals with the trade-off between increase in goodness of fit of the model and the increase in complexity by the addition of clusters. Analyses were performed using the clogit and lclogit function in STATA (version 13.1, StataCorp, 4905 Lakeway Drive, College Station, Texas, USA).

## RESULTS

In total 156 doctors completed the questionnaire (128 rheumatologists and 28 trainees), 128 of which completed the questionnaire at the annual conference Of 174 rheumatologists that had not yet participated at the annual conference and received an invitation by e-mail, 28 (16%) completed the questionnaire online. Eleven rheumatologists did not provide demographic data because of technical problems or by their own wishes. Characteristics of the study sample are shown in Table 2.

**Table 2.** Characteristics of study sample.

| | Rheumatologists (n=117)* | Trainee (n=28) |
|---|---|---|
| Age (years) median (IQR) | 47 (40-57) | 34 (31-36) |
| Female, n (%) | 60 (51%) | 20 (71%) |
| Work experience (years), median (IQR) | 10 (5 – 23) | - |
| Self-reported number of RA patients in practice, median (IQR) | 350 (200 – 1000) | 70 (25-100) |
| Self-reported prevalence of biological among RA patients in practice, median (IQR) | 25 (20 – 30) | 30 (20 – 35) |
| Working in academic hospital, n (%) | 19 (16%) | 10 (36%) |

*11 out of 128 rheumatologists did not provide information due to technical problems or by their own wish.

De-escalation of therapy was preferred in 74% of the patient choice sets evaluated by the rheumatologists. To quantify how patient characteristics influence doctor's preferences for de-escalating DMARDs, a conditional logit model was estimated (Table 3). The interpretation of such a model is somewhat different than of a linear or logit regression model. Each of the patient characteristics played a role in the decision to de-escalate DMARDs, as all coefficients of the model showed significance. The opt-out option was chosen if a rheumatologist deemed neither patient of a pair suitable for treatment de-escalation. De-escalation was chosen in 74% of cases, while the opt-out was chosen in 26% of cases. Therefore, in general, the opt-out was less preferred than de-escalation (the reference category), which is reflected by a negative sign for the opt-out (Table 3). Coefficients for the other factors have a similar interpretation, as will be further explained.

For each characteristic, we chose the level we expected to be most preferable for de-escalation to be the reference level, e.g. no swollen joints, DAS<2.6 (see footnotes Table 3). Therefore, the ideal patient that doctors would like to consider for de-escalation of DMARDs is a patient having all the reference characteristics, i.e.: came in remission easily, has no erosions, a remission duration of one year, no swollen joints and has DAS remission rather than DAS LDA. Hence, the coefficients represent the relative decrease in de-escalation preference when a patient presents with that feature (e.g. 2 swollen joints) relative to the reference of that feature (0 swollen joints). Presence of 2 swollen joints (-1.68, p<0.001) and a patient history of erosive disease in combination with difficulties achieving remission (-1.64, p<0.001) had the strongest influence on the decision not to de-escalate (Table 3). It should be emphasized that above results did not depend on the fashion in which DMARDs were de-escalated, as this was not specified in the questionnaire. Only after rheumatologists chose to de-escalate treatment in either patient they were offered a second question to select the strategy they most preferred (see below).

**Table 3. Overall preference of doctors for de-escalation based on a conditional logit model.**

| | Overall n=156 | |
|---|---|---|
| | **β** | **SE** |
| Opt out[1] chosen | 26% | |
| Opt out[1] | -2.96*** | 0.11 |
| DAS ≤ 3.2[2] | -0.98*** | 0.07 |
| Swollen joint count | | |
| 1[3] | -1.15*** | 0.08 |
| 2[3] | -1.68*** | 0.09 |
| Patient history | | |
| Erosive disease[4] | -0.69*** | 0.11 |
| Remission difficult[4] | -0.80*** | 0.09 |
| Erosive + remission difficult[4] | -1.64*** | 0.10 |
| Remission duration 6 months[5] | -0.52*** | 0.06 |
| Patient not willing to de-escalate at start of visit[6] | -1.09*** | 0.07 |

1: this option was included in case a rheumatologist did not want to de-escalate DMARDs in either of the patients presented in a pair
2: reference DAS<2.6
3: reference no swollen joints
4: reference easy remission and no erosions
5: reference remission duration 1 year
6: reference patient willing to de-escalate DMARDs at start of visit

* p<0.05
** p<0.01
*** p<0.001

Abbreviations:
β = Beta coefficient
SE = Standard Error

Although this model describes the preferences of rheumatologists for de-escalation of DMARDs on average, in reality subgroups of doctors may exist that weigh patient characteristics differently. Therefore we looked whether we could distinguish subgroups based on answering patterns. Using a latent class model, we identified 5 subgroups of rheumatologists as shown in Table 4. Each of the groups made different tradeoffs whom to de-escalate DMARDs in given the relative weight in the patient characteristics and opt out. Opt-out preference ranged from 1% in class 4 to 53% in class 5. For each subgroup the relative weights of the patient characteristics that drove de-escalation were analyzed (absolute weights of coefficients cannot be directly compared between subgroups because coefficients are on different scales). Table 4 shows that presence of swollen joints was the most important characteristic for rheumatologists to consider in subgroups 2 and 5, whereas in subgroups 1 and 3 patient history was most important. Of note, in

**Table 4.** Preference of doctors for de-escalation of DMARDs by subgroups based on answering patterns.

| | Group 1 n=48 | | Group 2 n=22 | | Group 3 n=26 | | Group 4 n=30 | | Group 5 n=30 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | β | SE | β | SE | β | SE | β | SE | β | SE |
| Opt out[1] chosen | 38% | | 21% | | 9% | | 1% | | 53% | |
| Opt out[1] | -2.78*** | 0.23 | -5.33*** | 0.97 | -4.98*** | 0.83 | -5.70*** | 0.64 | -4.72*** | 0.41 |
| DAS ≤ 3.2[2] | -0.59*** | 0.15 | -1.60** | 0.49 | -2.55*** | 0.57 | -0.59*** | 0.15 | -1.87*** | 0.27 |
| Swollen joint count | | | | | | | | | | |
| 1[3] | -1.01*** | 0.19 | -3.24*** | 0.59 | -1.02 | 0.53 | -0.79*** | 0.19 | -3.53*** | 0.48 |
| 2[3] | -1.90*** | 0.22 | -6.06*** | 0.99 | -0.63* | 0.28 | -1.25*** | 0.21 | -3.92*** | 0.51 |
| Patient history | | | | | | | | | | |
| Erosive disease[4] | -1.27*** | 0.20 | -0.73 | 0.40 | -1.23** | 0.38 | -0.58* | 0.24 | -1.29*** | 0.43 |
| Remission difficult[4] | -1.08*** | 0.20 | -0.95* | 0.46 | -1.42** | 0.42 | -0.44 | 0.27 | -1.79*** | 0.37 |
| Erosive + remission difficult[4] | -2.80*** | 0.25 | -1.14 | 0.62 | -2.99*** | 0.60 | -1.29*** | 0.30 | -2.79*** | 0.40 |
| Remission duration 6 months[5] | -0.41* | 0.16 | -1.17*** | 0.40 | -0.52 | 0.31 | -0.17 | 0.14 | -3.74 | - |
| Patient not willing to de-escalate at start of visit[6] | -1.61*** | 0.20 | -1.05*** | 0.30 | -0.98** | 0.30 | -1.14*** | 0.13 | -1.49*** | 0.27 |
| Class probabilities, median (range) | 0.99 (0.55 – 0.99) | | 0.99 (0.55 – 0.99) | | 0.94 (0.58 – 0.99) | | 0.99 (0.77 – 0.99) | | 0.98 (0.57 – 0.99) | |

1: this option was included in case a rheumatologist did not want to de-escalate DMARDs in either of the patients presented in a pair
2: reference DAS<2.6
3: reference no swollen joints
4: reference easy remission and no erosions
5: reference remission duration 1 year
6: reference patient willing to de-escalate DMARDs at start of visit

* p<0.05
** p<0.01
*** p<0.001

Abbreviations:
β = Beta coefficient
SE = Standard Error

subgroup 4 none of the patient characteristics dominated the decision to de-escalate, while their preference for de-escalation was strong. To further illustrate differences between the subgroups, 96 unique patient profiles were created, using the characteristics and levels as defined in Table 1. As shown in Figure 1, overall, patients 1-10 had a high probability to be considered for de-escalation (>80%) and patients 83-96 had a low probability (<20%). For the other patients (11-82), probabilities to be considered for de-escalation were variable among subgroups. Comparing subgroups with respect to

their willingness to de-escalation, group 4 had the greatest willingness to de-escalate and group 5 was least willing to de-escalate medication. Given the diagonal in Figure 1, group 3 had above average willingness to de-escalate, whereas group 1 was somewhat below average. Willingness to de-escalate for group 2 was in general above average for patients at the left side of the figure (patients 1-48) and less than average for patients at the right side (patients 49-96). A simple analysis to see whether differences related to age, sex or practice-related factors (Table 5) did not reveal particular characteristics of doctors. Being trainee was associated with lower preference to de-escalate.

After the decision whether to de-escalate or not the rheumatologists were presented with the choice which DMARDs to de-escalate. Three options were presented: de-escalating the TNF-blocker, de-escalating MTX or de-escalating MTX to half the dose followed by de-escalating the TNF-blocker. Of de-escalation strategies, rheumatologists chose de-escalating the TNF-blocker in majority of cases (61%), followed by de-escalating the TNF-blocker after de-escalating MTX to half dosage (33%).

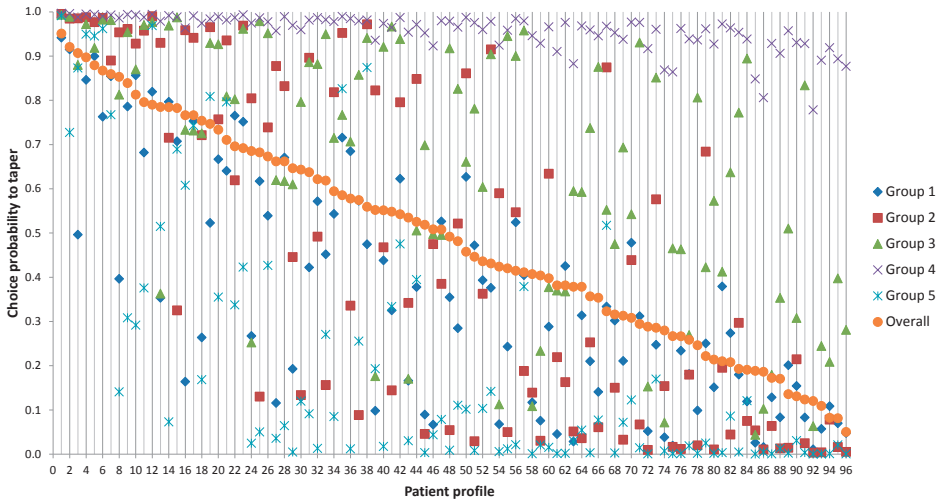


**Figure 1.** The probability rheumatologists choose to taper specific patients, shown for 96 unique patient profiles. Overall probability (average for all rheumatologists, orange rounds) and probabilities by subgroups (other shapes) are shown.

**Table 5.** Characteristics of subgroups.

| | Group 1 n=48 | Group 2 n=22 | Group 3 n=26 | Group 4 n=30 | Group 5 n=30 | P-value* |
|---|---|---|---|---|---|---|
| Age (years) median (IQR) | 43 (35 – 51) | 49 (40 – 56) | 39 (35 – 45) | 50 (40 – 60) | 41 (37 – 52) | 0.038 |
| Female, n (%) | 22 (51%) | 12 (55%) | 15 (60%) | 15 (50%) | 20 (67%) | 0.663 |
| Trainee, n (%) | 11 (26%) | 2 (9%) | 7 (29%) | 1 (3%) | 7 (26%) | 0.051 |
| Work experience (years), median (IQR) | 7 (0 – 15) | 13 (5 – 25) | 5 (0 – 8) | 12 (5 – 25) | 4 (0 – 18) | 0.027 |
| Self-reported number of RA patients in practice, median (IQR) | 375 (100 – 800) | 425 (200 – 1100) | 450 (100 – 2000) | 300 (200 – 1000) | 300 (100 – 500) | 0.492 |
| Self-reported prevalence of biological among RA patients in practice, median (IQR) | 23 (20 – 30) | 20 (20 – 33) | 30 (20 – 30) | 29 (20 – 33) | 20 (15 – 30) | 0.641 |
| Working in academic hospital, n (%) | 9 (21%) | 4 (18%) | 6 (24%) | 5 (17%) | 7 (23%) | 0.955 |
| No data, n(%) | 5 (10%) | 0 (0%) | 2 (8%) | 1 (3%) | 3 (10%) | <0.001 |

* Kruskall – Wallis test

## DISCUSSION

By semi-structured interviews, we identified 5 patient characteristics rheumatologists take into account in their decision to de-escalate DMARDs: number of swollen joints, presence of DAS remission/LDA, patient history, duration of remission/LDA and patient willingness to de-escalate. Using a discrete choice experiment among Dutch rheumatologists, number of swollen joints and patient history were identified as factors of greatest importance. However, rheumatologists were not uniform in their decision to de-escalate DMARDs. Based on a further (latent class) analysis of the answering patterns, five subgroups of rheumatologists were identified that traded off patient characteristics differently in their decision to de-escalate: 1) rheumatologists that always tapered 2) rheumatologists tapering in the absence of swollen joints 3) rheumatologists tapering in the absence of swollen joints and in the presence of a favorable patient history 4) rheumatologists tapering in case of DAS remission and favorable patient history and 5) rheumatologists taking into account all factors. That heterogeneity among rheuma-

tologists exists with respect to decision-making was further demonstrated by calculating the probability rheumatologists would decide to de-escalate medication for 96 unique patient profiles (figure 1). This showed that subgroup probabilities were highly variable for most of the profiles, especially those for which one or more characteristics were less favorable (e.g. presence of 1 rather than 0 swollen joints or DAS LDA rather than DAS remission). This means that no general consensus exists on which patients are suitable for de-escalation. Eliciting details on rheumatologist subgroups resulted in mixed demographic characteristics, so other person related factors are likely to play a role. We only observed that trainees were less willing to taper, possibly due to lack of experience and confidence. Of de-escalation strategies rheumatologists could choose from, de-escalating the TNF-blocker first and de-escalating the TNF-blocker after reducing MTX to half dosage were chosen in 94% of cases.

To date there is no standardized way to determine the patient for whom de-escalation of DMARD therapy is appropriate. (8) Of clinical factors, conflicting results have been reported for deeper remission (14, 15) and shorter disease duration (14-16) to be associated with successful tapering, while observations from CORRONA registry suggested that a rapid response to DMARDs is associated with better maintenance of remission when the agents are tapered later on (8, 17). In this DCE, rheumatologists regarded presence of swollen joints, a patient history of erosive disease and difficulties achieving remission and patient fulfilling DAS LDA rather than remission as most important factors to not de-escalate. Although swollen joints may be regarded as a direct indication of inflammation and contra-indication for de-escalation, this is not necessarily true for the DAS28 score itself, which could be high because of psychosocial distress or comorbidities. Rheumatologists in clinical practice may therefore sometimes decide to de-escalate in case of DAS LDA in the absence of other signs of inflammation. Future research, may aid to clarify which clinical factors are really important for predicting successful de-escalation. Ultrasound (18-20) or biomarkers (14, 21) may have an additional role in detecting in which patients subclinical synovitis is still present increasing the risk of flare after treatment withdrawal. It would also be of interest to study whether (a combination of) clinical, ultrasonographic and/or serum factors can adequately predict which patients can successfully de-escalate treatment.

This study was conducted using a DCE, which in comparison to other quantified preference techniques, bears most resemblance to real-world decision-making (22). A strength of this design is that several patient characteristics can be evaluated at once in which the weight of each characteristic contributes to the decision to de-escalate medication. Another strength of this study is that we identified relevant characteristics using semi-structured interviews with a random sample of rheumatologists to identify relevant factors (characteristics and levels) for the DCE questionnaire. As no new factors were mentioned during the final interviews, we assumed that saturation was reached

and hence no important factors had been missed. One inherent limitation of a DCE is that rheumatologists were asked to evaluate virtual RA patients on screen. Consequently, as the decision to de-escalate does not have real clinical implications, rheumatologists may have been more risks taking than they would be when dealing with real patients. This could then have resulted in an over-estimation of rheumatologists' willingness to de-escalate. Another limitation of this study is that, although the majority of rheumatologists attending the annual conference participated in the study, response rates were low for rheumatologists not attending the conference that were invited to participate from home. Although this could for a large part be explained by the method of recruitment, we could not fully exclude the possibility of a relationship between non-responders and tendency to de-escalate DMARDs.

In designing the questions for the DCE we made several choices that need clarification. We refrained from including side effects in the decision to de-escalate. Several rheumatologists remarked that presence of side-effects is relevant in the decision of de-escalation therapy. Although we agree this is likely to influence the decision to de-escalate a particular medicine first due to side-effects, it not necessarily relates to the decision of de-escalation in patients achieving LDA or remission. The presence of severe side-effects would likely result in de-escalation or switching medication before sustained remission or LDA is achieved.



Second, a simple choice was given on what to de-escalate. Rheumatologists could choose between de-escalating the TNF-inhibitor or MTX completely, or to de-escalate the TNF-inhibitor completely after reducing MTX to half dosage. As more strategies are imaginable, different strategies can and will be adopted in reality. Therefore, more work on preference of what to de-escalate first given both the medication characteristics and patient characteristics would help to further understand de-escalation of therapy decisions.

Third, due to the definition of levels assigned to the disease characteristics, the relative importance of characteristics could change if levels had been defined differently (e.g. remission duration of 2 years rather than 1 year). Therefore, the relative importance of characteristics can only be interpreted taking the definition of the levels into consideration.

## CONCLUSION

Swollen joint count and patient history were the most important characteristics rheumatologists take into consideration in the decision to de-escalate. However rheumatologists are not uniform in their decision in whom to de-escalate. Five subgroups of rheumatologists could be identified: Those that taper 1) always, 2) in absence of swollen joints, 3) in

absence of swollen joints and favorable patient history, 4) if DAS remission and favorable patient history and 5) taking into account all factors.

To improve uniform decision-making in the future, more research is needed assessing the predictive value of patient characteristics for successful de-escalation of DMARDs.

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**Supplement 1.** Topics for semi-structured interview.

Introduction:

Thank you for cooperating with this interview.
We would like to get ourselves an idea about how rheumatologists de-escalate DMARDs in clinical practice in patients with RA.
The following questions will focus on the de-escalation of conventional and biological DMARDs in patients with RA in remission.

Topics to discuss:

- Age/gender/years of clinical practice of rheumatologist
- Have you ever de-escalated biological or conventional DMARDs?
- What are, in your opinion, advantages of de-escalation?
- And disadvantages?
- Which factors make that you consider treatment de-escalation for a certain patient?

(first have rheumatologist come with an answer by himself, thereafter check whether any of below topics are relevant as well)



- Disease duration of RA
- Severity and course of disease
- DMARD history
- "Difficulties" to achieve remission in a patient
- Remission duration
- Doctor-patient relationship (mutual trust, extent to which shared decision making is possible
- Other

  - Do you sometimes de-escalate medication for a patient for whom it was difficult to achieve a state of remission.
  - In your opinion, how long should a patient be in remission before one should consider tapering or stopping medication?
  - How do you evaluate whether a patient is in remission and can commence de-escalation (DAS, other factors?)
  - If you were to assess remission exclusively by using the DAS28, then which value of the DAS28 would, in your opinion, reflect remission? (Officially 2.6, but especially the feeling of the doctor is relevant here)
  - In clinical practice, the DAS is not always a perfect measure to assess remission. Are there perhaps components of the DAS you feel are a decisive factor to indicate remission.
  - In case you de-escalate etanercept (Enbrel) in patients that use the regular dose (50 mg/ week), then in what fashion do you generally do this? (extending the dose interval, half the dose, stop immediately).
  - Are you aware that etanercept (Enbrel) is also available as a 25 mg injection? Do you sometimes prescribe it?
  - Which would have your preference? De-escalating etanercept (Enbrel) by doubling the interval or by halving the dose by prescribing the 25 mg / week injection?

- o Whenever you de-escalate methotrexate in patients using the full dose (20-25 mg/week), how do you usually do this? (half the dosage at once, taper by 1-2 tablets each time? Stop at once?)
- o In case a patient uses the combination of etanercept (Enbrel) and methotrexate, do you have a preference which agent to de-escalate (first)? How would you de-escalate?
- o What makes that you have a preference?

  - § Adverse effects
  - § Co-morbidity
  - § Preference of the patient
  - § Other

- o In case a patient uses the combination of adalimumab (Humira) and methotrexate, do you have a preference which agent to de-escalate first? Why? (does the formation of anti-drug antibodies play a role?) How would you de-escalate?
- o In case a patient uses another TNF blocker (certolizumab (Cimzia) 200mg/2 weeks or golimumab (Simponi) 50mg/month), how would you commence de-escalation? (would you then use another de-escalation strategy?)

- Can you imagine that you would decide not to de-escalate medication in a patient that has reached a state of low disease activity or remission for a long period of time? What are the reasons?
- Are there any non-medical reasons that play a role in your decision to de-escalate, such as biological costs or branch recommendations?
- Are there patients whom you never de-escalate after negotiation?
- How many patients do you estimate are in your practice and how many use a biological?

**Supplement 2.** Utility functions for the conditional logit and latent class models.
Utility function for the conditional logit model:

$V = \beta_0 + \beta_1$*opt out + $\beta_2$*DAS28≤3.2 + $\beta_3$*SJC=1 + $\beta_4$*SJC=2 + $\beta_5$*history erosive disease + $\beta_6$*history difficult achieving remission + $\beta_7$*history erosive disease and difficult achieving remission + $\beta_8$*remission duration 1 year + $\beta_9$*patient unwilling to taper

V: Observable utility that rheumatologists have for tapering medication in a patient.

$\beta_1$-$\beta_9$: Coefficients for the patient characteristics. These represent the relative weight doctors attach to a certain characteristics when it comes to their decision to taper medication

Utility function for the cluster (latent class) model:

$V_{|c} = \beta_{0|c} + \beta_{1|c}$*opt out + $\beta_{2|c}$*DAS28≤3.2 + $\beta_{3|c}$*SJC=1 + $\beta_{4|c}$*SJC=2 + $\beta_{5|c}$*history erosive disease + $\beta_{6|c}$*history difficult achieving remission + $\beta_{7|c}$*history erosive disease and difficult achieving remission + $\beta_{8|c}$*remission duration 1 year + $\beta_{9|c}$*patient unwilling to taper

$V_{|c}$: Observable utility for tapering medication for doctors belonging to that class.

$\beta_1$-$\beta_{9:}$ Represent the coefficients of the attributes indicating the relative weight rheumatologists of a class place on a certain attribute level.

**Supplemental Table 1.** Priors used in the design of the questionnaire.

| Characteristic | Levels | Priors |
|---|---|---|
| Duration of remission | - 1 year | 0 (ref) |
| | - 6 months | -0.1 |
| Patient preference for tapering at the start of the consult | - Patient is not willing to taper | 0.15 |
| | - Patient is willing to taper | 0 (ref) |
| Number of swollen joints | - 0 | 0.2 |
| | - 1 | 0.1 |
| | - 2 | 0 (ref) |
| DAS28 | - < 2.6 | 0.1 |
| | - ≤ 3.2 | 0 (ref) |
| Medical history | - Difficult to accomplish remission | -0.1 |
| | - Easy to accomplish remission | 0 (ref) |
| | - Non-erosive | 0 (ref) |
| | - Erosive | -0.15 |

**Supplemental Table 2.** Example of a choice set as presented in the questionnaire.

| | Patient A | Patient B | Opt-out |
|---|---|---|---|
| Duration of remission | 1 year | 6 months | - |
| Patient preference for tapering at start of visit | Patient is not willing to taper | Patient is willing to taper | - |
| Number of swollen joints | 1 | 0 | - |
| DAS28 | < 2.6 | ≤ 3.2 | - |
| Medical history | Difficult to accomplish remission<br>Non-erosive | Easy to accomplish remission | - |

| *In case A or B was chosen:* | Strategy A | Strategy B | Strategy C |
|---|---|---|---|
| Preferred tapering strategy | Tapering MTX to 0 mg | Tapering biological to 0 mg | Decrease MTX (50% of initial dosage), then taper biological to 0 mg |

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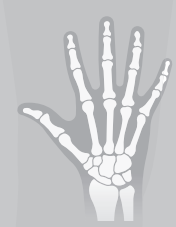
# Chapter 9

## General discussion


## GENERAL DISCUSSION

The medical treatment of RA has improved greatly over the previous two decades (1). As a result, disabling joint deformations, once the hallmark of the disease, have become a rare manifestation that the new generation of rheumatologists will mainly know from medical textbooks. Nonetheless since RA is a chronic non-curable disease, challenges to further optimize care for patients remain and two main challenges have been the focus of this work. First, despite the better medical outcomes the burden of disease in RA patients is still higher compared to the general population, which may be attributed, at least in part, to higher levels of psychological distress patients experience (2). Second, continuous medical drug treatment for patients in remission is only justified if the benefits outweigh the disadvantages such as potential overtreatment, safety considerations and treatment costs (3). These challenges resulted in the main objectives of this thesis:

1. To study the impact of psychosocial factors on patients with early RA, with special interest in the relationships between psychosocial factors and disease activity score and achievement of treatment goals
2. To study the effects of treatment de-escalation in patients with low disease activity or remission and aid rheumatologists in making informed decisions with regard to treatment de-escalation

In this chapter, I will discuss how the findings of this thesis may aid in tackling these challenges and which issues remain unresolved. I will address methodological considerations and finally make recommendations for further research.



### Impact of psychological factors

In chapter 2 we showed that RA patients experience a quality of life that is substantially lower than the general population. Furthermore, this difference remains after the first year of medical treatment. Of course, many factors could be responsible for this difference in quality of life. The most obvious being that the disease is not yet adequately controlled. However, in tREACH, at 12 months 81% of patients had achieved their treatment goal of DAS<2.4 and 53% of patients were in DAS remission (4). Although residual disease activity with associated pain and disability may explain part of the difference in quality of life, it is probably not the only factor at play. As I described in the introduction, RA has previously been associated with psychological distress such as anxiety, depression and fatigue (2, 5). Likely, these factors contribute to the lower feeling of well-being of RA patients.

The relationship between psychosocial factors and RA is likely bidirectional (6, 7). On the one hand rheumatoid arthritis may result in higher levels of anxiety and depression because of pain and disability associated with the disease. On the other hand, higher levels of psychosocial distress may result in higher disease activity measures like the

DAS, by patients scoring higher on subjective components tender joint count and global health (6). A bidirectional relationship between RA and depression by inflammatory pathways is also possible. Depression and depressed mood have been associated with a pro-inflammatory cytokine spectrum. In this light, the higher prevalence of depression in RA may also be explained by higher levels of inflammation present in these patients (6). Reversely, depression might cause higher levels of inflammation leading to higher disease activity measures because of increased swollen joint count and ESR. Placing these theories in light with my own findings in chapters 3 and 5, the psychosocial factors appear to be associated with disease activity measures at the subsequent visit mostly by their association with the more subjective components of the disease activity score tender joint count and VAS global health, although some associations with objective components (ESR and swollen joint count) were also observed. Therefore, effects through subjective components and through a direct inflammatory pathway may both take place, although indirect mechanisms, such as non-adherence, could also be responsible for an increase in inflammatory parameters (6).

Over the first year of disease, a shift in relative importance of individual psychosocial factors influencing DAS during the chronic phase of the disease was observed as well. At baseline, anxiety and coping with pain were the most important psychosocial factors affecting DAS at subsequent visit, while at 12 months, fatigue came out as independent predictor. Care should be taken in drawing definitive conclusions from this observed shift, as results are from one sample only and psychosocial factors are highly correlated. However, from the perspective of disease progression, the shift may be plausible from a psychological point of view. At baseline, when disease is active and patients need to cope with a new situation of having a chronic disease it is imaginable that coping with pain and anxiety play a large role, whereas at 12 months, when disease is under control and patients have adapted more to their new situation, the fatigue that remains comes to the foreground.

In chapter 4 we showed the patterns of fatigue during the first year after diagnosis of RA. Fatigue is a common symptom in auto-immune disorders (8) and cancer (9) and is often notoriously unresponsive to drug treatment. This is also the case in RA. Although intensive treatment with a combination of conventional DMARDs or biologic agents are effective in reducing pain and disability and stopping progression of joint damage (10), a recent meta-analysis found that they only have a very limited effect in reducing fatigue (11). In cancer, however, physical therapy (12) and cognitive behavioral therapy (13) have been shown to be effective in part of the patients. From meta-analyses it was concluded that these interventions have a small benefit on self-reported fatigue in patients with rheumatoid arthritis as well (14). However, fatigue is a complex entity that may encompass both physical and mental aspects (8). Measuring these aspects of fatigue more specifically may also aid in deciding which intervention is most appropriate

for individual patients and understanding why certain interventions may work in some but not in others.

In conclusion, we found that RA patients experience a lower quality of life compared to the general population, which may in part be attributed to a higher burden of psychosocial distress. We found that higher levels of psychosocial factors are associated with higher disease activity scores at subsequent visits. The nature of this relationship was mainly explained by an association between psychosocial factors and the subjective components of the disease activity score. However, as some associations with objective components were observed as well, the existence of an association by a direct inflammatory pathway cannot be ruled out. In addition a shift was observed in the relative importance of psychosocial aspects during the first year of follow-up. With respect to fatigue, almost half of patients classify as being fatigued during the first year of follow-up, despite a tight controlled treatment strategy. One third of fatigued patients at baseline classify as being suspect for clinical depression. Monitoring for symptoms of depression and fatigue should be considered in newly diagnosed RA patients, so that appropriate interventions can be performed.

### Aspects of remission and tapering



Identifying patients that are not likely to respond to initial treatment with (combination) DMARD therapy could aid in developing a more personalized treatment regimen in which such patients can be switched early to a more intensive therapy, for instance with TNF-blocking agents. Although clinical factors are able to predict differences in response at group level, predictions are not accurate enough at the individual level to base treatment decisions on. In chapter 5 we identified predictors for attaining remission in early RA. We found that, in addition to clinical factors, psychosocial factors have additional value in predicting which patients attain the treatment goal. However, as the association is likely to take place mainly through the subjective components of DAS (chapter 3), adding the psychosocial factors to a predictive model that is used to inform decisions on treatment intensification may not be desirable. Therefore, enhancement of the predictive abilities of such a model may be better sought by, for instance, the inclusion of genetic factors or biomarkers. Nonetheless, the association we observed between psychosocial factors and treatment response should make clinicians aware that patients with high levels of psychological distress can affect outcome measures used for making treatment decisions. Therefore, in some patients with high DAS, psychological rather than medical interventions may be warranted.

Once remission has been achieved, a new question emerges whether DMARD therapy may be safely de-escalated or should be continued for an unlimited period of time. Evidence from this thesis and recent literature (3, 15) suggests that a substantial part of patients can de-escalate biological DMARDs (chapter 7) and conventional DMARDs

(chapter 6) without experiencing a flare within the first year of follow-up. Furthermore, treatment de-escalation appears to be reasonably safe: Of patients that do experience a flare, the majority regains remission within 6 months of follow-up. With respect to structural damage, the studies evaluating this outcome in the systematic review found limited to no progression.

Although our results suggest that treatment de-escalation may be safely attempted, several aspects warrant future research. Although the studies evaluating joint damage under treatment de-escalation found limited to no progression, this outcome was only investigated in a limited number of studies. Although not significant, some studies in the systematic review showed a non-significant trend towards more progression in the group de-escalating therapy. A question of specific interest would be if such damage progression occurs at all and if so, whether it can be prevented if therapy is reinitiated immediately after relapse.

Another area of interest lies in the identification of patients that may successfully de-escalate DMARDs without experiencing a subsequent flare. As was mentioned in the introduction, identifying these patients by clinical factors alone is not yet possible (3). As a consequence, rheumatologists in clinical practice differ greatly in their assessments of which patients are eligible for treatment de-escalation (chapter 8). Addition of imaging data and/or biomarkers might improve this identification, but is not guaranteed to be successful.

In conclusion, we found that in addition to clinical factors, psychosocial factors are associated with treatment response. Rheumatologists should be aware that patients that psychological distress can affect outcome measures like the DAS and take this fact into consideration in the decision of treatment intensification. We found evidence that de-escalation of biological and conventional DMARDs without a short-term flare is possible in a substantial part of patients in remission or low disease activity. In patients that do experience a flare available evidence suggests that the majority of patients regains a state of remission within 6 months after treatment intensification with little or no progression of joint damage. Identification of patients that can successfully de-escalate medication is not yet possible. As a consequence, we found that rheumatologists in clinical practice differ greatly in their assessment which patients are eligible for treatment de-escalation.

## Methodological considerations

When it comes to study limitations, three issues may affect validity that I will further discuss: Selection bias, information bias, confounding and generalizability.

*Selection bias*

Selection bias is a distortion of the results because the sample obtained for the analysis is not a representative sample of the target population.

Most of the studies included in this work were based on data obtained from the tREACH study (4). The tREACH study was a randomized clinical trial in patients with arthritis in at least one joint and a duration of complaints shorter than 1 year. Based on the risk of developing persistent arthritis (Visser model (16)) patients were categorized into three groups (Low, Intermediate, High), each of which had three treatment arms. Primary aim of the tREACH study was to compare the response treatment response of different initial treatment strategies. In this work, all data from tREACH comprises the High risk group, of which 98% of patients fulfilled the later developed 2010 classification criteria for RA (4). Therefore, with respect to the 2010 classification criteria (17), patients in tREACH High may be assumed to be representative.

The target population of tREACH may be defined as all patients fulfilling the inclusion criteria being referred to a rheumatologist in a participating hospital during the inclusion time of the study. A distortion in this selection may be caused by rheumatologists not asking eligible patients to participate or by eligible patients not willing to participate themselves. As long as these effects play completely at random, a representative sample will still be obtained. However, in clinical trials, usually some systematic effects are at play. In general, patients willing to participate in clinical trials tend to be more highly educated, have more free time and are more adherent to therapy. Furthermore, in tREACH a tendency by rheumatologists to select patients with a typical presentation of RA was observed, as inclusion rate in the High group was much higher compared to the Low group. As focus of this work has been on the High group, of which 98% (4) fulfill the 2010 classification criteria for RA (17) and the target population of this work are newly diagnosed patients with RA, this tendency is not likely to have much affected the results. On the other hand, certain groups (lower educated, non-Dutch ethnicity, people with very demanding jobs or familial obligations) may have been underrepresented in the trial, which could have implications for the generalizability of results to these groups. However, the mere inclusion of members of such subgroups in the study sample does not mean that the overall results automatically hold for these subgroups. For instance, in a clinical trial studying the effects of a certain drug, the inclusion of two 90 year olds in the sample does not mean that overall trial results can be applied to a population of 90 year olds. Therefore, if there is doubt whether results can be applied to certain subgroups, this should be the focus of a separate study or analysis.



*Information bias*

Information bias is a distortion in the results by measurement error or misclassification. In the tREACH trial and this work, the main outcome studied was the disease activity score (DAS). Although the DAS is measured using certain guidelines, there is large potential for variability between raters, especially in their assessment of presence of joint swelling and tenderness. As in tREACH, the DAS was directly used to steer treatment, raters

scoring overly liberal or sensitive may result in the under- and overtreatment of patients respectively. To make sure the different raters evaluate the DAS in a similar fashion (i.e. to increase the inter-rater reliability), annual training sessions were organized in which trainers all rated the same set of patients, after which scores were compared. Raters rating too sensitive or liberal were encouraged to adjust their evaluation of DAS. Despite the annual training sessions, some inter-rater variability will always remain. Furthermore, by increasing the inter-rater variability, the internal validity of the study will increase, but variability between different studies may remain and hence affect generalizability. For instance, part of the heterogeneity in flare rates observed in the systematic review may be explained by inter-rater variability in assessing the disease activity across studies. However, it should be remarked that in this example, most heterogeneity is likely to be caused by differences in studies with respect to remission criteria, included patients and therapeutic management. Another potential source of information bias is the registration of DMARDs in tREACH. These were extracted from the paper or electronic patient records (most hospitals changed from paper to electronic patient records during the inclusion and follow-up period of tREACH). Because of their busy practice, rheumatologists sometimes fail to register the exact medication used by a patient at certain visits. In the case of paper patient records, sometimes the medication used is registered but difficult to decipher. Especially small changes in medication, such as performed when tapering or de-escalating therapy, may have been missed. This could lead to some over or under-estimation of the occurrence of tapering or flare at these time points. However, in most cases, registration at subsequent visits will be adequate, so that these events will be detected later in time. A more serious problem may be patient non-adherence. Generally, non-adhering patients use less than the prescribed dosage of the drugs, but in de-escalation studies the opposite may occur as well. Underuse of DMARDs may decrease remission rates and increase flare rates, while overuse of DMARDs during tapering my decrease flare rates. Although non-adherence affects the outcomes, one could argue that non-adherence takes place in the general population as well (likely even more so than in clinical trial), making the outcomes of the study more similar to its expected efficacy when the intervention would be implemented in clinical practice.

*Confounding*

Confounding is a distortion of the observed association between a certain factor of interest and outcome by a (often unobserved) third factor, called the confounder. The confounder and the factor of interest need to be associated to each other and to the outcome. My father used to tell a practical joke on statistics about a research on fire damage. The researchers had found that the more fire trucks were sent to a fire, the larger was the damage. So they concluded that only one fire trucks should be sent to a fires to prevent damage. The example shows that if we are naive and only study the

relationship between the confounder (number of fire trucks) and outcome (fire damage), this can lead us to draw false conclusions. Although this example is of course a bit silly, in reality confounding factors are often not so easily identified. For this reason, in medical research, identifying and adjusting for confounders is of great importance to be able to find the true relationships of interest.

There are several ways to deal with confounding, so that the true association between the factor of interest is observed. One of these methods, which was also applied in this work, is to control for confounding by using multivariable regression models. By regressing the relationship of the confounder and factor if interest simultaneously on the outcome, one can control for the confounder so that the relationship between factor of interest, conditional on the confounders can be observed. In chapter 3, interest lied in the independent effects of psychosocial factors measured at the current visit on the DAS 3 months later. Therefore, other factors having a relationship with DAS (confounders), age, sex, RF status ACPA status and DAS at the current visit, were adjusted for in the model. Similarly, in chapter 5 these factors were controlled for to assess the additional effect of psychosocial factors on attaining remission. Although confounders can be controlled for in statistical models, the method is still no absolute guarantee that the true relationship between the factor of interest and outcome is observed. This is because the model can only adjust for confounders that were observed. If important confounders were left out of the model, either because they were not measured or because they are unknown, the observed relationship will still be biased.



Taking all methodological considerations into account, I feel that the conclusions presented in this work are likely to be applicable to the general population of RA patients. Although not used as an inclusion criterion, almost all patients in tREACH fulfilled the ACR/EULAR 2010 criteria for RA. Information bias by misclassification of medication use or inter-rater variability in DAS scores, may have occurred, but the impact is not likely to be large. Known potential confounders were adjusted for in the analyses. Hence, this work can provide more insight in the impact of psychosocial factors on patients with early RA and aid rheumatologists in making more informed decisions with respect to treatment de-escalation. Nonetheless, many questions remain that warrant future research, for which I will make recommendations in the section that follows.

### Future recommendations

The medical treatment of RA has improved greatly over the previous two decades. This success may for a great part be attributed to two factors. First, a paradigm shift in the way the disease is managed in which early and tight-controlled are paramount (1). Second, the development of a wide spectrum of therapeutic agents, all of which have shown to be effective at the group level (1). Yet, further improvement may be realized in several ways. As already noted in the introduction, guidelines are frequently not adhered to by

rheumatologists in clinical practice, even if they do agree with the recommendations (18). A seemingly obvious, but important recommendation is to make sure that guidelines are more strictly implemented in clinical practice.

A second opportunity to further optimize care in rheumatoid arthritis may be personalized health care. Although treatments may be effective when studied at the group level, this does not mean that they are equally effective for every patient. While some patients may benefit a lot, other patients may not benefit at all, but may still be exposed to (serious) side effects. Hence, identification of subgroups of patients that are likely, or unlikely, to respond to a certain therapy may lead to a more effective, safe and efficient use of therapeutics. Personalized healthcare is most suited for therapeutic areas that are characterized by highly heterogeneous patient populations, low response rates, high burden of side effects originating from traditional trial and error prescription and a high cost of the given therapy (19). Arguably, rheumatoid arthritis fulfills most of these criteria. As we showed in chapter 6, only 27% of patients achieved sustained remission within 6 months and 57% within 2 years of follow-up period in tREACH. This may indicate that part of the patients are unsatisfactorily treated. Furthermore, the heterogeneity in response may suggest different underlying molecular etiology in the disease may exist, even though presenting as the same disease (19). Also, the costs of biological treatments for RA are high and DMARD treatment often comes with side-effects. Therefore, a personalized health care approach could be of great interest for RA. However, such an approach would require that the individual response to certain treatments can be accurately predicted. The model presented in chapter 5 allowed us to associate baseline patient and disease characteristics to treatment response (remission) in treated with (combination) DMARD therapy. Despite several strong associations, the predictive power of the model was not adequate to allow for accurate individual predictions. To get closer to a personalized health care approach, studies looking to identify genetic factors and biomarkers associated with treatment response are emerging, some with promising results (19). Unfortunately, the predictive power of these technologies have mostly been investigated independently, while optimal prediction may be achieved by the combination of clinical, genomic and serologic biomarkers. Successful combination and validation of these modalities will require increased collaboration across research groups and consortiums (19).

A third challenge lies in the further optimization of rheumatoid arthritis care to patient needs. While rheumatologists often mainly focus on treatment targets, patients' needs remain unmet across domains such as pain, physical function, mental function and fatigue (20). Therefore, it is important that doctors recognize these needs and address them, where possible, with appropriate interventions (20). Some of these interventions, that have shown to be effective in other areas, may require further evaluation in rheumatoid arthritis before they are offered to patients on a large scale. As an example, both

cognitive behavioral therapy and physical therapy have shown to be effective in reducing fatigue in cancer patients. Fatigue continues to have a considerable negative impact on more than half of patients with RA (21) and DMARD treatment often fails to produce meaningful improvements in levels of fatigue in RA patients. Therefore, it could be of interest to investigate whether cognitive behavioral therapy and physical therapy are effective in reducing levels of fatigue in RA patients in a randomized controlled clinical trial.

At last, while current evidence seems to indicate that for the average patient in clinical remission, treatment de-escalation may be safely attempted in shared decision with the patient, it is possible that there is a small subgroup of that experiences a disproportionally high burden of negative effects. Therefore, it may be worthwile to more closely study the effects of treatment de-escalation on individual patients. Outcomes of interest could for instance be radiographic progression and functional limitations (e.g. limitations at work) during flare. While the randomized controlled trial is still te gold standard to measure causal effects of an intervention such as treatment de-escalation, it may not be feasible to address these questions for practical reasons. While patient inclusion is known to be difficult in treatment de-escalation studies in general, this will be an even a bigger problem when studying rare outcomes that only occur in a small subset of patients. Furthermore, now that treatment de-escalation has been included in the guidelines and is more common in daily clinical practice, it may be even more difficult to find eligible patients willing to participate. Either because patients have a very strong wish have an to attempt to de-escalate treatment, or because they already had such an attempt that failed and do not wish to have another attempt. Therefore, it is possible that these questions may only be adequately addressed by means of observational data. To this end, hospital registries should be built, in which relevant patient and disease characteristics are stored. Such a database should minimally include relevant patient characteristics such as disease duration and RF/ACPA status, as well as outcomes such as DAS, X-ray data and patient-reported outomes that are measured at a regular basis, as well as adequate prescription data on DMARDs. Ideally, concensus should be reached by different hospitals on the set of data that is gathered so that registries from different hospitals can be combined. Because of the observational and repeated nature of the data, combinations of more advanced statistical methods such as multiple imputation, longitudinal models and causal inference methods may be used to gain maximal insight from these data.

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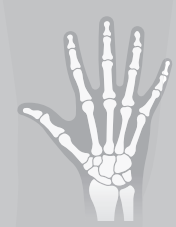
# ADDENDUM




## SUMMARY

Although many advances have been made in the medical treatment of RA, challenges to further optimize care for patients remain. One of these challenges is that, despite medical outcomes have improved, the burden of disease in RA patients is still higher compared to the general population. This may be attributed, at least in part, to higher levels of psychological distress patients experience. Another challenge is the question whether or not medical drug treatment with DMARDs should be continued in patients that have reached a disease state of remission, or that treatment may be de-escalated. Continuous medical drug treatment for patients in remission is only justified if the benefits outweigh the disadvantages such as potential overtreatment, safety considerations and treatment costs. These challenges resulted in the main objectives of this thesis:

1. To study the impact of psychosocial factors on patients with early RA, with special interest in the relationships between psychosocial factors and disease activity score and achievement of treatment goals
2. To study the effects of treatment de-escalation in patients with low disease activity or remission and aid rheumatologists in making informed decisions with regard to treatment de-escalation

In chapter 2 we showed that health related quality of life in newly diagnosed RA patients improves over time, but remains lower than that of the general population. A similar pattern was observed for patients with joint complaints without synovitis. Improvements over time were also observed for pain scores and functional ability, whereas fatigues score remained relatively constant over time in both groups. Health care consumption levels were comparable between groups. In RA patients, more health care consumption was associated with a shorter time since diagnose, shorter duration of complaints, higher baseline physical health and lower chance locus of control.

In chapter 3 we investigated whether psychosocial factors have an additional effect on the disease activity score measured 3 months later and which compounds of psychosocial factors are the most influencing ones during the first year of follow-up. We found that baseline anxiety and coping with pain were associated with DAS at 3 months, coping with pain at 6 months was associated with DAS at 9 months and fatigue at 12 months was associated with DAS at 15 months. Psychosocial factors were moderately correlated to each other. Effects on DAS appeared to occur mainly through subjective components of the DAS: Tender joint count and global health.

In chapter 4 we investigated the prevalence and course of fatigue over time in newly diagnosed RA patients during the first year of follow-up. We found that, despite a treat to target strategy, almost half of the early rheumatoid arthritis patients show high levels of fatigue over the first year of diagnosis. On group level, fatigue only decreased slightly,

while on individual level fluctuation was seen. Predictors for the course of fatigue over time were also investigated. In the group with low fatigue at baseline, univariable analyses revealed tender joints, VAS global, DAS, anxiety, depression and SF36 mental component score to be associated with development of fatigue, of which depression and coping with limitations remained as independent predictors in multivariable analysis.

In chapter 5, we explored which factors predict early remission within 6 months and sustained remission at 6 and 9 months of follow-up in RA patients initiating DMARD therapy. We identified younger age, male sex, lower baseline DAS and lower levels of baseline anxiety as independent predictors for remission within 6 months. Younger age, male sex, ACPA negativity, and lower levels of baseline fatigue were independent predictors for sustained remission at 6 and 9 months.

In chapter 6, we investigated the tapering of DMARDs in patients with early arthritis in sustained remission, with a focus on conventional synthetic DMARDs. We found that, during 2 years of follow-up, sustained remission (DAS<1.6 at 2 consecutive visits) was achieved at least once by 159 (57%) of patients. Of these patients, 118 and 23 initiated tapering of conventional synthetic and biologic DMARDs respectively. Estimated flare rates at 1 year were 41% and 37% respectively. After flare, re-remission was achieved within 6 months by 65% of patients tapering csDMARDs after treatment intensification.

In chapter 7, we performed a systematic literature review about tapering or de-escalation of synthetic and biologic DMARDs in RA patients in a state of low disease activity or remission. Only four, mostly dated studies, evaluated synthetic DMARDs, in which flare rates ranged from 8% at 24 weeks to 63% at 4 months after de-escalation. On fifteen studies reporting on TNF-blockers we performed a meta-analysis and obtained a pooled 1-year flare rate of 33% (95% CI 23% – 73%). For other biologicals like abatacept and tocilizumab, flare rates ranged from 34% at 1 year to 72% at 6 months. Only 5 studies evaluated radiographic progression, all of which found limited to no progression. In 7 studies evaluating time to remission after flare, the majority of patients achieved re-remission within 6 months after treatment intensification.

In chapter 8, we explored the preferences of rheumatologists with respect their decision to de-escalate DMARDs in patients with rheumatoid arthritis. In semi-structured interviews of 12 randomly selected rheumatologists, the number of swollen joints, presence of DAS remission or low disease activity, patient history, duration of remission/LDA and patient willingness to de-escalate DMARDs were mentioned as being relevant for the decision to de-escalate DMARDs. These factors were incorporated into the DCE questionnaire, which was completed by 156 rheumatologists from across The Netherlands. In the analysis, all identified factors were significant, of which swollen joint count and patient history were most important. In a subsequent latent class analyses we explored heterogeneity. We found 5 different subgroups of doctors, showing differences with respect to willingness to de-escalate and the relative importance of the 5 patient characteristics.

For the majority of hypothetical patients, little consensus was observed among doctors with respect to the feasibility of tapering.

Chapter 9 provides a general discussion of the main findings of this thesis and their relevance to clinical practice. Methodological considerations and their potential implications on the findings are discussed. Finally, several recommendations for future research are presented.

## SAMENVATTING

De laatste jaren is veel vooruitgang geboekt in de medicamenteuze behandeling van RA. Echter, uitdagingen om de behandeling verder te verbeteren zijn er nog steeds. Eén van deze uitdagingen is dat patiënten, ondanks dat ziekte uitkomsten zijn verbeterd, nog steeds een slechtere kwaliteit van leven ervaren vergeleken met de algehele populatie. Dit kan onder meer worden toegeschreven aan een hogere mate van psychisch onwelbevinden bij deze patiënten. Een tweede uitdaging is de vraag of medicamenteuze behandeling met DMARDs moet worden voortgezet bij patiënten bij wie de ziekte tot rust is gekomen (remissie), of dat moet worden geprobeerd om de behandeling met medicijnen te verminderen. Het doorgaan met medicamenteuze behandeling bij patiënten in remissie is alleen gerechtvaardigd als de voordelen opwegen tegen de nadelen, waaronder mogelijke overbehandeling, veiligheidsrisico's en kosten van de behandeling. Deze uitdagingen hebben geleid tot de volgende doelstellingen van dit proefschrift:

1. Het onderzoeken van de impact van psychosociale factoren op patiënten met vroege RA, met als specifiek aandachtspunt de relaties tussen psychosociale factoren en de ziekte acitiviteitsscore (DAS) en het bereiken van behandeldoelen.
2. Het onderzoeken van de gevolgen van het afbouwen van medicijnen in patiënten met RA, wiens ziekte in een staat is van lage ziekteactiviteit of remissie en om reumatologen te helpen bij het maken van geïnformeerde beslissingen met betrekking tot het afbouwen van medicijnen.



In hoofdstuk 2 lieten we zien dat de kwaliteit van leven van patiënten met reumatoïde artritis, bij wie pas de diagnose is gesteld, verbetert met de tijd. Echter, de kwaliteit van deze patiënten blijft lager wanneer je die vergelijkt met die in van de algehele populatie. Een vergelijkbaar beeld kwam naar voren bij patiënten die zich presenteerden met gewrichtsklachten, maar bij wie de reumatoloog geen zwelling van de gewrichten (synovitis) vast kon stellen. Verbeteringen met de tijd werden ook gezien bij pijnscores en fysiek functioneren, terwijl scores voor vermoeidheid in beide groepen nauwelijks verbeterden. De twee groepen hadden een verglijkbare mate van gebruik van gezondheidszorg. Bij patiënten met reumatoïde artritis waren een kortere tijd sinds de diagnose, een kortere klachtenduur, een hogere score voor fysieke gezondheid en een lagere score voor "chance locus of control" geassocieerd met een hoger zorggebruik.

In hoofdstuk 3 onderzochten we of psychosociale factoren een toegevoegde waarde hebben in het kunnen verklaren van de ziekte activiteit score (DAS) 3 maanden later. Tevens onderzochten we welke psychosociale factoren het meeste invloed hadden op de DAS gedurende het eerste jaar dat de diagnose RA is gesteld. We vonden dat angst en coping met pijn op het moment van diagnose waren geassocieerd met de DAS 3 maanden later. Coping met pijn op 6 maanden was geassocieerd met de DAS na 9 maanden

en vermoeidheid op 12 maanden was geassocieerd met de DAS na 15 maanden. De psychosociale factoren waren matig gecorreleerd met elkaar. De effecten van psychosociale factoren op de DAS leken vooral plaats te vinden door beïnvloeding van de subjectieve componenten van de DAS: Tender joint count (aantal pijnlijke gewrichten bij lichamelijk onderzoek door de arts) en global health (algehele gezondheid volgens de patiënt).

In hoofdstuk 4 hebben we gekeken naar het voorkomen van (prevalentie) en het beloop over de tijd van vermoeidheid bij RA patiënten tijdens het eerste jaar nadat de diagnose is gesteld. We vonden dat, ondanks een behandelwijze waarbij wordt gestreefd naar een lage score voor de ziekteactiviteit (treat-to-target), bijna de helft van de patiënten hoge scores voor vermoeidheid hadden gedurende het eerste jaar na de diagnose. Op groepsniveau verbeterde de vermoeidheid maar minimaal, terwijl op individueel niveau schommelingen werden gezien. Voorspellende factoren voor het beloop van vermoeidheid over de tijd werden eveneens onderzocht. In de groep met een lage score voor vermoeidheid op het moment van diagnose waren het aantal pijnlijke gewrichten, VAS global, ziekteactiviteitsscore (DAS), angst, depressie en de SF36 mental component scale geassocieerd met het ontwikkelen van vermoeidheid. In multivariable analyses bleken depressie en coping met beperkingen onafhankelijke voorspellers te zijn voor vermoeidheid.

In hoofdstuk 5 verkenden we welke factoren vroege remissie (minimale ziekteactiviteit) binnen 6 maanden en remissie op zowel 6 als 9 maanden na diagnose voorspelden bij RA patiënten die begonnen met een behandeling met “disease modifying antirheumatic drugs” (DMARDs). We vonden dat een jongere leeftijd, mannelijk geslacht, een lagere DAS op het moment van diagnose en lagere scores voor angst op het moment van diagnose onafhankelijke voorspellers waren voor het bereiken van remissie binnen 6 maanden. Een jongere leeftijd, mannelijk geslacht, negatieve anti-CCP en lagere scores voor vermoeidheid op het moment van diagnose waren onafhankelijke voorspellers voor remissie op zowel 6 als 9 maanden.

In hoofdstuk 6 onderzochten we het afbouwen van DMARDs bij patiënten met reumatoïde artrtitis in persisterende remissie (DAS<1.6) op 2 of meer opéénvolgende 3-maandelijkse bezoeken, met speciale aandacht voor synthetische DMARDs. We vonden dat, gedurende 2 jaar na de diagnose, persisterende remissie tenminste 1 maal werd behaald door 159 (57%) van de patiënten. Van deze patiënten begonnen er respectievelijk 118 en 23 met het afbouwen van conventionele synthetische DMARDs (csDMARDs) en biologische DMARDs. Het risico op opvlammen van de ziekte binnen 1 jaar werd geschat op respectievelijk 41% en 37%. Na het optreden van een opvlamming van de ziekte werd remissie opnieuw behaald binnen 6 maanden door 65% van de patiënten die csDMARDs afbouwden na het intensiveren van de behandeling.

In hoofdstuk 7 verrichtten we een systematisch literatuuronderzoek naar het afbouwen van synthetische en biologische DMARDs bij RA patiënten die in een staat van remissie of lage ziekteactiviteit verkeerden. In slechts 4, veelal gedateerde, publicaties werden synthetische DMARDs onderzocht, waarbij het risico op een opvlamming varieerde van 8% 24 weken tot 63% 4 maanden nadat werd begonnen met afbouwen. Op 15 studies die rapporteerden over TNF-blockers verrichtten we een meta-analyse en vonden een gezamenlijk risico op opvlamming binnen 1 jaar van 33% (95% betrouwbaarheidsinterval 23%-73%). Voor andere biologische DMARDs, zoals abatacept en tocilizumab, varieerden de risico's op een opvlamming van 34% na 1 jaar tot 72% na 6 maanden. Slechts 5 onderzoeken keken naar het voortschrijden van gewrichtsschade op röntgenfoto's, allen vonden weinig tot geen toename. In 7 onderzoeken die de tijd tot het opnieuw bereiken van remissie bekeken, behaalde het merendeel van de patiënten opnieuw remissie na het intensiveren van de behandeling.

In hoofdstuk 8 onderzochten we de voorkeuren van reumatologen met betrekking tot het besluit om DMARDs af te bouwen bij patiënten met RA. Uit interviews met 12 willekeurig gekozen reumatologen kwamen het aantal gezwollen gewrichten bij lichamelijk onderzoek, het hebben van remissie of lage ziekteactiviteit volgens de DAS, voorgeschiedenis van de patiënt, duur van remissie of lage ziekteactiviteit en de bereidheid van de patiënt zelf om af te bouwen naar voren als relevante factoren in de overweging van de reumatologen om DMARDs af te bouwen. Deze factoren weden opgenomen in de DCE (discrete choice experiment) vragenlijst, die werd ingevuld door 156 reumatologen afkomstig uit heel Nederland. In de analyse hiervan waren alle eerder genoemde factoren significant, waarvan het aantal gezwollen gewrichten en de voorgeschiedenis van de patiënt het belangrijkste bleken. In een vervolganalyse (latent class analyse) keken we of er sprake kon zijn van heterogeniteit (dat reumatologen verschillen in de afwegingen die ze maken). We vonden 5 subgroepen van dokters, die verschilden van elkaar wat betreft hun algehele bereidheid om af te bouwen en de mate waarin zij belang hechtten aan de 5 verschillende factoren. Bij het merendeel van de denkbeeldige patiënten voor wie de reumatologen moesten besluiten, werd er weinig overeenstemming gezien tussen de dokters of zij wel of niet gingen afbouwen.

Hoofdstuk 9 betreft een algehele discussie van de belangrijkste bevindingen van dit proefschrift en hun relevantie voor de klinische praktijk. Methodologische overwegingen en hun mogelijke consequenties voor bevindingen worden besproken. Als laatste worden enkele aanbevelingen voor toekomstig onderzoek gepresenteerd.

## PHD PORTFOLIO

**Name:** Tjallingius Martijn Kuijper
**PhD period:** 2010 – 2018
**Promotor:** Prof.dr. J.M.W. Hazes
**Copromotors:** dr. J.J. Luime, dr. A.E.A.M. Weel

**General academic and research skills**

| | | |
|---|---|---|
| - | BROK | 2012 |
| - | EndNote course (medical library) | 2012 |

**In-depth statistical courses, NIHES**

| | | |
|---|---|---|
| - | Courses for the Quantitative Researcher | 2011 |
| - | Repeated Measurements | 2011 |
| - | Missing Values in Clinical Research (EP16) | 2012 |
| - | Bayesian Statistics (CE09) | 2012 |
| - | Bayesian Adaptive Methods for Clinical Trials | 2012 |

**In-depth courses, other**

| | | |
|---|---|---|
| - | Decision Analytic Modelling for Economic Evaluation, Foundations and Advanced course, University of Glasgow | 2014 |

**Courses part of Master of Science in Statistical Data Analysis, UGent**

| | | |
|---|---|---|
| - | Principles of Statistical Data Analysis | 2016 |
| - | Statistical programming | 2016 |
| - | Analysis of Continuous Data | 2016 |
| - | Statistical Inference | 2016 |
| - | Clustered and Longitudinal Data Analysis | 2016 |
| - | High Dimensional Data Analysis | 2016 |
| - | Categorical Data Analysis | 2017 |
| - | Causality and Missing Data | 2017 |
| - | Big Data Science | 2017 |

**Teaching activities**

| | | |
|---|---|---|
| - | Critical assessment of medical literature, first year Medicine students | 2012 – 2014 |
| - | Assistant lab on clinical trial design, fourth year Medicine students | 2014 |
| - | Supervising bachelor thesis, student Health Policy and Law | 2013 |
| - | Supervising master thesis, student Health Policy and Law | 2014 |

**Other**

| | | |
|---|---|---|
| - | Co-organizor of regional symposia for health care providers in rheumatology | 2012, 2014 |
| - | Coordination of regional studies (tREACH, TARA, POET) | 2011- 2015 |

**National and international conferences**

**2012**

**Kuijper TM**, Hazes JMW, Bindels PJE, Luime JJ
Health Care Utilization (HCU) in Patients with Multiple Joint Complaints Being Diagnosed as Non-Arthritis by the Rheumatologist, NVR September 2012, Papendal (poster presentation)

**2013**

**Kuijper TM**, Xiong H, Weel AEAM, Gerards AH, van Zeben J, de Jong PHP, Tchetverikov I, de Sonnaville PBJ, Krugten MV, Grillet, BA, Luime JJ, Hazes JMW
Coping Style is an Independent Predictor for Disease Activity at Three Months in Early Arthritis Patients Initiating Therapy with Disease Modifying Anti-Rheumatic Drugs, ACR October 2013, San Diego (poster presentation)

**2014**

**Kuijper TM**, Xiong H, Luime JJ, de Jong PHP, Weel AEAM, Gerards AH, van Zeben D, Tchetverikov I, de Sonnaville PBJ, Krugten MV, Grillet BA, Hazes JMW

Higher Levels of Baseline Anxiety is an Independent Predictor of Disease Activity in RA, WEON mei 2014, Leiden (oral presentation)

**Kuijper TM**, Hazes JMW, de Jong PHP, Gerards AH, van Zeben D, Tchetverikov I, de Sonnaville PBJ, Krugten MV, Grillet BA, Luime JJ, Weel AEAM
Better Functional Ability with Less Biologicals after Induction Combination DMARD Therapy versus methotrexate Monotherapy, EULAR juni 2014, Paris (oral presentation)

**Kuijper TM**, Hazes JMW, de Jong PHP, Gerards AH, van Zeben D, Tchetverikov I, de Sonnaville PBJ, Krugten MV, Grillet BA, Luime JJ, Weel AEAM
Betere Functionaliteit met Minder Biologicals na Inductie met Combinatie DMARD Therapie versus methotrexaat Monotherapie: 2-jaars data van de tREACH trial, NVR september 2014 (oral presentation)

**Kuijper TM**, Luime JJ, de Jong PHP, Gerards AH, van Zeben D, Tchetverikov I, de Sonnaville PBJ, van Krugten MV, Grillet B, Hazes JMW, Weel AEAM

Better Functional Ability with Less Biologicals 2 years after Induction with Combination DMARD Therapy versus methotrexate Monotherapy, ACR November 2014, Boston (oral presentation)

**2015**

**Kuijper TM**, Luime JJ, de Jong PHP, Gerards AH, van Zeben D, Tchetverikov I, de Sonnaville PBJ, van Krugten M, Grillet B, Hazes JMW, Weel AEAM
Tapering DMARDs in the tREACH trial – Flare Rates, Sustained Remission and Radiological Progression, EULAR Rome 2015 (abstract presentation)

**Kuijper TM**, Luime JJ, de Jong PHP, Gerards AH, van Zeben D, Tchetverikov I, de Sonnaville PBJ, Krugten MV, Grillet BA, Hazes JMW, Weel AEAM
Afbouwen van DMARDs 2 jaar follow-up van de tREACH trial, NVR September 2015, Papendal (oral presentation)

**Kuijper TM**, Luime JJ, de Jong PHP, Gerards AH, van Zeben D, Tchetverikov I, de Sonnaville PBJ, van Krugten M, Grillet B, Hazes JMW, Weel AEAM
Predictors for early remission in newly diagnosed RA patients, ACR San Francisco 2015, (abstract presentation)

**2016**

**Kuijper TM**, Luime JJ, de Jong PHP, Gerards AH, van Zeben D, Tchetverikov I, de Sonnaville PBJ, van Krugten M, Grillet B, Hazes JMW, Weel AEAM
Predictors for early remission in newly diagnosed RA patients, EULAR London 2016, (abstract presentation)

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### This thesis

**Kuijper TM**, Luime JJ, Xiong H, de Jong P, van der Lubbe P, van Zeben D, Tchetverikov I, Hazes J, Weel A. Effects of psychosocial factors on monitoring treatment effect in newly diagnosed rheumatoid arthritis patients over time: response data from the tREACH study. Scandinavian Journal of Rheumatology. (Accepted for publication).

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## ABOUT THE AUTHOR

Tjallingius Martijn Kuijper (Martijn) was born on the 16th of August in 1981 in Delft and grew up most of his youth in the village of Bleiswijk near Rotterdam.

In 2001 he graduated at the Erasmiaans Gymnasium in Rotterdam. After two attempts at studying applied physics in Delft and medical informatics in Amsterdam, he started his medicine study in Rotterdam in 2003, from which he graduated in 2010. Meanwhile, he followed a secondary master in clinical epidemiology, for which he obtained his master degree in 2009 under the supervision of prof.dr.ir. A.P.N. Themmen with the thesis "LH receptor gene expression is essentially absent in breast tumor tissue: implications for treatment".

In 2010 he started to work on this PhD thesis at the department of Rheumatology of the Erasmus MC, Rotterdam under the guidance of prof. dr. J.M.W. Hazes, dr. J.J. Luime and dr. A.E.A.M. Weel. During this time, he coordinated the tREACH, TARA and POEET clinical trials in the region of Southwest Netherlands.

From 2015 onwards, he continued to finish the work on this thesis at the department of Rheumatology of the Maasstad hospital in Rotterdam. There he also assisted with the design and data analysis of several new and ongoing research projects on value-based healthcare, among which the IMPACT trial, the Joint Referral trial and the Joint Compassion project.

From 2015 onwards, he follows a master on Statistical Data Analysis at Ghent University, from which he expects to graduate in the Autumn of 2018.

From March 2016 onwards, he works as a statistical consultant at the Maasstad hospital, providing guidance on statistics, data analysis and study design for researchers and master students working at the Maasstad hospital. In addition, he works as a data analyst for the value-based healthcare projects in collaboration with the Santeon group of cooperating hospitals.

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Beste Angelique, mijn andere copromotor. Door mijn onderzoek op de tREACH data ben je betrokken geraakt bij mijn promotietraject en ben je hierin een steeds grotere rol gaan spelen. Ik weet nog goed dat toen je me probeerde over te halen om mijn promotietra-

ject in het Maasstad ziekenhuis af te ronden ik hier aanvankelijk mijn bedenkingen bij had. Voor onderzoek en complexe analyses moest je toch immers niet in een perifeer ziekenhuis zijn? Ik ben blij dat ik toch naar je heb geluisterd. Het Maasstad ziekenhuis bleek zo'n vervelende plek nog niet en ik werd enthousiast ontvangen door de vakgroep reumatologie. Niet alleen kreeg ik de gelegenheid om dit proefschrift af te ronden, ook kon ik mijn analytische vaardigheden inzetten bij nieuwe en lopende onderzoeken op de afdeling, waaronder de Impact, Joint Care en het value-based healthcare project. Daarnaast reed ik ook nog 2 of 3 keer in de week op en neer naar Gent om in deeltijd een master statistiek te volgen kon ik meteen het geleerde in de praktijk toepassen met het geven van statistische consulten in het ziekenhuis. Achteraf gezien had ik me geen betere werkplek kunnen wensen en daarvoor ben ik jou (en Marc en de rest van de vakgroep reumatologie natuurlijk) enorm dankbaar voor de kans die jullie mij gegeven hebben. Daarbij was (en is) het altijd prettig om met je te werken. Je gaf me de ruimte en door je enthousiasme en positieve instelling wist je me toch altijd te motiveren en te inspireren om door te zetten en de zaken af te maken.

Pascal, de tREACH-man mag uiteraard ook niet ontbreken in dit dankwoord! Een groot deel van dit boekje gaat over de tREACH studie welke jij vanaf het begin zo succesvol hebt opgezet en gecoördineerd! Toen ik de taken van je overnam was je altijd bereid om me op weg te helpen en adviezen te geven. Daarbij was het altijd leuk om met je samen te werken zoals bij het organiseren van het "Future of RA" symposium!

Myrthe, het coördineren van de TARA was best een klus met zoveel ziekenhuizen en alsmaar tegenvallende inclusies, maar samen hebben we er toch het beste van gemaakt! Het was altijd fijn om met je te werken en je had altijd leuke ideeën voor acties om de dokters tot includeren aan te moedigen. Ik wens je heel veel geluk toe met je lieve kleine (en grote) man en hoop op een mooi vervolg van je carrière met je PhD titel!

Maar natuurlijk zat ik niet alleen met Myrthe op de kamer. Annelieke, om je grappige uitspraken (zowel tegen mensen als computers) moest ik altijd lachen! En ook David, Sjel, Hilal, Jenny, Florentien, Marie-Louise en Albert wil ik bedanken voor de leuke en gezellige tijd op de kamers. En natuurlijk ook onze buren, Esther, Kim en Lonneke. En Maren, dank je voor je geduldige uitleg hoe ik nu eindelijk de plakjes kaas op de goede manier uit het plastic krijg. :)

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organisatorische skills hebben we in korte tijd een heel discrete choice experiment kunnen opzetten en uitvoeren onder alle reumatologen op tijdens de NVR najaarsdagen. Als team vulden we elkaar perfect aan, wat heeft geleid tot hoofdstuk 8 van dit boekje en een publicatie. En Margot, bedankt voor de fijne samenwerking aan hoofdstuk 4, waar we veel werk aan hebben gehad, maar waar we binnenkort hopelijk ook een mooi journal voor zullen vinden.

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Verder wil ik graag alle reumatologen en andere medewerkers uit de ziekenhuizen bedanken, zonder wiens inzet mijn onderzoek niet mogelijk was geweest en uiteraard ook alle patiënten die zich alle jaren belangeloos hebben ingezet om de kennis rondom hun ziekte te vergroten en de zorg een stukje beter te maken.



Ron, bij vragen en problemen met de database kon ik altijd bij jou terecht en meestal wist je met wat speurwerk het probleem ook nog snel te verhelpen. Joyce, jou wil ik bedanken voor het organiseren van de leuke uitjes, waarvan met name de eendenrace me nog goed bij staat! En voor dat je altijd wel iets wist te verzinnen als Miekes agenda helemaal vol stond, maar ik haar toch echt even nodig had.

Het laatste deel van mijn promotie heb ik vanuit het Maasstad ziekenhuis afgerond. De afdeling reumatologie van het Maasstad ziekenhuis heb ik leren kennen als een ambitieuze afdeling met een fijne werksfeer, waar hard gewerkt wordt maar zeker ook met elkaar gelachen. Daarbij wordt er flink aan de weg getimmerd op het gebied van wetenschappelijk onderzoek en value-based healthcare. Ik vind dat best iets om trots op te zijn en ben dan ook blij dat ik hier aan heb mogen bijdragen en nog steeds mag doen.

Met veel plezier heb ik er samengewerkt met de andere onderzoekers op de verdieping, eerst Sandhya en later Arno, Deirisa, Nienke en Maha en de research verpleegkundigen Iris en Elise. En bovendien heb ik hier ook mijn twee prachtige paranimfen gevonden!

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Maar natuurlijk hebben ook buiten mijn werkkring mensen mij gesteund bij de totstandkoming van dit proefschrift die ik hier graag wil bedanken.

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Dear Marta, It was always fun playing tennis with you. Now that we have both finished our PhD's, I hope we will find the time to meet and play again soon! And I would love to see Heidelberg too!

Thomas, het was altijd plezant om samen te studeren en aan de groepsopdrachten te werken voor de statistiek master. Heel veel geluk gewenst met je nieuwe functie!

Fien, je grappige berichtjes vrolijken me altijd op! Heel veel succes met het afronden van je studie en je PhD! Het is nu veel werk, maar het komt goed!