# Management of Early Rheumatoid Arthritis: Solving the Unresolved.

## the tREACH trial

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# Management of Early Rheumatoid Arthritis: Solving the Unresolved.

## the tREACH trial

# Behandeling van vroege reumatoïde artritis: Het onopgeloste opgelost

## het tREACH onderzoek

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Pascal Hendrik Pieter de Jong

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## PROMOTIECOMMISSIE

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CHAPTER 1

# General introduction

## RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a systemic auto-immune disease, which is characterized by chronic inflammation of multiple joints. About 1% of the people in western countries have RA, and each year in 5 – 50 per 100.000 persons the diagnose of RA is made. The prevalence of RA varies geographically.[1] In the Netherlands the prevalence of RA in 2007, based of primary care registries, was 0.7% (95% confidence interval (CI): 0.48% - 1.03%) for men and 1.1% (95% CI: 0.76% - 1.60%) for women. The mean annual incidence in the Netherlands in 2007 was respectively 75 and 120 per 100.000 for men and women. Disease onset is most often between 40 and 60 years of age. The mortality rate for men and women with RA in 2010 was respectively 0.3 and 0.9 per 100.000.[2]

Clinical and radiographic outcomes have improved enormously in the last two decades, due to major paradigm changes in the management of RA.[3-4] Evolvement of clinical trial methodology, emergement of new therapeutic options – in particular biologicals – and reevaluating treatment strategies caused these major paradigm changes. These paradigm changes are:

- Early detection of the disease;
- Early initiation of 'intensive' therapy;
- A treat-to-target approach

The 2010 ACR/EULAR classification criteria for RA and formulation of the EULAR recommendations for the management of RA were developed, so rheumatologists could apply these changes in daily practice.[3-4] The 2010 EULAR recommendations advocate, in patients with newly diagnosed RA, that: (1) the initial treatment strategy encompasses at least methotrexate (MTX) with or without glucocorticoids (GCs), (2) treatment is targeted to achieve remission, or low disease activity, preferably within 3 months, and (3) treatment should be adjusted, every 1-3 months, until the target is reached.[4] Complying with these recommendations result in better functional and radiological outcomes.[1, 5]

Despite of the new classification criteria and treatment recommendations, important unresolved questions for daily practice remain. Therefore, the focus of this thesis will be on the management of early RA. In the next section I will elaborate on the argumentation for each paradigm change and accentuate the unresolved questions, which need to be solved for daily practice.

### Early detection of the disease

Various studies suggest the existence of a 'window of opportunity', which encompasses the first 12 weeks after symptom onset. Early initiation of Disease Modifying Anti-Rheumatic Drugs (DMARDs) during this 12 week period improved clinical outcome and delayed or even prevented radiographic damage.[6-11] Distinguishing RA from other arthritic disorders is rather difficult, especially in the very early stages of the disease. Until 2010 only the 1987 classification criteria for RA, made by the American College of

Rheumatology (ACR), were available (table 1).[12] The 1987 criteria for RA are not sensitive enough to detect RA in the earlier stages of the disease. Therefore, different algorithms for recognizing RA in a very early phase were developed. Examples of algorithms are the models made by van der Helm *et al*[13] and Visser *et al.*[14] At the time of writing the protocol of our clinical trial 'treatment in the Rotterdam Early Arthritis Cohort' (tREACH), the foundation of this thesis, we chose to use the Visser model since this model had proven to detect more patients within an earlier phase of the disease compared with the 1987 ACR criteria.[14]

**Table 1: The 1987 ACR classification criteria for RA**

| To make the diagnosis of RA, four of the following criteria must be present. Criteria 1- 4 must have been present for at least six weeks |
|---|
| 1. Morning stiffness ≥1 hour |
| 2. Synovitis or hydrops in ≥ 3 joints, including proximal interphalangeal joints (PIP), metacarpophalangeal (MCP) joints, wrists, elbows, ankles and metatarsophalangeal (MTP) joints |
| 3. Synovitis or hydrops in MCP joints, PIP joints and/or wrists |
| 4. Symmetrical distribution |
| 5. Rheumatoid nodules |
| 6. Rheumatoid factor positivity |
| 7. Radiographic changes typical for RA |

Visser et al[14] developed a prediction model which could discriminate between self-limiting and persistent (erosive) arthritis at the first visit. The Visser model consisted of 7 variables. Odds ratios of each variable were simplified to weighted scores. Added scores range from 0 to 13 points. One point corresponds with a 10% probability of developing persistent arthritis and 13 points with a 99% probability (table 2).[14]

**Table 2: (A) Diagnostic criteria of the Visser model and (B) total scores and predictive values for persistent arthritis**

**A.**

| Criteria | Score |
|---|---|
| Symptom duration | |
| • ≥6 weeks but <6 months | 2 |
| • ≥6 months | 3 |
| Morning stiffness ≥1 hour | 1 |
| Arthritis in ≥3 joint groups* | 1 |
| Bilateral compression pain in MTPs | 1 |
| RF positivity | 2 |
| ACPA positivity | 3 |
| Erosions on radiograph | 2 |

**B.**

| Total score | Probability of persistence |
|---|---|
| 0 | 0.10 |
| 1 | 0.15 |
| 2 | 0.23 |
| 3 | 0.34 |
| 4 | 0.46 |
| 5 | 0.59 |
| 6 | 0.71 |
| 7 | 0.80 |
| 8 | 0.87 |
| 9 | 0.92 |
| 10 | 0.95 |
| 11 | 0.97 |
| 12 | 0.98 |
| 13 | 0.99 |

*joint groups are: sternoclavicular, shoulder, elbow, wrist, knee, ankle, MTP, MCP, PIP and DIP on left and right side (22 groups in total). The MTP, MCP, PIP and DIP were counted as 1 joint. Abbreviations: ACPA, anti-citrullinated protein antibody; DIP, distal interphalangeal; MCP, metacarpophalangeal; MTP, Metatarsophalangeal; PIP, proximal interphalangeal and RF, rheumatoid factor.

In our trial eligible patients were stratified into three groups according to their likelihood of progressing to persistent arthritis based of the Visser model. The three strata (low (grey), intermediate (white), and high (black), table 2) correspond with probability tertiles of developing persistent arthritis.[14]

In 2010 new classification criteria for RA were developed (table 3).[3] Although in the rheumatic field classification criteria are often used as diagnostic criteria, they are not the same. In the meanwhile studies have shown that for RA the 2010 ACR/EULAR classification criteria can be used as diagnostic criteria, since the performance has been investigated in several studies, including the REACH study.[15] A recent review summarized the results of these studies and showed that the 2010 criteria for RA had an overall sensitivity of 82% and specificity of 61% to identify persistent arthritis.[16] The difference in sensitivity and specificity between the 2010 and 1987 criteria for RA was respectively +11% and -4%. In others words, the 2010 criteria detect an additional 11 out of 100 patients with persistent arthritis and misclassify 4 out of 100 patients without persistent arthritis, as having persistent arthritis in comparison with the 1987 criteria for RA. Consequently, 11 patients will start treatment earlier in the disease course and subsequently 4 patients might be overtreated.[16] The beneficial effect of starting treatment in a earlier phase will probably outweigh the negative effect of overtreatment. Interestingly, the Visser algorithm and 2010 criteria for RA have similar discriminative abilities to identify patients at risk of persistent arthritis at 1 year.[15]

Since its publication, the 2010 ACR/EULAR classification criteria for RA are more and more incorporated in daily practice of rheumatologists. All current guidelines for the management of RA, however, are based upon data from studies in patients fulfilling 1987 criteria for RA. Thus trials in the early phase of RA, like our tREACH trial, are needed for validation of those guidelines and to solve this unresolved question.

Furthermore, there are still some pitfalls for managing early RA. For example, feet are frequently affected in the early stages of the disease, while for assessing disease activity, rheumatologists often use disease activity indices (DAIs), which exclude the feet, because of their user-friendliness.[17] Thus, measuring disease activity with mentioned DAIs in early RA needs to be improved. Another challenge is the valid interpretation of DAIs. Although all DAIs have been developed in cohorts comprising patients with RA according to the 1987 criteria[12], DAIs already have been used in undifferentiated arthritis[18-20], since validation is lacking in this early population.

**Early initiation of 'intensive' therapy**

Several studies showed that early initiation of 'intensive' DMARD therapy improved clinical efficacy and may even prevent radiographic damage.[8, 11, 21-22] Aletaha et al[23], as one of the first, demonstrated that high disease activity during the first 3 months of treatment is significantly related to high disease activity at 1 year, which subsequently led to more destructive and disabling disease. Since the time span for the optimal effect of DMARDs is at least 6–12 weeks, the right choice of the initial treatment regimen has an important role in improving clinical efficacy.[24]

**Table 3: The 2010 ACR/EULAR classification criteria for RA**

| | Score |
|---|---|
| Target population (Who should be tested?): | |
| 1. Patient with <u>at least 1 joint</u> with definite clinical synovitis (swelling)* | |
| 2. Synovitis is not better explained by another disease | |
| Classification criteria for RA (score-based algorithm: add score of categories A-D; A score of ≥6/10 is needed for classification of a patient as having definite RA) | |
| A. Joint involvement§ | |
| • 1 large joint¶ | 0 |
| • 2–10 large joints | 1 |
| • 1–3 small joints (with or without involvement of large joints)** | 2 |
| • 4–10 small joints (with or without involvement of large joints) | 3 |
| • >10 joints (at least 1 small joint) | 5 |
| B. Serology (at least 1 test result is needed for classification)‡‡ | |
| • Negative RF *and* negative ACPA | 0 |
| • Low-positive RF *or* low-positive ACPA | 2 |
| • High-positive RF *or* high-positive ACPA | 3 |
| C. Acute-phase reactants (at least 1 test result is needed for classification) | |
| • Normal CRP *and* normal ESR | 0 |
| • Abnormal CRP *or* abnormal ESR | 1 |
| D. Duration of symptoms¶¶ | |
| • <6 weeks | 0 |
| • ≥6 weeks | 1 |

*The criteria are aimed at classification of newly presenting patients.
§ Joint involvement refers to any swollen or tender joint on examination, which may be confirmed by imaging. Categories of joint distribution are classified according to the location and number of involved joints, with placement into the highest category possible based on the pattern of joint involvement.
¶ Large joints refers to shoulders, elbows, hips, knees and ankles.
**'Small joints refers to the metacarpophalangeal joints, proximal interphalangeal joints, second to fifth metatarsophalangeal joints, thumb interphalangeal joints and wrists.
‡‡ NEG refers to IU values ≤upper limit of normal (ULN) for the laboratory and assay; low-positive refers to IU values >ULN but ≤3x ULN; high-positive refers to IU values >3x the ULN. When RF information is only available as POS or NEG, a POS should be scored as low-positive for RF.
¶¶ Duration of symptoms refers to patient self-report of the duration of signs of synovitis.
Abbreviations: ACPA, anti-citrullinated protein antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IU, International Unit; and RF, Rheumatoid Factor.

Therefore, the aim of many clinical trials, in the past 20 years, was to compare different treatment strategies. Besides comparing different treatment strategies, also optimal dosing and route of administration of different DMARDs were reevaluated. However, still no consensus has been reached about what the most appriorate initial 'intensive' treatment regimen should be. Most important unresolved question herein is that of initital monotherapy versus a combination of DMARDs and the role of glucocorticoids (GCs).

Several clinical trials concluded that initial combination therapy had superior clinical efficacy over initial monotherapy, however, most rheumatologists have not implemented this in daily practice.[8, 21, 25-26] Moreover, the 2010 EULAR guideline recommends MTX monotherapy rather than a combination of DMARDs as initial treatment regimen, in patients with newly diagnosed RA.[4] Most important reason to disregard the outcomes of mentioned trials, is the fact that all these trials were biased

by GCs.[27] Moreover, other trials invalidate this supposed superior efficacy. [28-29] Trials comparing triple DMARD therapy versus MTX monotherapy in DMARD naïve patients are, however, sparse. Other reasons not to implement combination therapy in daily practice is due to safety concern issues and practical feasibility.[29] These safety concerns consist primarily of the fact that multiple drug usage, due to (1) synergistic effects and (2) higher prior chance, leads to more adverse events.

GCs are often used as bridging therapy for active disease in the period between initiation of DMARD treatment and onset of their therapeutic effect.[30] GCs have disease-modifying traits with long-lasting benefits even after withdrawal.[30] Gorter *et al*[31] reviewed the literature for the 2010 EULAR recommendations, looking at the efficacy of GCs in RA. They concluded that GCs relieved symptoms and inhibited radiographic progression. However, research is needed to optimise GC bridging therapy with DMARDs, especially determination of optimal dosage and tapering schemes.

For the above mentioned unresolved questions about initial treatment strategies, we compared, within the tREACH trial, the clinical efficacy of (1) initial triple DMARD therapy versus MTX monotherapy, and (2) different GC bridging therapies: oral versus a single intramuscular injection.

Ideally, a tailor-made treatment approach is used in this very early phase, especially since about 60% will respond sufficiently to the initial treatment. Moreover, problems as over-treatment and accompanying (serious) adverse events are circumvented by this tailor-made treatment approach. In view of aforementioned problems, we think it would be helpful if treatment response to the initial DMARD treatment could be adequately measured and, ideally, predicted as soon as possible after initiation. This would be a major improvement in the management of early RA, because it could ultimately lead to a 'tailor made' treatment approach.

**Treat-to-target**

Grigor *et al*[32] introduced the treat-to-target approach in their TICORA trial, in which intensive outpatient management of patients with RA was compared with routine care. Intensive management led to improvement of disease activity and functional ability and less radiographic progression without additional costs. The CAMERA trial confirmed improvement of clinical efficacy using intensive management, in this case making use of a strict protocol and a computerized decision program.[33] The BeSt study was the first trial to compare different initial treatment strategies with a treat-to-target approach in their follow-up.[25]

In a treat-to-target approach rheumatologists strive to reach a predefined therapeutic goal as soon as possible. The 2010 EULAR recommendations recommend to strive for remission within 3 months.[34] To achieve this goal mentioned guideline recommends that patients should be monitored strictly ('tight control'), every 1-3 months, with a DAI and if the target is not reached, treatment should be intensified.[34] Consequently, intensifying treatment will be more expensive since most international guidelines recommend starting expensive biologicals after failing on 2 conventional

DMARDs in an optimal dosage.[4, 35] On the other hand tightly controlled intensive treatment also had an increased remission rate compared with routine care.[27-28] Therefore, DAI usage might expand to giving guidance in tapering treatment in case of sustained remission.[5]

For health economic reasons efficient use of expensive drugs is needed to be able to continue optimal rheumatic care in the future. In order to manage the exponentially increasing health care costs health insurance companies and governments will judge the compensation of prescribed drugs by evidence based data on cost-effectiveness.[33,36] Previous cost analyses showed that a strategic approach with rapid treatment intensification to biological agents is cost-effective. [36-37] However, it is still unclear which initial treatment regimen has the best cost-effectiveness ratio. Furthermore, all previous cost-effectiveness analysis were performed in patients fulfilling 1987 classification criteria for RA.[12] Until now no data on cost-effectiveness in patients fulfilling 2010 criteria for RA were available.[3] Trials in the early phase of RA, like our tREACH trial, are needed to evaluate if aforementioned approach is also cost-effective in very early RA.

**Table 4: Formulas and thresholds for disease activity indices (DAIs).**

| DAI | Formula | Thresholds[1] |
|---|---|---|
| DAS | 0.53938√(RAI) + 0.06465(SJC44) + 0.33ln(ESR) + 0.00722(GH) | <1.6/<2.4/<3.7 |
| DAS (3var) | 0.53938√(RAI) + 0.06465(SJC44) + 0.33ln(ESR) + 0.224 | |
| DAS (CRP) | 0.53938√(RAI) + 0.06465(SJC44) + 0.17ln(CRP+1) + 0.00722(GH) + 0.45 | |
| DAS (CRP/3var) | 0.53938√(RAI) + 0.06465(SJC44) + 0.17ln(CRP+1) + 0.65 | |
| DAS28 | 0.56√(TJC28) + 0.28√(SJC28) + 0.70ln (ESR) + 0.014(GH) | <2.6/<3.2/<5.1 |
| DAS28 (3var) | (0.56√(TJC28) + 0.28√(SJC28) + 0.70ln (ESR))1.08 + 0.16 | |
| DAS28 (CRP) | 0.56√(TJC28) + 0.28√(SJC28) + 0.36ln (CRP+1) + 0.014(GH) + 0.96 | |
| DAS28 (CRP/3var) | (0.56√(TJC28) + 0.28√(SJC28) + 0.36ln (CRP+1))*1.10 + 1.15 | |
| SDAI | SJC28 + TJC28 + PGA + EGA + CRP | ≤3.3/≤11/≤26 |
| CDAI | SJC28 + TJC28 + PGA + EGA | ≤2.8/≤10/≤22 |

[1]Thresholds for respectively remission / low disease activity / moderate disease activity

*Abbreviations:* CDAI, Clinical Disease Activity Index; CRP, C-reactive protein (DAS → *mg/l* & SDAI → *mg/dl*); DAS, Disease Activity Score; DAS(3var), DAS without GH*;* DAS(CRP), DAS with CRP instead of ESR*;* DAS(CRP/3var), DAS with CRP and without GH*;* DAS28, DAS using a 28 joint count*;* EGA, Evaluator Global Assessment of disease activity (*VAS of 10cm*); ESR, Erythrocyte Sedimentation Rate; GH, General Health (*VAS of 100mm*); PGA, Patient Global Assessment of disease activity (*VAS of 10cm*); RAI, Ritchie Articular Index (53 joints in 26 units, graded for tenderness); SDAI, Simplified Disease Activity Index*;* SJC, Swollen Joint Count; TJC, Tender Joint Count.

There are various DAIs available (table 4) for monitoring disease activity in RA.[38-41] A DAI is a pooled index that involves the incorporation of various parameters into a formula to obtain a numerical indicator of disease activity. The following core set parameters were identified: tender and swollen joint counts, acute-phase reactants and general evaluator's and patient's global assessment of disease activity.[42] All DAIs have their own thresholds for remission, low, moderate and high disease activity (table 4).[41] However, there is no consensus about which DAI should be used, because direct comparison of all DAIs is not yet investigated. Moreover, mentioned DAIs need to be validated in patients with RA according to 2010 criteria, since all DAIs were developed in cohorts comprising patients fulfilling 1987 criteria for RA.

In the tREACH we used a treat-to-target approach, aiming for low disease activity, defined as a DAS<2.4.[38,43] Patients were examined every three months and treatment was adjusted, if the target was not reached. Although current guidelines recommend to target treatment at achieving remission, no trials comparing different predefined treatment goals have been conducted.[4-5]

## OUTLINE OF THE THESIS

Early detection of the disease is one of the paradigm changes in the management of RA. Because the Visser algorithm and 2010 criteria for RA have similar discriminative abilities to identify persistent arthritis at 1 year, the results of the tREACH trial may be used to validate current guidelines for patients within an earlier phase of the disease.

Early initiation of 'intensive' therapy is another important paradigm change. However, still no consensus has been reached about what the most appropriate initial 'intensive' treatment regimen should be. Most important discussion herein is that of initial MTX monotherapy versus a combination of DMARDs. Therefore, in ***chapter 2 and 3***, the efficacy of initial triple DMARD therapy is compared with MTX monotherapy, unbiased for GCs, using respectively the 3 months and 1 year data of the tREACH trial.

For health economic reasons efficient use of expensive drugs is needed to be able to continue optimal rheumatic care in the future. Therefore, we investigated, in ***chapter 4***, which initial treatment regimen had the best cost-effectiveness ratio.

A treat-to-target approach is advocated in order to obtain better functional and radiological outcomes in RA. To achieve the predefined treatment goals patients should be monitored strictly with a DAI. There are various DAIs available for monitoring RA. In ***chapter 5*** we investigate how inconsistencies between DAIs influence therapeutic decisions and accompanying costs in early RA.

Although the management of RA has underwent major paradigm changes, there is still room for improvement, particularly in the areas of efficiency. Ideally a 'tailor made' treatment approach is used to circumvent problems as over-treatment and accompanying (serious) adverse events. However, until now no clinical applicable predictors for early treatment response were available. In ***chapter 6*** we link the early effect of GCs to the initial DMARD response.

Incorporation of the 2010 criteria for RA in daily practice leads to changing disease characteristics of a 'typical' RA patient. Feet are frequently affected in the early stages of the disease, while rheumatologists often use DAIs, which exclude feet, because of their user-friendliness. Thus, measuring disease activity with mentioned DAIs needs to be improved when used in early RA. Therefore, in ***chapter 7***, we analyzed whether disease activity assessments could be improved, for patients with early RA, by adding the squeeze test of forefeet.

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**CHAPTER 2**

# Induction therapy with a combination of DMARDs is better than methotrexate monotherapy: first results of the tREACH trial

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**Background**
To determine the most effective induction disease-modifying antirheumatic drug (DMARD) strategy in early rheumatoid arthritis (RA), second to compare one single dose of intramuscular glucocorticoids (GCs) with daily oral GCs during the induction phase.

**Methods**
The 3-month data of a single-blinded clinical trial in patients with recent-onset arthritis (tREACH) were used. Patients were included who had a high probability (> 70%) of progressing to persistent arthritis, based on the prediction model of Visser. Patients were randomised into three induction therapy strategies: (A) Combination therapy (methotrexate (MTX) + sulfasalazine + hydroxychloroquine) with GCs intramuscularly, (B) Combination therapy with an oral GC tapering scheme, and (C) MTX with oral GCs similar to B. A total of 281 patients were randomly assigned to (A) (n=91), (B) (n=93) or (C) (n=97).

**Findings**
The Disease Acitivity Score (DAS) after 3 months was lower in patients with initial combination therapy than in those receiving MTX monotherapy (0.39 (0.67 to 0.11, 95% confidence interval)). DAS did not differ between the different GC bridging therapies. After 3 months 50% fewer biologicals were prescribed in the combination therapy groups. Although the proportion of patients with medication adjustments due to adverse events differed significantly between the treatment arms, no differences were seen in these adjustments after stratification for drug.

**Interpretation**
Triple DMARD induction therapy is better than MTX monotherapy in early RA. Furthermore no differences were seen in medication adjustments due to adverse events after stratification for drug. Intramuscular and oral GCs are equally effective as bridging therapy and can both be used.

**Key words**
- Rheumatoid Arthritis; early arthritis; combination therapy; glucocorticoids; induction therapy

## INTRODUCTION

The EULAR recommendations suggest use of methotrexate (MTX) with or without glucocorticoids (GCs) as adequate induction therapy for patients with newly diagnosed rheumatoid arthritis (RA).[1] Furthermore, rheumatologist should strive for remission within 3 months in order to obtain better functional and radiological outcomes.[1-3] However, some points of these recommendations should be discussed.

First, although several clinical trials concluded that combination therapy had better clinical efficacy than monotherapy, current guidelines recommend MTX monotherapy. This is mainly because in all these trials the results were biased by GCs.[4] Another reason to recommend MTX monotherapy is due to safety concerns.[5]

Second, GCs are often used as bridging therapy for active disease in the period between induction of disease-modifying antirheumatic drug (DMARD) therapy and onset of their therapeutic effect.[6] However, the extend and rapidity of clinical effectiveness may differ between the different GC bridging therapies.

Finally, new ACR/EULAR criteria for RA[7] have been published and rheumatologists will increasingly begin to use these criteria in their daily practice. The EULAR recommendations for treatment[1], however, were all based upon data from studies performed in patients fulfilling 1987 ACR classification criteria.[8] Therefore, rheumatologists need data to make a valid choice of induction DMARD therapy in the early phase of RA.

To obtain answers to all these objectives we studied within the tREACH trial the clinical efficacy of (1) induction combination DMARD therapy versus MTX monotherapy and (2) different GC bridging therapies: oral tapering versus a single injection. All objectives were carried out in patients with a high probability of developing persistent arthritis and two subgroups comprising patients with RA according to 1987 and 2010 criteria.[7, 8]

## PATIENTS AND METHODS

### Patients

For this study data were used of a clinical trial (ISRCTN26791028), namely Treatment in the Rotterdam Early Arthritis Cohort (tREACH).[9] tREACH, a multicenter, stratified single-blinded trial, is performed in eight rheumatology centres in the southwestern part of the Netherlands. The medical ethics committee at each participating centre approved the study protocol, and all patients gave written informed consent before inclusion.

An extended description of the tREACH has already been published.[9] Inclusion criteria for the tREACH are: Age ≥18 years, arthritis in one or more joints and symptom duration <1 year. Patients were excluded if (1) they were diagnosed with a crystal arthropathy, (post)infectious arthritis, or autoimmune disorder other than RA; (2) were receiving DMARD therapy or GCs; or (3) had contraindications for the initial study

medication (chronic liver disease; excessive alcohol and drug use; pregnancy (wish) ; or laboratory abnormalities: leucopenia (< $3.0 \times 10^9$/l), thrombocytopenia (< $150 \times 10^9$/l), aspartate aminotransferase/ alanine aminotransferase > 2x upper normal value and creatinine level > 150 µmol/l).

Eligible patients were stratified into three groups according to their likelihood of progressing to persistent arthritis based of the prediction model of Visser.[10] The three strata (low, intermediate and high) correspond to probability tertiles of developing persistent arthritis according to the Visser model. For this analysis we only included the high probability group since for the other strata recruitment is still continuing.

**Randomisation and masking**

Patients were randomised, using variable block randomisation stratified for centre, by an independent call-centre during working hours. Trained research nurses were blinded for the allocated treatment arm throughout the study. Research nurses examined the patients and calculated the Disease Activity Score (DAS), on which treatment decisions are based.

**Design**

Patients were randomised into one of following induction therapy arms:

A. Combination therapy (MTX, Sulfasalazine (SASP) and hydroxychloroquine (HCQ)) with GCs intramuscularly)
B. Combination therapy with an oral GC tapering scheme
C. MTX with an oral GC tapering scheme

Concurrent therapy with non-steroidal anti-inflammatory drugs and intra-articular GC injections (max. two per 3 months) was allowed during the study.

DMARD dosages were: MTX 25 mg/week orally (dosage reached after 3 weeks), SASP 2 g/day and HCQ 400 mg/day. GCs were either given intramuscularly (methylprednisolone 120mg or triamcinolone 80mg) or in an oral tapering scheme (weeks 1-4: 15 mg/day, weeks 5-6: 10 mg/day, weeks 7-8: 5 mg/day, and weeks 9-10: 2.5 mg/day). All patients received folic acid (10 mg/week) during MTX prescription. Osteoporosis prophylaxis (risedronate 35 mg/week and calcium/vitamin D combination 500/400 mg/IU/day) was given to patients allocated to treatment arms B and C, during the first 3 months.

Treatment strategies were 'tightly controlled', with patients being examined every 3 months and treatment decisions are based upon the original DAS thresholds for low disease activity.[9, 11] When treatment failed, defined as DAS≥2.4, medication is intensified to MTX with etanercept (50 mg/week). Treatment intensifications were the same in each stratum for each treatment arm.[9]

**Assessment of clinical efficacy**

For assessment of clinical efficacy the primary outcomes were (1) disease activity (state), and (2) functional ability. Disease activity is measured with the original DAS and its corresponding thresholds were used for the disease state categorizations.[11] Functional ability was measured with the Dutch version of the Health Assessment Questionnaire (HAQ).[12] Higher HAQ scores indicate poorer function. Secondary endpoints were: EULAR response criteria[13] and self assessed disease activity, measured with the Rheumatoid Arthritis Disease Activity Index questionnaire (RADAI).[14] EULAR response criteria are based on attained level and change in DAS. They classify patients as good, moderate or none-responder (see supplementary figure S1). Higher RADAI scores correspond with more active disease.

**Safety monitoring and toxicity**

Safety monitoring was carried out according to Dutch guidelines[15, 16] and included laboratory tests at fixed intervals. The study drug was either stopped or dosage lowered in accordance with the protocol if (serious) adverse events,[9] using WHO's adverse reaction terminology,[17] were seen by the attending rheumatologist. MTX could be given subcutaneously if patients had gastrointestinal complaints. If MTX needed to be stopped for safety reasons, leflunomide (20 mg/day) was substituted.[9]

**Statistical Analyses**

Sample-size calculation was based upon the area under the curve (AUC) of the HAQ, using data from the BeSt study[18], where mean AUC HAQ of combination therapy and monotherapy respectively was 7.7 (SD 5.5) and 10.5 (SD 7.4). A target sample size of 270 patients per probability stratum (90 patients per arm) was needed to detect mentioned difference in AUC HAQ with a power of 80% and a two-sided $\alpha$=0.05. This number of patients is sufficient to detect a difference of 6.1 AUC DAS ($\alpha$ = 0.05; power 80%).

Clinical efficacy was calculated in an intention-to-treat, using all available data, and per-protocol analysis. Statistical comparison between baseline characteristics and outcome measures of the treatment allocations were made by the Student t test, $\chi^2$ test, or the Wilcoxon rank-sum test, when appropriate. Multivariate analyses for the primary outcomes were performed, if imbalances in baseline characteristics between treatment groups existed.

All analyses were performed for patients in the high-probability stratum and for two subgroups consisting of patients with RA according to 1987 and 2010 classification criteria.[7, 8] All statistical analyses were carried out using STATA version 11.1. A p value $<0.05$ was considered statistically significant.

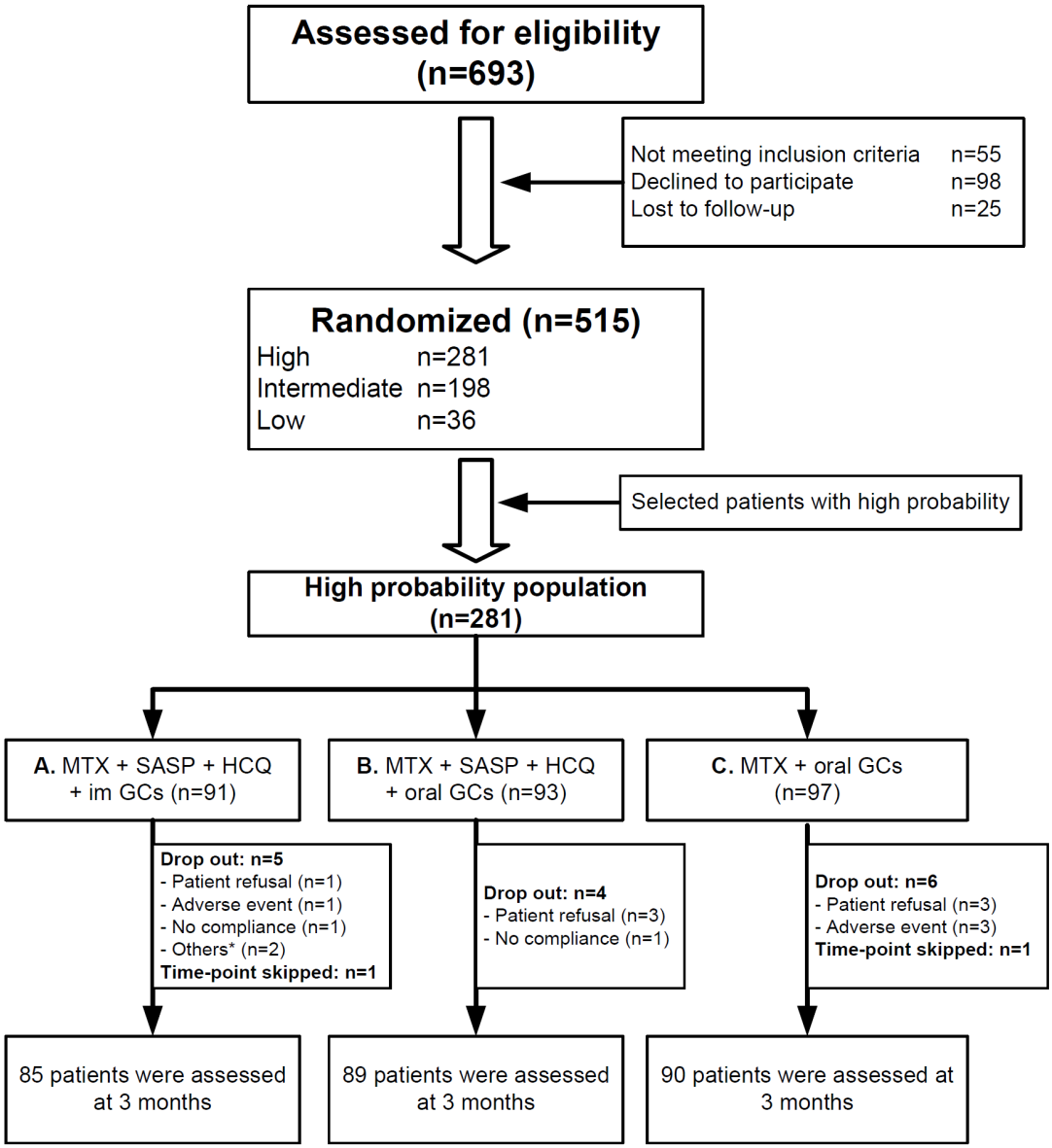



**Figure 1: Trial profile.**

*Other reasons to drop out were: incorrect randomisation and problems with communication.

Abbreviations: GCs, glucocorticoids; HCQ, hydroxychloroquine; im, intramuscular; MTX, methotrexate and SASP, sulfasalazine.

## RESULTS

### Patients

Up to now, a total of 693 patients have been assessed for eligibility and of those, 515 patients were included in the tREACH (figure 1). A total of 281 patients were included in the high-probability stratum and randomly assigned to (A) (n=91), (B) (n=93) or (C) (n=97). Four patients (1%) had protocol violations because of non-compliance (respectively 1, 2, and 1 patient in arm A, B, and C), but these patients were not lost to follow-up. All patients, who were assessed at 3 months, were included in our intention-to-treat (ITT) analysis (n=264). For the per protocol analysis we excluded only the four patients with non-compliance, because medication adjustments due to adverse events (AEs) are taken up in the medication protocol.

Table 1 shows the baseline characteristics per treatment arm. The symptom duration, occurrence of erosions and proportion of patients who fulfilled the 1987 criteria for RA differed significantly between treatment arms (table 1). Therefore, we also performed multivariate analyses for the primary outcomes.

### Clinical outcomes

The DAS after 3 months, was 0.39 (0.11 to 0.67, 95% confidence interval (CI)) lower in patients with initial combination therapy than those receiving MTX monotherapy. The difference in DAS between the different GC bridging therapies was 0.03 (-0.24 to 0.31, 95% CI) (table 2). About 78% of the patients, using combination therapy, had a DAS<2.4, compared with 60% of the patients using MTX monotherapy (table 2). Consequently, induction therapy failed for about 22% and 40% of the patients treated with respectively combination therapy and MTX monotherapy and, therefore, treatment was intensified to MTX with etanercept (table 2). Baseline DAS was the only factor associated with active disease (DAS≥2.4) after 3 months in all treatment arms. Odds ratios (95% CI) were respectively 2.27 (1.12 – 4.62), 4.36 (2.15 – 8.19) and 2.50 (1.47 – 4.26) in treatment arm A, B and C.

Functional improvement was seen in all patients. The difference in functional ability between the treatment arms was not significant and only a trend could be observed (table 2). Secondary endpoints - namely, EULAR response criteria and RADAI - are shown in table 2.

In the multivariate analyses we corrected for following factors: gender, rheumatoid factor, anti-citrullinated protein/peptide antibodies, presence of erosions, complaint duration and baseline DAS. A significant difference in disease activity (state) at 3 months persisted between MTX monotherapy versus combination therapy, but now also functional ability differed significantly between both groups (table 3). Again disease activity (state) and HAQ did not differ significantly between both GC bridging therapies (table 3).

**Table 1: Baseline characteristics of patients with a high probability of developing persistent arthritis, stratified for induction therapy.**

| | A. MTX + SASP + HCQ + im GCs (n=91) | B. MTX + SASP + HCQ + oral GCs (n=93) | C. MTX + oral GCs (n=97) |
|---|---|---|---|
| Age (yrs), *mean (sd)* | 53 (15) | 54 (14) | 54 (14) |
| Sex, female, *no(%)* | 55 (60) | 67 (72) | 68 (72) |
| Symptom duration (days), *mean (sd)*[*] | 162 (97) | 184 (92) | 154 (83) |
| RF positivity, *no(%)* | 55 (60) | 51 (55) | 51 (53) |
| ACPA positivity, *no(%)* | 59 (65) | 50 (54) | 56 (58) |
| Erosion, *no(%)*† | 24 (26) | 12 (13) | 12 (12) |
| Fullfillment RA criteria, *no(%)* | | | |
| • *1987*‡ | 69 (76) | 57 (61) | 63 (65) |
| • *2010* | 83 (91) | 80 (86) | 83 (86) |
| DAS, *mean (sd)* | 3.28 (1.06) | 3.39 (1.07) | 3.38 (0.97) |
| DAS28, *mean (sd)* | 4.81 (1.12) | 4.83 (1.28) | 4.78 (1.27) |
| TJC44, *median (IQR)* | 8 (4 - 14) | 9 (5 - 15) | 10 (4 - 14) |
| SJC44, *median (IQR)* | 8 (5 -12) | 7 (4 - 12) | 7 (4 - 12) |
| VAS global (0 -100mm), *median (IQR)* | 52 (34 - 70) | 55 (29 – 69) | 53 (38 – 70) |
| ESR in mm/hr, *median (IQR)* | 27 (14 - 40) | 22 (13 – 40) | 24 (14 – 42) |
| CRP in mg/L, *median (IQR)* | 8 (3.5 - 23) | 6.5 (4 -19) | 11 (5 - 26) |
| HAQ, *mean (sd)* | 0.98 (0.67) (n=84) | 0.96 (0.64) (n=84) | 1.06 (0.68) (n=92) |
| RADAI (0-10), *mean (sd)* | 3.97 (1.83) (n=81) | 3.94 (1.63) (n=80) | 4.21 (1.82) (n=87) |

Not everyone filled in a (complete) questionnaire and therefore n is different for HAQ and RADAI.

*p=0.018 for B vs C.

†p=0.021 and p=0.015 for respectively A vs B and A vs C.

‡p=0.034 for A vs B.

Abbreviations: ACPA, anti-citrullinated protein/peptide antibodies; CRP, C-reactive protein; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; GCs, glucocorticoids; HAQ, Health Assessment Questionnaire; HCQ, hydroxychloroquine; IQR, interquartile range; MTX, methotrexate; RADAI, Rheumatoid Arthritis Disease Activity Index questionnaire; RF, rheumatoid factor; SASP, sulfasalazine; sd, standard deviation; SJC44, swollen joint count (44 joints); TJC44, tender joint count (44 joints); VAS, visual analogue scale.

**Table 2: Clinical response after 3 months for each induction therapy group, intention-to-treat analysis.**

| | A. MTX + SASP + HCQ + im GCs (n=85) | B. MTX + SASP + HCQ + oral GCs (n=89) | C. MTX + oral GCs (n=90) |
|---|---|---|---|
| DAS, *mean (sd)*† | 1.86 (0.96) | 1.82 (0.86) | 2.21 (1.04) |
| ΔDAS (T3 - T0), *mean (sd)*‡ | -1.39 (1.00) | -1.54 (0.98) | -1.19 (1.02) |
| Disease state according to DAS, *no (%)* | | | |
| • *moderate to high disease activity (DAS≥2.4)*§* | 20 (24) | 19 (21) | 36 (40) |
| • *low disease activity (1.6≥DAS<2.4)* | 28 (33) | 32 (36) | 26 (29) |
| • *remission(DAS<1.6)* | 37 (44) | 38 (43) | 28 (31) |
| EULAR response criteria, *no(%)* | | | |
| • *good* | 45 (53) | 43 (48) | 39 (43) |
| • *moderate* | 23 (27) | 30 (34) | 23 (26) |
| • *None*¶ | 17 (20) | 16 (18) | 28 (31) |
| TJC44, *median (IQR)*# | 1 (0 - 4) | 1 (0 - 5) | 3 (0 – 7) |
| SJC44, *median (IQR)* | 1 (0 - 3) | 1 (0 - 3) | 1 (0 – 4) |
| VAS global (0 -100mm), *median (IQR)*** | 24 (13 - 36) | 26 (15 - 48) | 39.5 (21 - 54) |
| ESR in mm/hr, *median (IQR)* | 14 (6 – 27) | 10 (5 – 21) | 12.5 (7 - 22.5) |
| CRP in mg/L, *median (IQR)*†† | 4.4 (1.2 - 8) | 3.2 (1 - 5.6) | 5 (2 - 9) |
| HAQ, *mean (sd)* | 0.53 (0.54) (n=73) | 0.52 (0.55) (n=83) | 0.69 (0.64) (n=79) |
| ΔHAQ (T3 - T0), *mean (sd)* | -0.41 (0.50) (n=69) | -0.40 (0.53) (n=78) | -0.37 (0.57) (n=78) |
| RADAI (0 - 10), *mean (sd)*‡‡ | 1.99 (1.78) (n=71) | 1.93 (1.81) (n=79) | 2.57 (2.02) (n=76) |
| ΔRADAI (T3 - T0), *mean (sd)* | -1.95 (1.73) (n=67) | -1.96 (1.92) (n=71) | -1.54 (1.75) (n=73) |

Not everyone filled in a (complete) questionnaire and therefore n is different for HAQ and RADAI.

Abbreviations: CRP, C-reactive protein; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; GCs, glucocorticoids; HAQ, Health Assessment Questionnaire; HCQ, hydroxychloroquine; IQR, interquartile range; MTX, methotrexate; RADAI, Rheumatoid Arthritis Disease Activity Index questionnaire; SASP, sulfasalazine; sd, standard deviation; SJC44, swollen joint count (44 joints); TJC44, tender joint count (44 joints); VAS, visual analogue scale.

*Starting biological agent.

†p=0.021 and p=0.007 for respectively A vs C and B vs C. ‡p=0.020 for B vs C. ¶p=0.04 for B vs C. #p=0.018 for A vs C

§p=0.020 and p=0.007 for respectively A vs C and B vs C. **p=0.0009 for A vs C. ††p=0.035 for B vs C. ‡‡p=0.038 for B vs C

**Table 3: Multivariate analyses for primary outcomes for monotherapy versus combination therapy and both GC bridging therapies: oral tapering versus a single injection, intention-to-treat analysis.**

| | Monotherapy (C) (ref.) vs. Combination therapy (B) | Bridging: oral tapering (B) (ref.) vs. 1x im. injection (A) |
|---|---|---|
| **Linear regression, *beta (95% CI)*** | | |
| Diff. in DAS at 3 months | -0.39 (-0.65 to -0.14)† | 0.15 (-0.11 to 0.41) |
| Diff. in HAQ at 3 months | -0.19 (-0.34 to -0.03)‡ | 0.08 (-0.07 to 0.24) |
| | | |
| **Logistic regression, *OR (95% CI)*** | | |
| Disease state according to DAS | | |
| • *moderate to high disease activity** | 0.31 (0.15 - 0.68)§ | 1.89 (0.82 – 4.35) |
| • *low disease activity* | 1.31 (0.69 - 2.49) | 0.83 (0.43 - 1.59) |
| • *remission* | 1.90 (0.95 - 3.81) | 0.89 (0.45 - 1.76) |

Primary outcomes were corrected for gender, rheumatoid factor positivity, anti-citrullinated protein/peptide antibodies positivity, presence of erosions, complaint duration and baseline DAS. The first mentioned treatment strategy in each column is used as reference group.

*Starting biological agent.

†p=0.002 for B vs. C

‡p=0.017 for B vs. C

§p=0.003 for B vs. C

Abbreviations: CI, confidence interval; DAS, Disease Activity Score; GCs, glucocorticoids; HAQ, Health Assessment Questionnaire; im, intramuscular; OR, odds ratio and ref, reference.

**Table 4: Number (%) of patients with (serious) adverse events and treatment alterations due to side-effects for each induction therapy group.**

| | A. MTX + SASP + HCQ + im GCs (n=85) | B. MTX + SASP + HCQ + oral GCs (n=89) | C. MTX + oral GCs (n=90) |
|---|---|---|---|
| Serious AE(s) | 1 (1) | 4 (4) | 6 (7) |
| Patients with ≥1 AE(s)* | 61 (72) | 67 (75) | 50 (56) |
| no.of AEs per patient, *median(IQR)* | 1 (0 - 2) | 2 (1 - 2) | 1 (0 - 2) |
| Medication changes due to AE(s) | | | |
| • *Patients with medication changes* | 19 (22) | 18 (20) | 14 (16) |
| • *lowering MTX dosage <20 mg/wk* | 8 (9) | 6 (7) | 9 (10) |
| • *STOP MTX* | 5 (6) | 6 (7) | 5 (6) |
| • *STOP SASP* | 9 (11) | 7 (8) | NA |
| • *STOP HCQ* | 2 (2) | 2 (2) | NA |

Results are shown as number (%) unless stated otherwise.

*p=0.026 and p=0.006 for respectively A vs C and B vs C.

Serious AEs per treatment arm are respectively: [A] 1× hospitalisation (pneumonia); [B] 4× hospitalisation (for respectively severe obstipation, transient ischaemic attack, gastroenteritis and unexplained chest pain); [C] 1× myocardial infarction, 1× colon carcinoma, 4× hospitalisation (for respectively pneumonia, blood transfusion, syncope and exacerbation of rheumatoid arthritis).

Abbreviations: AE, adverse event; GCs, glucocortoids; HCQ, hydroxychloroquine; im, intramuscular; MTX, methotrexate; SASP, sulfasalazine.

All mentioned analyses were based upon ITT. We also performed a per-protocol analysis for all primary and secondary outcomes, which showed similar results to those of the ITT analysis (data not shown). We also performed all the abovementioned analysis for both subgroups – namely, RA according to the 1987 and 2010 classification criteria, which produced similar results (see supplementary tables S1 to S4).

**Adverse events (AEs)**

Table 4 shows the number (%) of patients with (serious) adverse events and treatment alterations due to adverse events for each treatment arm. The proportion of patients with medication adjustments differed significantly between the treatment arms. However, no differences were seen in medication adjustments due to AEs, after stratification for drug.

The reasons for lowering the MTX dosage were (1) gastrointestinal complaints n=6, n=2 and n=4; (2) raised liver enzymes n=1, n=2 and n=4; (3) distorted kidney function n=0, n=2 and n=1 and (4) bone marrow depression n=1, n=0 and n=0 in treatment arms A, B and C, respectively. MTX was switched to subcutaneous injections in 4 (5%), 14 (16%) and 5 (6%) patients in arms A, B and C, respectively. MTX was stopped in 5 patients (6%) in arm A, because of gastrointestinal complaints (n=4) and skin rash (n=1). In arm B MTX was stopped in 6 patients (7%), because of gastrointestinal complaints (n=5) and raised liver enzymes (n=1). Gastrointestinal complaints (n=2), elevated liver enzymes (n=1), bone marrow depression (n=1) and hair loss (n=1) were the reasons for stopping MTX in 5 patients in arm C.

SASP was stopped in 9 (11%), and 7 (8%) patients in arm A and B, respectively. Reasons for stopping SASP were (1) gastrointestinal complaints, n=7 and n=6, and (2) skin rashes, n=2 and n=1, in arms A and B, respectively. The HCQ discontinuation rate was 2% in both arms (A + B). In both arms, the reasons for stopping HCQ were gastrointestinal complaints (n=1) and skin rashes (n=1). Gastrointestinal complaints and fatigue were the most commonly reported AEs (table 5).

## DISCUSSION

In this study, unbiased for GCs, induction therapy consisting of a combination of DMARDs is better than MTX monotherapy in early RA. The combination therapy groups achieved more often a DAS<2.4 wihin 3 months, which led to 50% less frequent treatment intensifications to biological agents compared with MTX monotherapy. A difference in functional ability was seen, which became significant after correction for baseline imbalances. Bridging therapy consisting of one single dose of intramuscular GCs is as effective as a 10-week intermediate dose of oral GCs. Although the proportion of patients with medication adjustments due to AEs differed significantly between the treatment arms, no differences were seen in medication adjustments, after stratification for drug.

**Table 5: Number(%) of patients reporting adverse events per treatment arm.**

| | A. MTX + SASP + HCQ + im GCs (n=84) | B. MTX + SASP + HCQ + oral GCs (n=89) | C. MTX + oral GCs (n=90) |
|---|---|---|---|
| Malaise | 11 (13) | 8 (10) | 9 (11) |
| Fatigue | 18 (21) | 20 (24) | 18 (21) |
| Gastrointestinal complaints | 43 (51) | 46 (55) | 25 (30) |
| Hypertension | 1 (1) | 2 (2) | 0 (0) |
| Oedema | 2 (2) | 1 (1) | 4 (5) |
| Infection | 3 (4) | 4 (5) | 9 (11) |
| Skin rashes | 8 (10) | 8 (10) | 7 (8) |
| Hair loss | 3 (4) | 2 (2) | 6 (7) |
| Muscle weakness | 0 (0) | 1 (1) | 3 (4) |
| Headache | 8 (10) | 10 (12) | 8 (10) |
| Visual impaiment | 1 (1) | 9 (11) | 2 (2) |
| Feeling 'sad' | 2 (2) | 9 (11) | 8 (10) |
| Sleepdisorder | 2 (2) | 6 (7) | 2 (2) |
| Dizziness | 1 (1) | 7 (8) | 1 (1) |
| Palpitations | 2 (2) | 2 (2) | 1 (1) |
| Bone marrow depression | 13 (15) | 4 (5) | 4 (5) |
| High Creatinine | 0 (0) | 6 (7) | 3 (4) |
| Elevated liver enzymes | 4 (5) | 7 (7) | 9 (11) |
| Hyperglycemia | 0 (0) | 1 (1) | 0 (0) |

Results are shown as number (%).

Bone marrow depression is defined as an anaemia, thrombocytopenia or leucopenia with respectively a haemoglobin level, platelet and white blood cells count below the lower limit of the normal range. High creatinine, raised liver enzymes and hyperglycaemia are defined as having respectively a creatinine, liver transaminases and glucose level above the upper limit of the normal range.

Abbreviations: GCs, glucocorticoids; HCQ, hydroxychloroquine; im, intramuscular; MTX, methotrexate; SASP, sulfasalazine.

This study was designed to start DMARD treatment in the early phase of RA. At the time of writing the protocol no international accepted criteria for classifying the early phase of RA were defined. Therefore, we based our design on the Visser model reflecting patients in a early phase of persisting arthritis.[10] Interestingly, the Visser algorithm and 2010 criteria for RA have similar discriminative abilities to identify patients at risk of persistent arthritis at 1 year.[19] Moreover, subgroup analyses in patients with RA according to the 2010 and/or 1987 classification criteria[7, 8] were performed and produced similar results.

In this study we analysed the effect of MTX monotherapy in comparison with combination DMARD therapy without making any concessions on GC bridging therapy. Our findings are in contrast to the present EULAR recommendations on RA[1] and favour induction therapy with a combination of DMARDs rather than MTX monotherapy. Current recommendations are based upon a systemic review[5], which concluded that in DMARD-naïve patients the efficacy/toxicity ratio favours MTX monotherapy over combination therapy. However, in that review triple DMARD therapy versus MTX monotherapy in DMARD-naïve patients was not compared. Furthermore, trials favouring triple DMARD therapy (BeSt, FIN-RACo and COBRA trial) were excluded from that review[18, 20, 21], because a MTX monotherapy control arm (without GCs) was missing.

A recent systemic review, made by Graudal and Jürgens[22], supports the results found in our study.

The second strength of our study is the higher proportion of patients reaching lower disease activity states than previous trials. A DAS<2.4 was reached in 80% of our patients compared with 60% in the BeSt trial[18]. Remission (DAS<1.6) rates were respectively 40% in tREACH versus 20% in BeSt. This difference is probably due to: (1) the choice of induction therapy and (2) a lower baseline DAS. Important differences in initial combination therapy between our trial and the BeSt were higher MTX dosage (respectively 25 mg/week vs. 7.5 mg/week), and addition of hydroxychloroquine. Our baseline DAS was lower than in the BeSt trial (3.4 vs. 4.5), but this is probably correlated with the phase of the disease.

This study underlines current perspective of treating patients in an earlier phase of RA, for which the 2010 ACR/EULAR classification criteria are developed. Furthermore, induction combination therapy contributes to achieving the desired remission within 3 months, recommended by the current recommendations, in order to obtain better functional and radiological outcomes.[1-3] A tailor-made treatment approach might be preferable in this very early phase of RA, because 60% of the patients respond well to MTX monotherapy. However, clinical applicable predictors for early treatment response are still missing.

GC bridging therapy is used to treat active disease in the period between induction of DMARD therapy and onset of their therapeutic effect.[6] We find that intramuscular and oral GCs are equally effective as bridging therapy, but one single dose of GCs intramuscularly might be more feasible. GCs have disease-modifying traits with longlasting benefits even after withdrawal.[6] Therefore, the oral GC tapering scheme might be superior in the long-term. Furthermore, the duration and dosage of our GC tapering scheme was short (10 weeks) and at a low level (initial dosage 15mg) in comparison with, for example, the original COBRA regimen (respectively 28 weeks, initial dosage 60mg).[20] For current EULAR recommendations Gorter *et al*[23] reviewed the literature, looking at the efficacy of GCs in RA. They concluded that GCs relieve symptoms and inhibit radiographic progression. However, future research is needed to optimise GC bridging therapy with DMARDs, especially determination of optimal dosage and tapering schemes.[23]

Our study had certain limitations. First, despite randomisation, an important difference in prognostic factors was present at baseline. However, these imbalances were in favour of MTX monotherapy. Moreover, correcting for these imbalances by multivariate analyses led to a significant difference in functional ability at 3 months (favouring combination therapy).

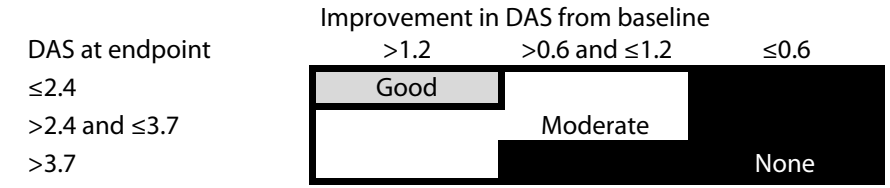
Second, in our study only the research nurses, who performed the disease activity assessments on which treatment decisions are based, were blinded. This design was chosen, because we wanted to conduct a trial which closely represents daily practice of rheumatologists. Single blinding, however, might be a potential source of bias - namely, an information bias.

Third, MTX was in some cases given subcutaneously because of gastrointestinal complaints. The distribution of parenteral MTX is imbalanced over the treatment arms. The bioavailability of parenteral MTX is higher than with MTX given orally, which is associated with an increased efficacy.[24] However, similar results were found if patients with parenteral MTX were omitted.

Several studies have demonstrated that the choice of induction therapy influences the initial clinical response and indirectly the amount of joint destruction and treatment changes needed to achieve low disease activity, with cost possibly increasing over many years.[18, 20, 21] The current RA treatment recommendation, however, is cost-effective when a strategic approach with rapid treatment intensification to biological agents is used, when the response is inadequate.[25] In tREACH 20% of patients need biological agents after 3 months, compared with 40% in the BeSt study, which suggest a 50% reduction in biological usage.[18] However, we included patients in an earlier phase of RA, representing a larger population than the BeSt study, which might lead to higher costs. On the other hand if patients are in sustained remission medication can be tapered swiftly.[26] The results of the long-term follow-up of the tREACH trial, including analyses of joint destruction and cost-effectiveness, should clarify aforementioned issues for patients with early RA.

In conclusion, we recommend induction therapy consisting of a combination of DMARDs (MTX + SASP + HCQ) as first choice in patients with newly diagnosed RA, because combination therapy reduced disease activity more rapidly after 3 months than MTX monotherapy. Consequently, 50% fewer biological agents were prescribed in the combination therapy groups. Although the proportion of patients with medication adjustments due to AEs differed significantly between the treatment arms, no differences were seen in medication adjustments after stratification for the drug. One single intramuscular GC injection or an oral GC tapering scheme can be used, because they are equally effective as bridging therapy.

## Supplement figure 1: EULAR response criteria




## Supplement 2: Subgroup analyses for patients with RA according to 2010 ACR/EULAR criteria

### Table 1: Baseline characteristics of patients with RA according to 2010 ACR/EULAR criteria, stratified for induction therapy.

| | A. MTX + SASP + HCQ + im GCs (n=83) | B. MTX + SASP + HCQ + oral GCs (n=80) | C. MTX + oral GCs (n=83) |
|---|---|---|---|
| Age (yrs), *mean (sd)* | 52 (15) | 54 (14) | 53 (14) |
| Sex, female, *no(%)* | 50 (60) | 59 (74) | 60 (72) |
| Symptom duration (days), *mean (sd)* | 160 (96) | 179 (92) | 154 (80) |
| RF pos., *no(%)* | 55 (66) | 50 (63) | 51 (61) |
| ACPA pos., *no(%)* | 58 (70) | 49 (61) | 56 (67) |
| Erosion, *no(%)** | 24 (29) | 12 (15) | 12 (14) |
| DAS, *mean (sd)* | 3.35 (0.79) | 3.52 (1.09) | 3.51 (0.96) |
| DAS28, *mean (sd)* | 4.86 (1.10) | 5.02 (1.25) | 4.91 (1.26) |
| TJC44, *median (IQR)* | 9 (5 - 14) | 10.5 (5 – 17.5) | 11 (5 – 15) |
| SJC44, *median (IQR)* | 8 (5 - 12) | 8 (4 – 12) | 8 (4 – 13) |
| VAS global (0 -100mm), *median (IQR)* | 53 (34 - 70) | 56 (29 – 70.5) | 55 (38 – 70) |
| ESR in mm/hr, *median (IQR)* | 25 (13 – 39) | 22 (13 – 45.5) | 24 (14 – 44) |
| CRP in mg/L, *median (IQR)* | 8 (4 -23) | 6.4 (3.75 - 19) | 11 (5 – 26) |
| HAQ, *mean (sd)* | 0.97 (0.68) (n=77) | 1.03 (0.63) (n=74) | 1.09 (0.70) (n=81) |
| RADAI (0-10), *mean (sd)* | 4.01 (1.87) (n=75) | 4.01 (1.62) (n=70) | 4.30 (1.84) (n=77) |

Not everyone filled in a (complete) questionnaire and therefore n is different for HAQ and RADAI.

*p=0.032 and p=0.024 for resp. A vs. B and A vs.C

Abbreviations: ACPA, anti-citrullinated protein/peptide antibodies; CRP, C-reactive protein; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; GCs, glucocorticoids; HAQ, Health Assessment Questionnaire; HCQ, hydroxychloroquine; im, intramuscular; IQR, interquartile range; MTX, methotrexate; RADAI, Rheumatoid Arthritis Disease Activity Index questionnaire; RF, rheumatoid factor; SASP, sulfasalazine; sd, standard deviation; SJC44, swollen joint count (44 joints); TJC44, tender joint count (44 joints); VAS, visual analogue scale.

**Table 2: Clinical response after 3 months for each induction therapy group in the subgroup of patients with RA according to 2010 criteria, intention-to-treat analysis.**

| | A. MTX + SASP + HCQ + im GCs (n=78) | B. MTX + SASP + HCQ + oral GCs (n=78) | C. MTX + oral GCs (n=77) |
|---|---|---|---|
| DAS, *mean (sd)*† | 1.86 (0.99) | 1.91 (0.85) | 2.34 (0.99) |
| ΔDAS (T3 - T0), *mean (sd)*‡ | -1.46 (1.00) | -1.56 (0.98) | -1.19 (1.06) |
| Disease state according to DAS, *no(%)* | | | |
| • *moderate to high disease activity (DAS≥2.4)*§* | 20 (26) | 19 (24) | 34 (44) |
| • *low disease activity (1.6≥DAS<2.4)* | 23 (29) | 29 (37) | 24 (31) |
| • *remission(DAS<1.6)*¶ | 35 (45) | 30 (38) | 19 (25) |
| EULAR response criteria, *no(%)* | | | |
| • *good* | 43 (55) | 38 (49) | 32 (42) |
| • *moderate* | 22 (28) | 27 (35) | 20 (26) |
| • *None#* | 13 (17) | 13 (17) | 25 (32) |
| TJC44, *median (IQR)*** | 1 (0 - 5) | 2 (0 – 6) | 4 (0 – 9) |
| SJC44, *median (IQR)* | 1 (0 - 4) | 1 (0 - 3) | 2 (0 - 5) |
| VAS global (0 -100mm), *median (IQR)*†† | 22 (12 - 36) | 28 (15 - 49) | 40 (22 – 55) |
| ESR in mm/hr, *median (IQR)* | 14 (6 – 27) | 10.5 (5 – 22) | 13 (8 – 24) |
| CRP in mg/L, *median (IQR)*‡‡ | 4 (1.2 – 8) | 3.35 (1 – 5.1) | 5 (2 – 9) |
| HAQ, *mean (sd)*§§ | 0.49 (0.55) (n=69) | 0.55 (0.56) (n=74) | 0.72 (0.65) (n=71) |
| ΔHAQ (T3 - T0), *mean (sd)* | -0.42 (0.51) (n=66) | -0.42 (0.54) (n=70) | -0.38 (0.58) (n=71) |
| RADAI (0 - 10), *mean (sd)*¶¶ | 1.95 (1.80) (n=68) | 2.01 (1.87) (n=70) | 2.69 (1.94) (n=68) |
| ΔRADAI (T3 - T0), *mean (sd)* | -1.95 (1.74) (n=65) | -1.98 (1.95) (n=63) | -1.56 (1.80) (n=66) |

Not everyone filled in a (complete) questionnaire and therefore n is different for HAQ and RADAI.

Abbreviations: CRP, C-reactive protein; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; GCs, glucocorticoids; HAQ, Health Assessment Questionnaire; HCQ, hydroxychloroquine; im, intramuscular; IQR, interquartile range; MTX, methotrexate; RADAI, Rheumatoid Arthritis Disease Activity Index questionnaire; SASP, sulfasalazine; sd, standard deviation; SJC44, swollen joint count (44 joints); TJC44, tender joint count (44 joints); VAS, visual analogue scale.

*Starting biological agent.

†p=0.003 and p=0.004 for resp. A vs. C and B vs. C

‡p=0.025 for B vs. C

§p=0.016 and p=0.009 for resp. A vs. C and B vs. C

¶p=0.008 for A vs. C

#p=0.022 and p=0.022 for resp. A vs. C and B

**p=0.008 for A vs. C

††p=0.0001 and p=0.033 for resp. A vs. C and B vs. C

‡‡p=0.034 for B vs. C

§§p=0.024 for A vs. C

¶¶p=0.023 and p=0.04 for resp. A vs. C & B vs.

## Supplement 3: Subgroup analyses for patients with RA according to 1987 ACR criteria

**Table 3: Baseline characteristics of patients with RA according to 1987 ACR/EULAR criteria, stratified for induction therapy.**

| | A. MTX + SASP + HCQ + im GCs (n=69) | B. MTX + SASP + HCQ + oral GCs (n=57) | C. MTX + oral GCs (n=63) |
|---|---|---|---|
| Age (yrs)*, mean (sd)* | 54 (16) | 55 (14) | 55 (14) |
| Sex, female*, no(%)* | 41 (59) | 39 (68) | 43 (68) |
| Symptom duration (days)*, mean (sd)* | 161 (94) | 174 (87) | 146 (73) |
| RF pos.*, no(%)* | 43 (62) | 37 (65) | 35 (56) |
| ACPA pos.*, no(%)* | 44 (64) | 30 (53) | 36 (57) |
| Erosion*, no(%)** | 23 (33) | 11 (19) | 9 (14) |
| DAS, *mean (sd)* | 3.43 (0.76) | 3.59 (1.06) | 3.57 (0.99) |
| DAS28, *mean (sd)* | 5.04 (0.99) | 5.13 (1.24) | 5.03 (1.22) |
| TJC44, *median (IQR)* | 9 (6 - 14) | 10 (5 - 15) | 10 (5 - 15) |
| SJC44, *median (IQR)* | 9 (6 - 12) | 11 (6 - 12) | 9 (6 - 13) |
| VAS global (0 -100mm), *median (IQR)* | 55 (37 - 69) | 58 (31 - 71) | 55 (35 - 70) |
| ESR in mm/hr, *median (IQR)* | 28 (15 - 44) | 24 (16 - 51) | 25 (20 - 44) |
| CRP in mg/L, *median (IQR)* | 9 (4 - 24) | 8 (4 - 24) | 13 (5.6 - 31) |
| HAQ*, mean (sd)* | 1.05 (0.67) (n=64) | 0.98 (0.64) (n=52) | 1.10 (0.68) (n=60) |
| RADAI (0-10), *mean (sd)* | 4.16 (1.86) (n=63) | 4.14 (1.55) (n=50) | 4.31 (1.98) (n=57) |

Not everyone filled in a (complete) questionnaire and therefore n is different for HAQ and RADAI.

*p=0.011 for A vs C

Abbreviations: ACPA, anti-citrullinated protein/peptide antibodies; CRP, C-reactive protein; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; GCs, glucocorticoids; HAQ, Health Assessment Questionnaire; HCQ, hydroxychloroquine; im, intramuscular; IQR, interquartile range; MTX, methotrexate; RADAI, Rheumatoid Arthritis Disease Activity Index questionnaire; RF, rheumatoid factor; SASP, sulfasalazine; sd, standard deviation; SJC44, swollen joint count (44 joints); TJC44, tender joint count (44 joints); VAS, visual analogue scale.

**Table 4: Clinical response after 3 months for each induction therapy group in the subgroup of patients with RA according to 1987 criteria, intention-to-treat analysis.**

| | A. MTX + SASP + HCQ + im GCs (n=65) | B. MTX + SASP + HCQ + oral GCs (n=55) | C. MTX + oral GCs (n=59) |
|---|---|---|---|
| DAS, *mean (sd)*† | 1.83 (0.77) | 1.83 (0.84) | 2.18 (1.07) |
| ΔDAS (T3 - T0), *mean (sd)* | -1.55 (0.90) | -1.77 (1.04) | -1.41 (1.00) |
| Disease state according to DAS, *no(%)* | | | |
| • *moderate to high disease activity (DAS≥2.4)*‡* | 15 (23) | 12 (22) | 23 (39) |
| • *low disease activity (1.6≥DAS<2.4)* | 22 (34) | 19 (35) | 17 (29) |
| • *remission(DAS<1.6)* | 28 (43) | 24 (44) | 19 (32) |
| EULAR response criteria, *no(%)* | | | |
| • *good* | 38 (58) | 32 (58) | 30 (51) |
| • *moderate* | 18 (28) | 15 (27) | 15 (25) |
| • *none* | 9 (14) | 8 (15) | 14 (24) |
| TJC44, *median (IQR)* | 1 (0 - 4) | 1 (0 - 5) | 3 (0 - 7) |
| SJC44, *median (IQR)* | 2 (0 - 4) | 1 (0 - 3) | 2 (0 - 5) |
| VAS global (0 -100mm), *median (IQR)*§ | 22 (13 - 34) | 21 (14 - 52) | 35 (18 - 55) |
| ESR in mm/hr, *median (IQR)* | 15 (7 - 27) | 11 (5 - 24) | 13 (7 - 24) |
| CRP in mg/L, *median (IQR)* | 4.4 (1.6 – 9) | 4 (1 - 7) | 5 (2 - 12) |
| HAQ, *mean (sd)* | 0.50 (0.51) (n=57) | 0.48 (0.53) (n=50) | 0.67 (0.70) (n=53) |
| ΔHAQ (T3 - T0), *mean (sd)* | -0.47 (0.54) (n=54) | -0.47 (0.55) (n=47) | -0.42 (0.52) (n=52) |
| RADAI (0 - 10), *mean (sd)*¶ | 1.93 (1.61) (n=56) | 1.62 (1.56) (n=46) | 2.70 (2.07) (n=52) |
| ΔRADAI (T3 - T0), *mean (sd)*# | -2.09 (1.58) (n=54) | -2.53 (1.74) (n=41) | -1.46 (1.77) (n=51) |

Not everyone fi lled in a (complete) questionnaire and therefore n is different for HAQ and RADAI.

Abbreviations: CRP, C-reactive protein; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; GCs, glucocorticoids; HAQ, Health Assessment Questionnaire; HCQ, hydroxychloroquine; im, intramuscular; IQR, interquartile range; MTX, methotrexate; RADAI, Rheumatoid Arthritis Disease Activity Index questionnaire; SASP, sulfasalazine; sd, standard deviation; SJC44, swollen joint count (44 joints); TJC44, tender joint count (44 joints); VAS, visual analogue scale.

*Starting biological agent.

†p=0.04 for A vs. C

‡p=0.047 for B vs. C

§p=0.011 for A vs. C

¶p=0.033 and p=0.005 for resp. A vs. C and B vs. C

#p=0.005 for B vs. C

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CHAPTER 3

# Initial triple DMARD therapy is more efficient than methotrexate monotherapy in recent onset rheumatoid arthritis; 1-year data of a randomized clinical trial (tREACH)

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**Importance:** There is still debate on the most appropriate initial treatment regimen in patients with newly diagnosed rheumatoid arthritis (RA). Most important discussion herein is that of methotrexate monotherapy versus a combination of DMARDs.

**Objectives:** To compare 1-year clinical efficacy of (1) initial triple DMARD therapy (iTDT) versus initial methotrexate (MTX) monotherapy (iMM) unbiased for glucocorticoids (GCs) (arm B versus C), and (2) different GC bridging therapies: oral versus a single intramuscular injection (arm A versus B) in very early RA.

**Design, Setting:** The tREACH trial, a multicenter, stratified single-blinded trial, is performed in eight rheumatology centres in the Netherlands. Outpatients aged 20 to 85 years were evaluated every 3 months for 1 year, from 2007 through 2012.

**Participants:** Patients with a high probability (> 70%) according to their likelihood of progressing to persistent arthritis, based of the prediction model of Visser, were included. The Visser algorithm and 2010 criteria for RA have similar discriminative abilities to identify patients at risk of persistent arthritis at 1 year.

**Intervention:** Random assignment to one of following initial treatment strategies: (A) iTDT (MTX + sulfasalazine + hydroxychloroquine) with GCs intramuscular (n=91), (B) iTDT with an oral GC tapering scheme (n=93), and (C) MTX with oral GCs similar to B (n=97).

**Main outcomes and measures:** Disease activity, functional ability, radiological damage, and adverse events were assessed.

**Results:** Over time disease activity and functional ability, measured with the area under the curve, were respectively -2.39 (-4.77 to -0.00, 95% confidence interval) and -1.67 (-3.35 to 0.02, 95% confidence interval) lower in patients with iTDT compared with iMM. After 3 months, less treatment failure occurred in the iTDT, resulting in the prescription of 40% fewer biologicals. This difference remained over time. No differences were seen between both GC bridging therapies. Respectively 19%, 23%, and 21% of patients in arm A, B, and C had radiographic progression after 1 year. No differences in serious adverse events were seen.

**Conclusion:** We recommend iTDT over iMM as first choice in newly diagnosed RA patients, because treatment goals are attained faster and maintained with less biologicals. Furthermore intramuscular and oral GCs are equally effective as bridging therapy and can both be used.

**Key words**

- Rheumatoid Arthritis; early arthritis; triple DMARD therapy; glucocorticoids; initial treatment

## INTRODUCTION

In last two decades major paradigm changes in the management of rheumatoid arthritis (RA) have occurred. These changes are: (1) early detection of the disease, hence development of 2010 criteria for RA[1], (2) early initiation of intensive therapy, and (3) treat-to-target, which is included in all current guidelines.[2-3] Functional and radiological outcomes improve if current guidelines are uphold.[4-5] Nevertheless, some major debate points still exist.

First, 2010 criteria for RA[1] are more and more incorporated in daily practice. All current guidelines, however, were formulated using data from studies in patients fulfilling 1987 RA criteria.[2-3, 6] Thus trials comparing initial treatment strategies in the early phase of RA are needed for validation.

Second, several clinical trials concluded that initial combination therapy had superior clinical efficacy over monotherapy, however, most rheumatologists have not implemented this in daily practice.[7-11] Moreover, current guidelines do not recommend combination therapy for all newly diagnosed RA patients.[2-3] Principal motive of disregarding combination therapy was the fact that (1) trials were biased by glucocorticoids (GCs), (2) patients were not DMARD naïve and (3) there are safety concern issues.[12-13]

Third, GCs have a rapid anti-inflammatory effect, and are therefore used as bridging therapy to treat active disease in between initiation of DMARD(s) and onset of their therapeutic effect.[14] However, trials specifically comparing GC bridging therapies are sparse. More trials are, therefore, needed to investigate optimal dosage and tapering schemes.

Finally, for health economic reasons efficient use of expensive drugs is needed to be able to continue optimal rheumatic care in the future.[15]

Therefore, our aim is to compare in patients with very early RA the 1-year clinical efficacy of (1) initial triple DMARD therapy (iTDT) versus methotrexate (MTX) monotherapy, unbiased for GCs, and (2) different GC bridging therapies: oral versus a single intramuscular injection.

## PATIENTS AND METHODS

### Patients

For this study data were used of a clinical trial (ISRCTN26791028), namely treatment in the Rotterdam Early Arthritis Cohort (tREACH).[16] tREACH, a multicenter, stratified single-blinded trial, is performed in eight rheumatology centres in the Netherlands. Medical ethics committees at each participating centre approved the study protocol, and all patients gave written informed consent before inclusion. Inclusion criteria for the tREACH are: Age ≥18 years, arthritis in ≥1 joint(s), and symptom duration <1 year. Exclusion criteria for the tREACH are given in appendix 1.

Eligible patients were stratified into three groups according to their likelihood of progressing to persistent arthritis based of the Visser model.[17] The three strata (low, intermediate, and high) correspond with probability tertiles of developing persistent arthritis. For this analysis we included the high probability stratum.

**Randomisation and blinding**

Patients were randomised, using variable block randomization stratified for centre, by an independent call-centre. Trained research nurses, blinded for allocated treatment arm throughout the study, examined patients and calculated the disease activity score (DAS).

**Design**

Patients were randomised into one of following initial treatment strategies:

A. iTDT (MTX, sulfasalazine, and hydroxychloroquine with GCs intramuscular)
B. iTDT with an oral GC tapering scheme
C. initial MTX monotherapy (iMM) with oral GCs similar to B

Concurrent therapy with non-steroidal anti-inflammatory drugs and intra-articular GC injections (maximum of two per three months) were allowed during the study.

DMARD dosages were: MTX 25 mg/week orally (dosage reached after three weeks), sulfasalazine 2 grams/day and hydroxychloroquine 400 mg/day, reduced to 200mg/day after 3 months. GCs were either given intramuscular (methylprednisolone 120mg or triamcinolone 80mg) or in an oral tapering scheme (weeks 1-4: 15 mg/day, weeks 5-6: 10 mg/day, weeks 7-8: 5 mg/day, and weeks 9-10: 2.5 mg/day). All patients received folic acid (10 mg/week) during MTX prescription. Osteoporosis prophylaxis (risedronate 35 mg/week and calcium/vitamin D combination 500/400 mg/IU/day) is given to patients in treatment arms B and C, during the first three months.

A treat-to-target approach was used, aiming for a DAS < 2.4.[18] If DAS≥2.4 medication is intensified. Intensification steps were subsequently (1) MTX + etanercept (50mg/week, subcutaneous), (2) MTX + adalimunab (40mg/ 2 weeks, subcutaneous), and (3) MTX + abatacept (500 – 1000 mg/ 4 weeks, intravenous, depending on weight). Treatment intensifications were the same for each treatment arm.

If DAS<1.6 at two consecutive visits, medication was tapered. Hierarchically ordered tapering steps are: (1) biological, (2) sulfasalazine, (3) MTX, and (4) hydroxychoroquine. Biological(s), MTX and sulfasalazine were gradually discontinued, whereas hydroxychloroquine was stopped immediately. A flare during tapering, defined as DAS ≥2.4, results in restarting full therapy, according to the stage in the protocol.

**Outcomes and assessments**

Patients were examined every 3 months for all outcomes, except for hand/foot radiographs, which were done at baseline and half-yearly.

Primary outcomes were (1) disease activity (state), (2) functional ability, and (3) radiographic progression. DAS and its thresholds are used for disease state categorizations.[18] Functional ability was measured with the Health Assessment Questionnaire (HAQ).[19] Higher HAQ scores indicate poorer function. Radiographic progression was measured with the modified Sharp-van der Heijde score (SHS).[20] Radiographs were read chronologically by 2 out of 5 qualified assessors, who were blinded for patient's identity and treatment allocation.[21] Mean SHS are reported.[22] Weighted kappa between assessors was 0.36 with 98% agreement. Proportion of patients with radiographic progression, defined as SHS change >0.5 and >1.2 (smallest detectable change ) per year, were also calculated.[22]

Secondary endpoints were: EULAR response criteria[23], Boolean-defined remission criteria[24], self-assessed disease activity, and medication usage. EULAR response criteria are based on attained level and change in DAS (appendix 2).[23] Boolean remission criteria are defined as having a tender joint count, swollen joint count, C-reactive protein (in mg/dl), and patient global assessment (0 -10 scale) of ≤1.[24] Self-assessed disease activity is measured with the Rheumatoid Arthritis Disease Activity Index questionnaire (RADAI).[25] Higher RADAI scores correspond with more active disease.

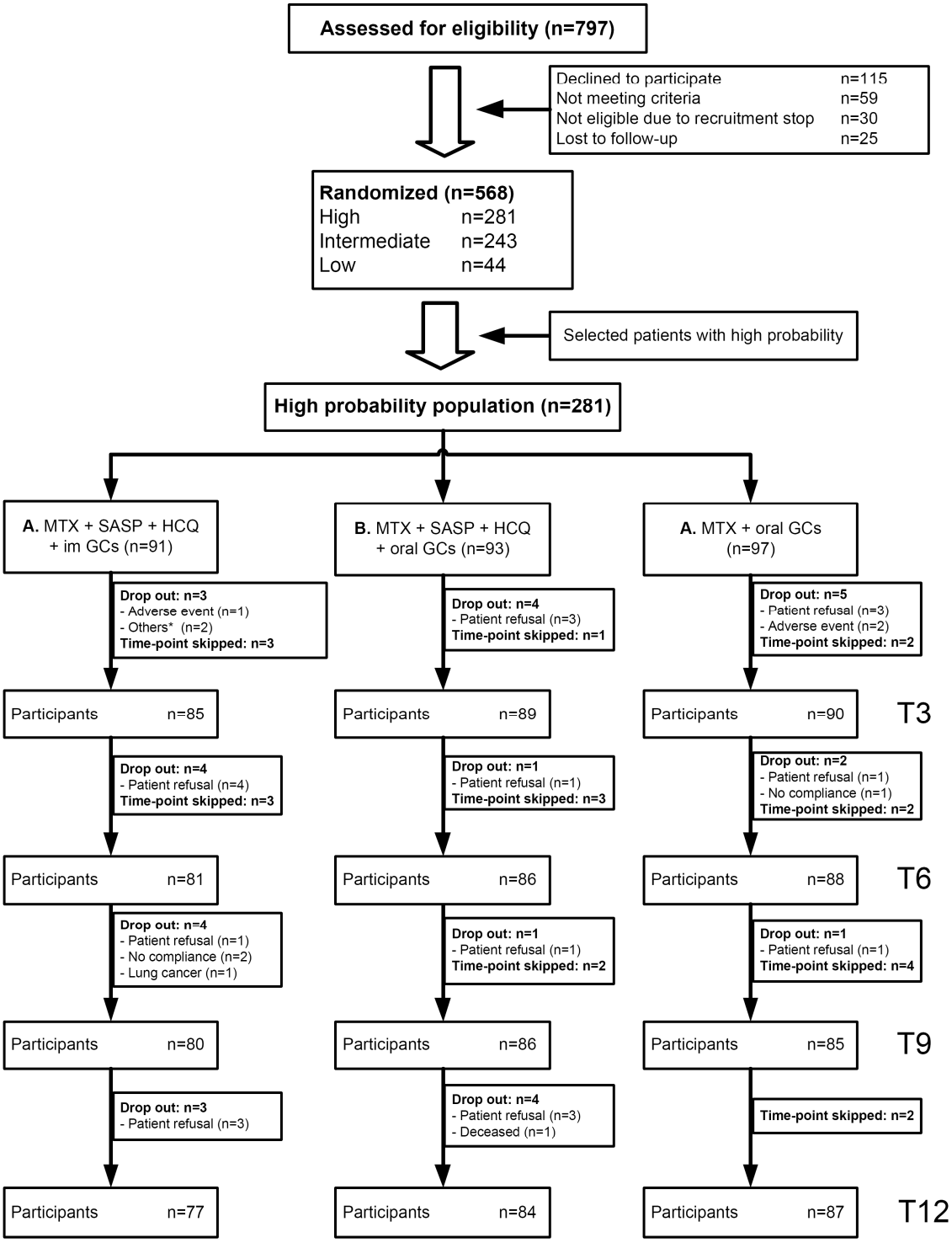
**Safety monitoring and toxicity**

Safety monitoring occurred according to Dutch guidelines[26-27], which included laboratory tests at fixed intervals. Study medication was either stopped or dosage lowered in accordance with the protocol if (serious) adverse events[16] were observed by the attending rheumatologist. MTX could be given subcutaneously if patients had gastro-intestinal complaints. If MTX needed to be stopped for safety reasons, it was substituted with leflunomide (20 mg/day).[16]

**Statistical Analysis**

Sample-size calculation was based upon the area under the curve (AUC) of the HAQ, using data from the BeSt study[8], where mean AUC HAQ of combination therapy and monotherapy respectively were 7.7 (SD 5.5) and 10.5 (SD 7.4). A target sample size of 270 patients per probability stratum,and thus 90 patients per arm, was needed to detect mentioned difference with a power of 80% and two-sided $\alpha$=0.05. This size is sufficient to detect a difference of 6.1 AUC DAS and 20% difference in radiographic progression.[16]

Clinical efficacy was calculated in an intention-to-treat and per-protocol analysis. Statistical comparison of the baseline characteristics and outcomes (after 12 months) between iTDT and iMM (arm B versus C) and both GC bridging therapies (arm A versus B) were made by student t test, $\chi^2$ test, or Wilcoxon rank-sum test, when appropriate.


Assessed for eligibility (n=797)
Declined to participate n=115
Not meeting criteria n=59
Not eligible due to recruitment stop n=30
Lost to follow-up n=25
Randomized (n=568)
High n=281
Intermediate n=243
Low n=44
Selected patients with high probability
High probability population (n=281)
A. MTX + SASP + HCQ + im GCs (n=91)
B. MTX + SASP + HCQ + oral GCs (n=93)
A. MTX + oral GCs (n=97)
Drop out: n=3
- Adverse event (n=1)
- Others* (n=2)
Time-point skipped: n=3
Drop out: n=4
- Patient refusal (n=3)
Time-point skipped: n=1
Drop out: n=5
- Patient refusal (n=3)
- Adverse event (n=2)
Time-point skipped: n=2
Participants n=85
Participants n=89
Participants n=90
T3
Drop out: n=4
- Patient refusal (n=4)
Time-point skipped: n=3
Drop out: n=1
- Patient refusal (n=1)
Time-point skipped: n=3
Drop out: n=2
- Patient refusal (n=1)
- No compliance (n=1)
Time-point skipped: n=2
Participants n=81
Participants n=86
Participants n=88
T6
Drop out: n=4
- Patient refusal (n=1)
- No compliance (n=2)
- Lung cancer (n=1)
Drop out: n=1
- Patient refusal (n=1)
Time-point skipped: n=2
Drop out: n=1
- Patient refusal (n=1)
Time-point skipped: n=4
Participants n=80
Participants n=86
Participants n=85
T9
Drop out: n=3
- Patient refusal (n=3)
Drop out: n=4
- Patient refusal (n=3)
- Deceased (n=1)
Time-point skipped: n=2
Participants n=77
Participants n=84
Participants n=87
T12

| | A. MTX + SASP + HCQ + im GCs (n=91) | B. MTX + SASP + HCQ + oral GCs (n=93) | C. MTX + oral GCs (n=97) |
|---|---|---|---|
| **Protocol violations** | | | |
| Skipped ≥1 time point(s) | 16 (18) | 12 (13) | 14 (14) |
| Postponing/withholding biological | 7 (8) | 11 (12) | 11 (11) |
| illicit treatment intensifications | 1 (1) | 1 (1) | 1 (1) |
| no tapering of treatment | 6 (7) | 11 (12) | 5 (5) |
| other[1] | 2 (2) | 2 (2) | 1 (1) |
| total | 32 (35) | 37 (40) | 32 (33) |

**Figure 1: Trial profile and protocol violations.**

Results shown are a number (%).

[1]Other reasons are: 3x No compliance, 1x pregnancy wish and 1x continuation of SASP after switch to etanercept.

The figure shows the flowchart of the tREACH trial, whereas the table shows the protocol violations within the tREACH trial during the first year of follow-up. Other reasons for dropping out, in the flowchart, were incorrect randomization and problems with communication.

Abbreviations: GCs, glucocorticoids; HCQ, hydroxychloroquine; im, intramuscular; MTX, methotrexate; SASP, sulfasalazine.

We used the AUC to compare DAS, and HAQ over time between treatment arms, in which missing values at each time-point were substituted with mean value of the corresponding treatment arm. Radiographic progression was extra- or interpolated if SHS was missing after 12 months. Analyses were corrected for baseline imbalances.

All analyses were performed for patients in the high probability stratum and two subgroups consisting of patients with RA according to 1987 and 2010 criteria.[1, 6] All statistical analyses were carried out using STATA version 12.0. A p value <0.05 was considered statistically significant.

## RESULTS

### Patients

A total of 797 patients have been assessed for eligibility and of those, 568 patients were included. In the high probability stratum 281 patients were randomly assigned to treatment arm A (n=91), B (n=93), or C (n=97) (figure 1). Besides an intention-to-treat (ITT) analysis, we also performed a per-protocol analysis. We excluded, from our per-protocol analysis, respectively 32 (35%), 37 (40%), and 32 (33%) patients randomised to arm A, B, and C (figure 1).

At baseline, the symptom duration and patients fulfilling 1987 criteria for RA differed significantly between arms (table 1). Our primary outcomes were corrected for these baseline imbalances and baseline HAQ, DAS or SHS, when appropriate, by making use of multivariate analyses.

**Table 1: Baseline characteristics and clinical response after 12 months for each induction therapy group, according to intention-to-treat.**

| | A. MTX + SASP + HCQ + im GCs (n=91) | B. MTX + SASP + HCQ + oral GCs (n=93) | C. MTX + oral GCs (n=97) |
|---|---|---|---|
| **Demographic** | | | |
| Age (yrs), *mean (sd)* | 53 (15) | 54 (14) | 54 (14) |
| Sex, female, *no(%)* | 55 (60) | 67 (72) | 68 (72) |
| **Disease characteristics** | | | |
| Symptom duration (days), *mean (sd)** | 162 (97) | 184 (92) | 154 (83) |
| RF pos., *no(%)* | 55 (60) | 51 (55) | 51 (53) |
| ACPA pos., *no(%)* | 59 (65) | 50 (54) | 56 (58) |
| Fulfillment RA criteria, *no(%)* | | | |
| *1987*† | 69 (76) | 57 (61) | 63 (65) |
| *2010* | 87 (96) | 88 (95) | 95 (98) |
| **Disease activity** | | | |
| • Baseline | | | |
| DAS, *mean (sd)* | 3.28 (1.06) | 3.40 (1.07) | 3.38 (0.97) |
| • After 12 months | | | |
| DAS, *mean (sd)* | 1.40 (0.68) | 1.61 (0.87) | 1.68 (0.89) |
| ΔDAS (T12 - T0), *mean (sd)* | -1.83 (-1.03) | -1.75 (-1.14) | -1.69 (-1.27) |
| Disease state according to DAS, *no(%)* | | | |
| *moderate to high disease activity (DAS≥2.4)* | 8/77 (10) | 15/84 (18) | 19/87 (22) |
| *low disease activity (1.6≥DAS<2.4)* | 22/77 (29) | 24/84 (29) | 24/87 (28) |
| *remission (DAS<1.6)* | 47/77 (61) | 45/84 (54) | 44/87 (51) |
| Boolean remission criteria, *no(%)*[1] | 17/77 (22) | 13/84 (16) | 14/87 (16) |
| EULAR response criteria (T12 - T0), *no(%)*[2] | | | |
| *good* | 54/77 (70) | 52/84 (62) | 57/87 (66) |
| *Moderate* | 13/77 (17) | 19/84 (23) | 9/87 (10) |
| *none* | 10/77 (13) | 13/84 (15) | 21/87 (24) |
| **Radiographs (hand/foot)** | | | |
| • Baseline | | | |
| Total SHS (0 - 488 ), *median (IQR)* | 0.5 (0 – 2) | 0.5 (0 – 2) | 1 (0 – 2.5) |
| Erosion score (0 - 280), *median (IQR)* | 0 (0 – 1) | 0 (0 – 1) | 0.5 (0 – 1) |
| JSN score (0 - 168), *median (IQR)* | 0 (0 – 1) | 0 (0 - 1) | 0 (0 – 1.5) |
| Erosion, *no(%)*[3] | 18/91 (20) | 18/93 (19) | 20/95 (21) |
| • After 12 months | | | |
| Total SHS (0 - 488 ), *median (IQR)* | 1 (0 – 3) | 1 (0 – 3) | 1 (0 – 3.5) |
| Erosion score (0 - 280), *median (IQR)* | 0.5 (0 – 1.25) | 0.5 (0 – 1.5) | 0.5 (0 – 1.5) |
| JSN score (0 - 168), *median (IQR)* | 0.5 (0 - 1.5) | 0 (0 – 1.5) | 0.5 (0 – 1.5) |
| ΔTotal SHS (T12 - T0), *median (IQR)* | 0.13 (0 – 1) | 0 (0 – 1) | 0 (0 - 1) |
| Patients with progression >0.5, *no (%)* | 25/76 (33) | 24/82 (29) | 28/84 (33) |
| Patients with progression >1.2, *no (%)* | 16/76 (21) | 20/82 (24) | 19/84 (23) |
| **Questionnaires**[4] | | | |
| • Baseline | | | |
| HAQ, *mean (sd)* | 0.98 (0.67) (n=84) | 0.96 (0.64) (n=84) | 1.06 (0.68) (n=92) |
| RADAI (0-10), *mean (sd)* | 3.97 (1.83) (n=81) | 3.94 (1.63) (n=80) | 4.21 (1.82) (n=87) |
| • After 12 months | | | |
| HAQ, *mean (sd)* | 0.38 (0.46) (n=69) | 0.51 (0.55) (n=78) | 0.63 (0.57) (n=82) |
| ΔHAQ (T12 - T0), *mean (sd)* | -0.48 (-0.63) (n=65) | -0.42 (-0.59) (n=74) | -0.47 (-0.53) (n=80) |
| RADAI (0 - 10), *mean (sd)* | 1.43 (1.24) (n=68) | 1.78 (1.51) (n=75) | 2.15 (1.81) (n=79) |
| ΔRADAI (T12 - T0), *mean (sd)* | -2.22 (-1.68) (n=63) | -2.06 (-1.87) (n=69) | -2.11 (-1.91) (n=74) |

[1]Boolean remission criteria are defined as having a TJC44≤1, SJC44≤1, VAS global≤10mm and CRP≤10 mg/L

[2]EULAR response criteria are based on attained level and change in DAS

[3]Erosive disease is defined as having a erosion score >1.2 (=smallest detectable change)

[4]Not everyone filled in a (complete) questionnaire and therefore n is different for HAQ and RADAI.

*p=0.018 for B vs C.

†p=0.034 for A vs B.

**Clinical outcome**

After 12 months DAS was 0.08 (-0.34 to 0.19, 95% confidence interval (CI)) lower in patients with iTDT than in those with iMM (arm B vs. C). Difference in DAS between the different GC bridging therapies was -0.20 (-0.45 to 0.04, 95% CI) (arm A vs. B). Similar results were found in our multivariate analyses (data not shown). No differences in disease activity states are found after 12 months between iTDT and iMM, or both GC bridging therapies (table 1). Difference in AUC DAS between iTDT and iMM was -2.39 (-4.77 to -0.00, 95%CI, p=0.05), and -0.91 (-3.17 to 1.34, 95% CI, p=0.42) between both GC bridging therapies. Adjusted differences were respectively -2.67 (-4.61 to -0.74, 95%CI, p=0.007) and -0.07 (-2.04 to 1.90, 95% CI, p=0.95). The largest difference in disease activity (states) between treatment arms is seen after 3 months, whereupon it gradually diminished (figure 2).

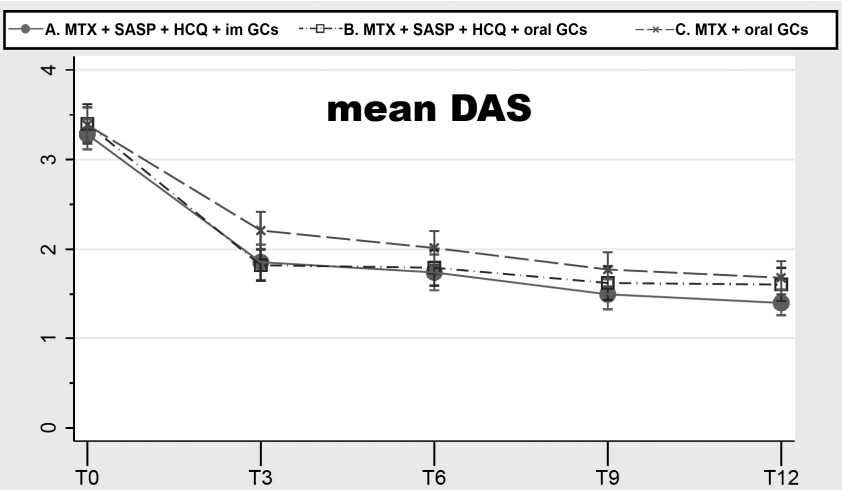
There was no significant difference in SHS after 12 months of therapy (table 1). Respectively 19%, 23%, and 21% of patients in arm A, B, and C had radiographic progression. The cumulative probability plot for the 3 treatment arms were superimposable (appendix 3).

Functional improvement was seen in all patients. No significant difference in functional ability was seen after 12 months (table 2). Difference in AUC HAQ between iTDT and iMM was -1.67 (-3.35 to 0.02, 95%CI, p=0.05), and -0.46 (-2.04 to 1.12, 95% CI, p=0.57) between both GC bridging therapies (figure 2). Adjusted differences were respectively -1.35 (-2.51 to -0.19, 95% CI, p=0.02) and 0.36 (-0.83 to 1.54, 95% CI, p=0.55). Secondary end points are shown in table 1 and figure 2.

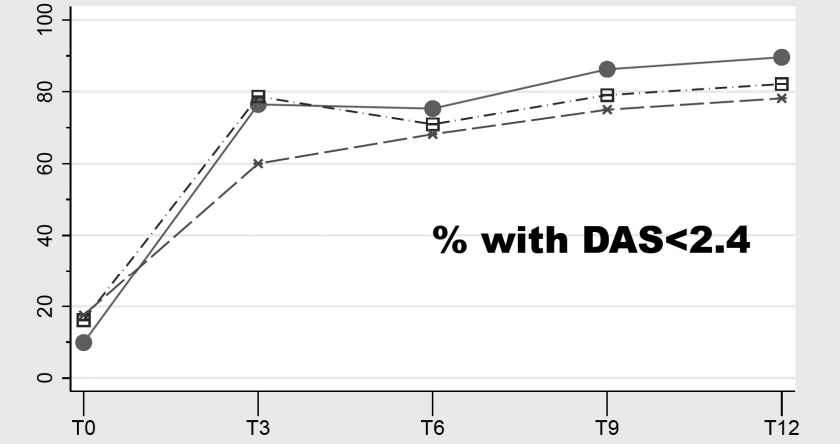
All mentioned analyses were based upon ITT. We also performed a per-protocol analysis, which showed similar results (data not shown). Above mentioned analyses were also performed in both subgroups, namely RA according to 1987 and 2010 criteria, which produced similar results (appendix 4 and 5).

**Medication**

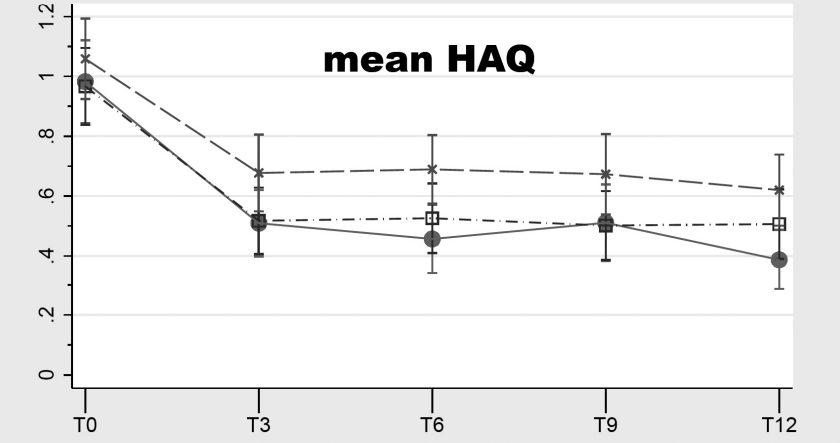
After 3 months 40% fewer biologicals were prescribed in the iTDT group compared with the iMM group (arm B vs. C). This difference remained over time (figure 3). After 12 months respectively 27% and 43% of patients, with iTDT and iMM, were using a biological (arm B vs. C, p=0.03) . Moreover, more patients with iMM failed on their first biological (16% vs. 6%, p=0.031) (figure 3). In 117/281 (42%) of patients treatment could be tapered, of those 14/117 (12%) flared. Treatment could be tapered more often in patients with iTDT compared with iMM, respectively 28% vs. 23%, without occurrence of more flares (6% vs. 7%) (figure 3). Biological usage did not differ between both GC bridging therapies (arm A vs. B) (figure 3). Aforementioned analysis were also performed in both subgroups and showed similar results (appendix 4 and 5).




| | T0 | T3 | T6 | T9 | T12 |
|---|---|---|---|---|---|
| **A** | 3.28 (1.06) | 1.86 (0.96) | 1.74 (0.94) | 1.50 (0.77) | 1.40 (0.68) |
| **B** | 3.40 (1.07) | 1.82 (0.86) | 1.80 (0.95) | 1.63 (0.89) | 1.61 (0.87) |
| **C** | 3.38 (0.97) | 2.21 (1.04) | 2.02 (0.91) | 1.78 (0.90) | 1.68 (0.89) |




| | T0 | T3 | T6 | T9 | T12 |
|---|---|---|---|---|---|
| **A** | 9/91 (10%) | 65/85(76%) | 61/81 (75%) | 69/80 (86%) | 69/77 (89%) |
| **B** | 15/93 (16%) | 70/89 (79%) | 61/86 (71%) | 68/86 (79%) | 69/84 (82%) |
| **C** | 17/97 (18%) | 54/90 (60%) | 60/88 (68%) | 64/85 (75%) | 68/87 (78%) |




| | T0 | T3 | T6 | T9 | T12 |
|---|---|---|---|---|---|
| **A** | 0.98 (0.67) | 0.51 (0.54) | 0.45 (0.53) | 0.51 (0.59) | 0.38 (0.46) |
| **B** | 0.97 (0.63) | 0.52 (0.54) | 0.53 (0.56) | 0.50 (0.55) | 0.51 (0.55) |
| **C** | 1.06 (0.68) | 0.68 (0.64) | 0.69 (0.55) | 0.67 (0.63) | 0.63 (0.57) |

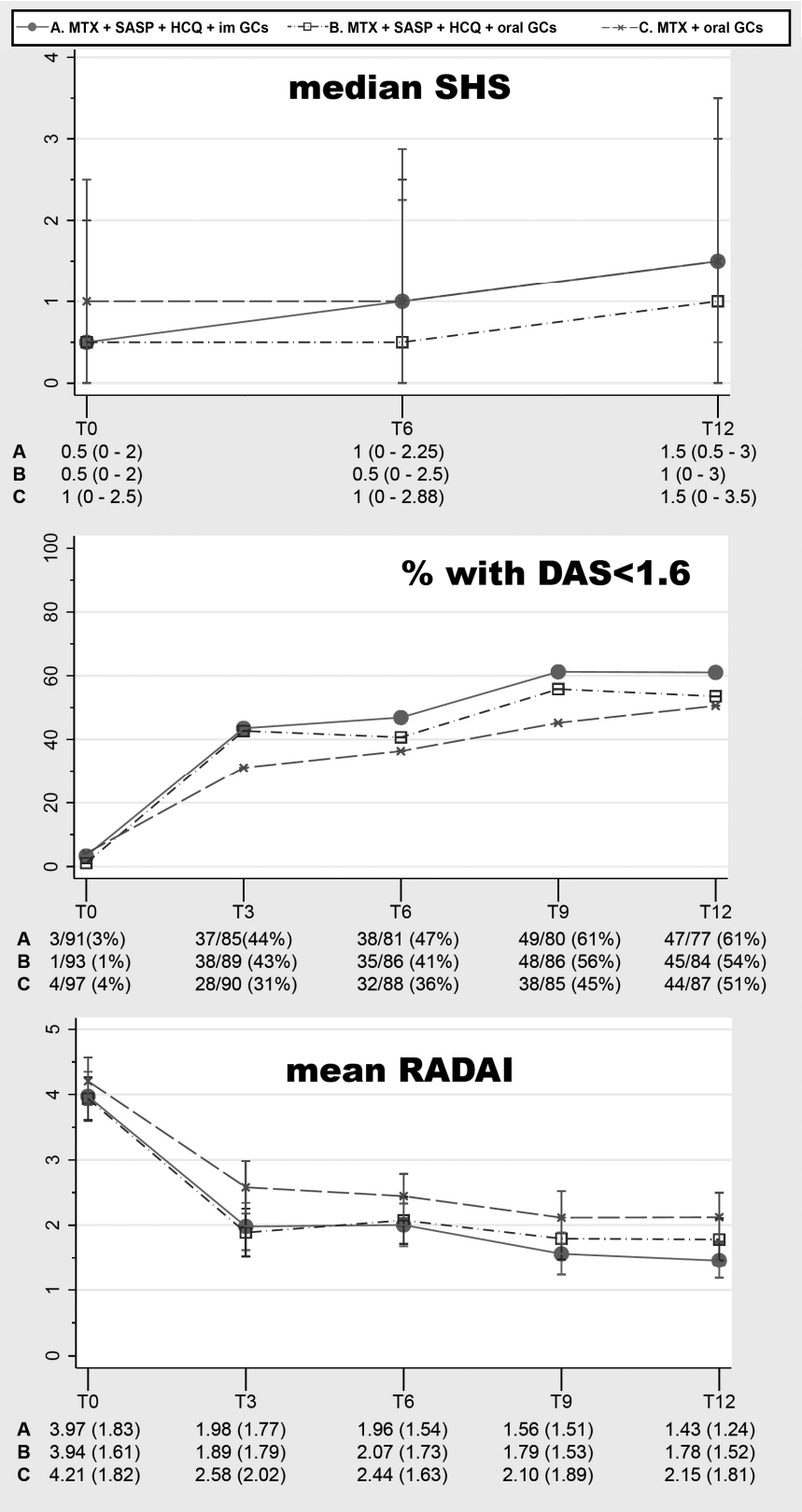
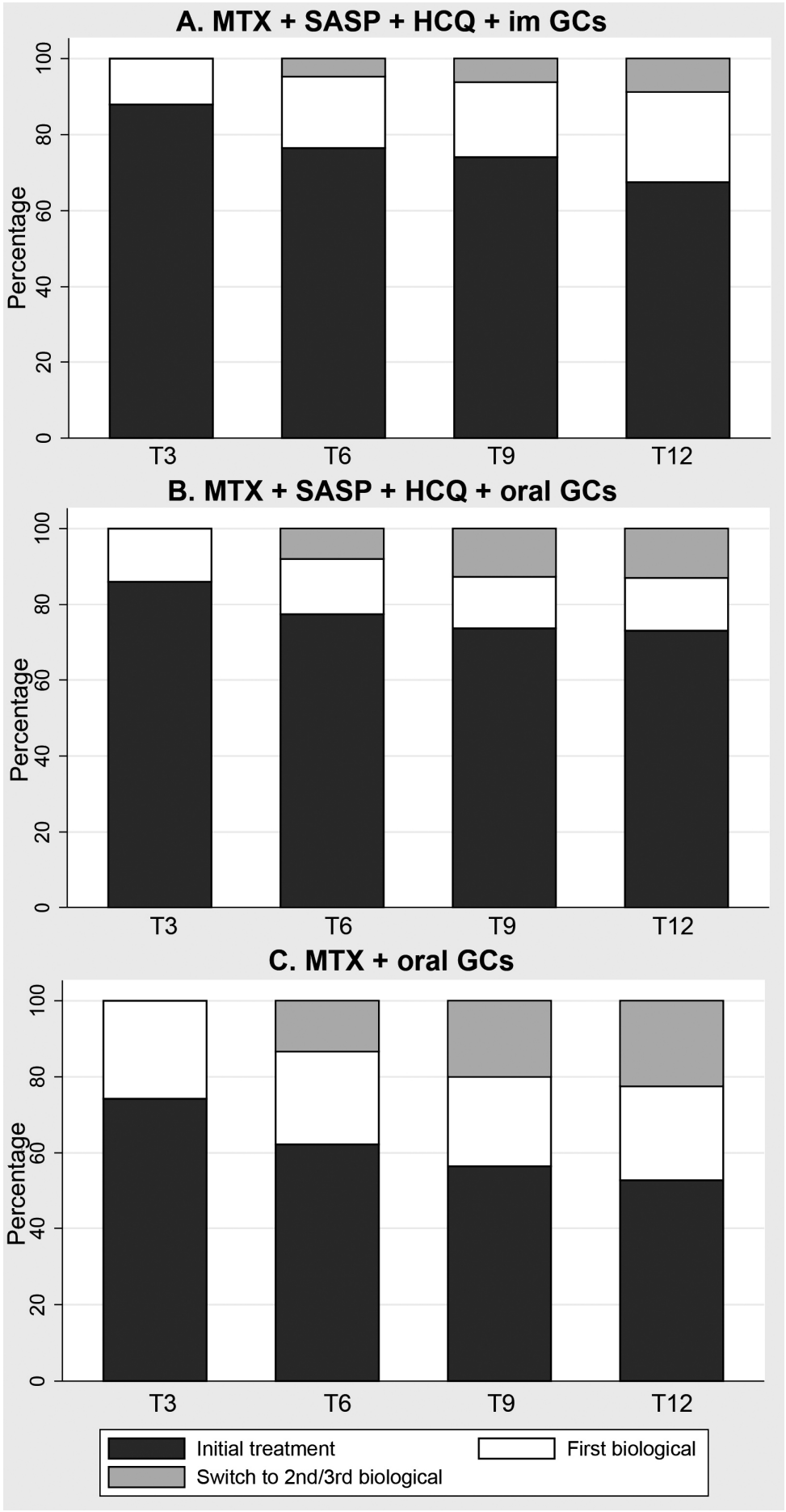



**Figure 2: (Self-assessed) disease activity, functional ability and radiographic joint damage over time, stratified for induction therapy.**

Error bars indicate respectively 95% confidence intervals and interquartile range for given means and median.


A. MTX + SASP + HCQ + im GCs
B. MTX + SASP + HCQ + oral GCs
C. MTX + oral GCs
Percentage
0
20
40
60
80
100
T3
T6
T9
T12
Initial treatment
First biological
Switch to 2nd/3rd biological

| | A. MTX + SASP + HCQ + im GCs (n=91) | B. MTX + SASP + HCQ + oral GCs (n=93) | C. MTX + oral GCs (n=97) |
|---|---|---|---|
| **Medication after 12 months** | | | |
| MTX | 73 (80) | 72 (77) | 82 (85) |
| MTX dosage, *median (IQR)* | 15 (7.5 - 25) | 15 (7.5 - 25) | 20 (7.5 - 25) |
| SASP | 27 (30) | 27 (29) | 2 (2) |
| HCQ | 51 (56) | 59 (63) | 8 (8) |
| Biological use* | 26 (29) | 24 (26) | 42 (43) |
| *Etanercept* | 18 (20) | 12 (13) | 22 (23) |
| *Adalimumab*† | 4 (4) | 6 (6) | 16 (16) |
| *Abatacept* | 3 (3) | 5 (5) | 4 (4) |
| *Other*[1] | 1 (1) | 1 (1) | 0 (0) |
| **Tapered treatment**[2] | | | |
| Taperings‡ | 88/238 (37) | 71/256 (28) | 60/260 (23) |
| at 1 time-point | 16 (18) | 19 (20) | 16 (16) |
| at 2 time-points | 12 (13) | 11 (8) | 10 (10) |
| at 3 time-points | 15 (16) | 10 (11) | 8 (8) |
| **Flare after tapering**[3] | 6/88 (7) | 4/71 (6) | 4/60 (7) |

**Figure 3: Withdrawal, flares and medication usage over time and after 12 months, stratified for induction therapy.**

Results shown are a number (%) unless stated otherwise.

[1]Other biologicals are: Infliximab (A) and Rituximab (B)

[2]Treatment could be tapered after 6 months. Therefore the total amount of possible taperings is the sum of all assessments at the last three visits per treatment arm.

[3]A flare is defined as a DAS≥2.4. The proportion is calculated by dividing the number of flares by the total amount of taperings

*p=0.011 for B vs C.

†p=0.031 for B vs C

‡p=0.028 for A vs B

Abbreviations: GCs, glucocorticoids; HCQ, hydroxychloroquine; im, intramuscular; IQR, interquartile range; MTX, methotrexate; SASP, sulfasalazine.

**Adverse events (AEs)**

No differences in serious AEs were seen between treatment arms (table 2). However, the proportion of patients with medications adjustments due to AEs differed significantly between iTDT and iMM (60/93 (65%) and 44/97 (45%), p=0.008). Besides switching to MTX subcutaneously, aforementioned differences vanished after stratification for drug (table 2). No differences were seen between both GC bridging therapies. Most treatment adjustments occurred in the first 3 months (51/159, 32%). Gastrointestinal complaints and fatigue were most commonly reported AEs, respectively 56% and 36% (table 2).

## DISCUSSION

In this study, unbiased for GCs, iTDT had a better clinical efficacy and efficiency than iMM in early RA. The burden of disease over time, reflected by the AUC, was less in the iTDT group compared with iMM. Treatment goals were attained faster and maintained with 40% fewer biologicals in the iTDT group. Moreover, more patients with iMM failed on their first biological, reducing therapeutic options. Radiographic progression did not differ between groups. No differences in serious AEs were seen. Treatment could also be tapered more often with iTDT, without the occurrence of more flares. On contrary, no differences were seen between both GC bridging therapies.

We based our design on the Visser model, because we wanted to initiate DMARD therapy in a very early phase of the disease and at the time of writing the protocol the 2010 criteria for RA still had to be developed.[17] Interestingly, the Visser algorithm and 2010 criteria for RA have similar discriminative abilities to identify patients at risk of persistent arthritis.[28] Our trial is, therefore, one of the first studies conducted in RA patients fulfilling 2010 criteria.

Because of early initiation of DMARD therapy more patients achieve their treatment goal in comparison with previous trials.[8-10] After 12 months 80% had a DAS<2.4 compared with 65% in the BeSt trial.[8] Adjacent to this less erosive disease and radiographic progression were seen in our trial.[8-10] Our intensive treatment strategy also contributed to aforementioned differences. Important differences in iTDT between tREACH and BeSt were MTX dosage (respectively 25 versus 7.5 mg/week), and addition of hydroxychloroquine. This underlines the importance of initiating DMARD therapy in an earlier phase.

We were able to analyse difference in efficacy between iTDT and iMM, unbiased for GCs and in DMARD naïve patients. Our findings do not support current guidelines[2-3] and favour iTDT over iMM, but reconfirm the findings found in previous studies.[7-12, 29] Although the TEAR trial concluded otherwise, similar results are found in their trial as in the tREACH trial. Like the TEAR trial, clinical outcomes did not differ after 12 months, which is obviously due to our treat-to-target approach (intensifying treatment until the target is reached). Therefore, not the endpoint, but what happens along the way is what matters most.

**Table 2: Number (%) of patients with (serious) adverse events, and treatment alterations due to side effects for each induction therapy group.**

| | A. MTX + SASP + HCQ + im GCs (n=91) | B. MTX + SASP + HCQ + oral GCs (n=93) | C. MTX + oral GCs (n=97) |
|---|---|---|---|
| **Adverse events (AE)** | | | |
| Serious AE(s)[1] | 5 (5) | 10 (11) | 10 (10) |
| Patients with ≥1 AE(s) | 76 (84) | 82 (88) | 77 (79) |
| no. of AEs per patient, *median (IQR)* | 2 (1 - 3) | 2 (1 - 4) | 2 (1 - 4) |
| **Medication changes due to AE(s)** | | | |
| Switch to MTX sc* | 12 (13) | 21 (23) | 11 (11) |
| lowering MTX dosage <20mg/wk† | 17 (19) | 10 (11) | 22 (23) |
| STOP MTX | 11 (12) | 14 (15) | 7 (7) |
| STOP SASP | 11 (12) | 8 (9) | NA |
| STOP HCQ | 4 (4) | 5 (5) | NA |
| STOP Biological | 0 (0) | 2 (2) | 4 (4) |
| **Observed AEs[2]** | | | |
| Malaise | 20 (22) | 19 (20) | 15 (15) |
| Fatigue | 23 (25) | 34 (37) | 40 (41) |
| Dizziness | 2 (2) | 10 (11) | 7 (7) |
| Headache | 10 (11) | 13 (14) | 13 (13) |
| Muscle weakness | 2 (2) | 8 (9) | 7 (7) |
| Hypertension | 2 (2) | 4 (4) | 0 (0) |
| Palpitations | 0 (0) | 4 (4) | 7 (7) |
| Edema | 3 (3) | 3 (3) | 6 (6) |
| Dyspnea | 0 (0) | 4 (4) | 7 (7) |
| Gastrointestinal complaints | 57 (63) | 59 (63) | 41 (42) |
| Infection | 12 (13) | 21 (23) | 22 (23) |
| Skin problems | 20 (22) | 25 (27) | 27 (28) |
| Hair loss | 8 (8) | 7 (8) | 14 (14) |
| Hearing loss | 1 (1) | 0 (0) | 0 (0) |
| Visual impairment | 7 (8) | 17 (18) | 7 (7) |
| Hyperglycemia | 0 (0) | 1 (1) | 0 (0) |
| Feeling "sad" | 7 (8) | 13 (14) | 12 (12) |
| Sleep disorder | 4 (4) | 13 (14) | 8 (8) |
| Bone marrow depression | 17 (19) | 8 (9) | 7 (7) |
| High Creatinine | 2 (2) | 6 (6) | 4 (4) |
| Elevated liver enzymes | 12 (13) | 15 (16) | 18 (19) |

Results shown are a number (%) unless stated otherwise.

[1]Serious AEs per treatment are respectively: [A] 4x Hospitalisation (2x pneumonia, kidney stones and inguinal hernia surgery), 1x lung carcinoma; [B] 5x Hospitalisation (MTX pneumonitis, Severe constipation, Transient Ischemic Attack, Gastroenteritis and Observation chest pain), 1x Deceased, 1x Myocardial infarction and 2x Carcinoma (lung and mamma); [C] 6x Hospitalisation (Pneumonia, Blood transfusion, Syncope, Cholecystectomie, Inguinal Hernia Surgery and active RA), 1x Myocardial infarction, 2x Colon carcinoma and 1x Maculopathy.

[2]Bone marrow depression is defined as an anemia, thrombocytopenia or leucopenia with respectively a hemoglobin level, platelet count and white blood cells count below the lower limit of the normal range. High creatinine, raised liver enzymes and hyperglycemia are defined as having respectively a creatinine, liver transaminases and glucose level above the upper limit of the normal range.

*p=0.039 for B vs C

†p=0.028 for B vs C

Abbreviations: GCs, glucocorticoids; HCQ, hydroxychloroquine; im, intramuscular; IQR, interquartile range; MTX, methotrexate; SASP, sulfasalazine; sc, subcutaneous.

Aletaha *et al*[30] already demonstrated that the initial clinical response is related to disease activity in the long-term, and indirectly the amount of joint destruction and treatment changes needed to achieve the predefined treatment goals, which corresponds with our results. The TEAR trial showed that the predefined treatment goal is 1.5x more often reached with iTDT compared with iMM (respectively 42% versus 28%), which matched our results.[11] Moreover, the difference in mean DAS between iTDT and iMM nullified after 36 weeks (favouring iTDT).[11] However, in our trial (and TEAR trial) no difference in joint destruction was seen, which was probably due to early initiation of intensive therapy, causing less joint destruction and thus less radiological progression.

In our trial switching to biologicals was already possible after three months, if the target was not reached. In the iMM group one could argue if triple DMARD therapy instead of biologicals should be the first step-up, especially since striking evidence of superior clinical efficacy of step-up therapy to biological over triple DMARD therapy is lacking.[11, 31-32] There again, current guidelines recommend switching to biologicals, after 3 months, in patients with active disease and poor prognostic factors (i.e. auto-antibody positivity and erosive disease).[2-3] In our trial 29/36 (81%) of iMM failures, after three months, had ≥2 aforementioned factors. Therefore, we think intensification to biologicals after failing on iMM was a valid choice.

For health economic reasons efficient use of biologicals is needed to be able to continue optimal rheumatic care in the future.[33] With iTDT treatment goals are attained faster and maintained with 40% fewer biologicals, which cuts down expenses enormously, also, because treatment can be tapered more often. Besides lowering medication costs, better disease control improves worker productivity and, therefore, reduces the costs due to loss of productivity.[34-35] However, the cost-utility analysis of the tREACH trial still has to re-confirm aforementioned statement.

Patients and/or rheumatologist, however, may have some aversion for iTDT, mainly because of the large amount of drugs that have to be taken. Medication adherence in RA is strongly influenced by patient's belief about the needfulness of the drugs.[36] These beliefs are moulded by rheumatologists through the information given about the disease and treatment approach.[36] A tailor-made treatment approach would be ideally in this very early phase, especially since 60% respond well to iMM. Determination of early GC response after treatment initiation is a promising predictor, possibly leading to a more tailor-made treatment approach.[37] Therefore, we think that the emphasis of future treatment trials should be more on efficiency rather than efficacy.

In 42% of patients treatment could be tapered, of those 12% flared. Therefore, we think tapering DMARDs and/or biologicals in case of sustained remission is justified. However, patients should still be monitored strictly during tapering. Data on tapering medication are sparse, especially in early RA.[3, 38] Future research is needed to determine (1) when to commence tapering, (2) how to taper and (3) what the optimal interval is between taperings.

We find that intramuscular and oral GCs are equally effective as bridging therapy, but one single injection might be more feasible. However, duration and dosage of our GC tapering scheme was short (10 weeks) and low (initial dosage 15mg) in comparison with, for example, the COBRA regimen (respectively 28 weeks and 60mg).[10] Because GCs have disease-modifying traits with long-lasting benefits even after withdrawal, a different GC oral tapering scheme might be superior.[14] Therefore, future research is needed for optimizing GC bridging therapies.

Our study had certain limitations. Foremost, baseline imbalances occurred, despite randomisation, which were in favour of iMM; after adjustment even AUC HAQ differed significantly (favouring iTDT). Additionally, only research nurses, who assessed the DAS, were blinded for allocated treatment arm. This design was chosen, since we wanted to mimic daily practice as well as possible. Single blinding, however, could be a potential source of bias, in our case possibly favouring iMM, because of the aversion for iTDT by rheumatologists and/or patients. Moreover, due to various reasons 101 (36%) patients were excluded from our per-protocol analysis, which was more than expected. Our exclusion percentage, however, was comparable with other trials.[10-11, 31]

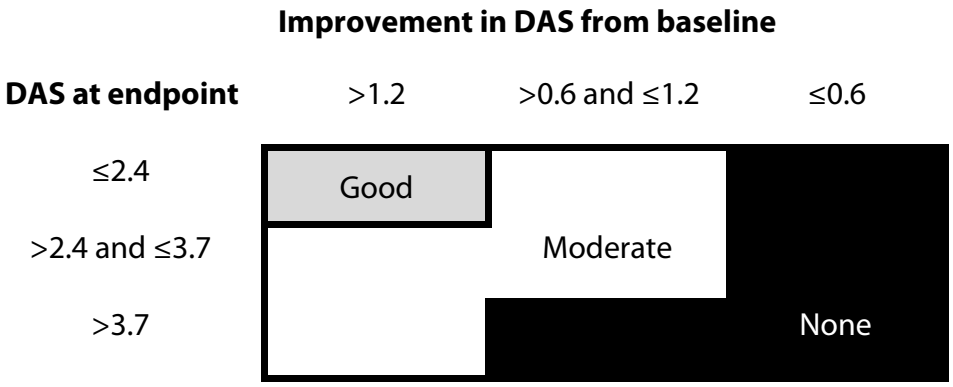
In conclusion, we recommend iTDT over iMM as first choice in newly diagnosed RA patients, because treatment goals are attained faster and maintained with 40% fewer biologicals. No differences were seen in dosage adjustments due to AEs, after stratification for drug. One single intramuscular GC injection as well as an oral GC tapering scheme would suffice as bridging therapy.

## Appendix 1: Exclusion criteria for the tREACH trial

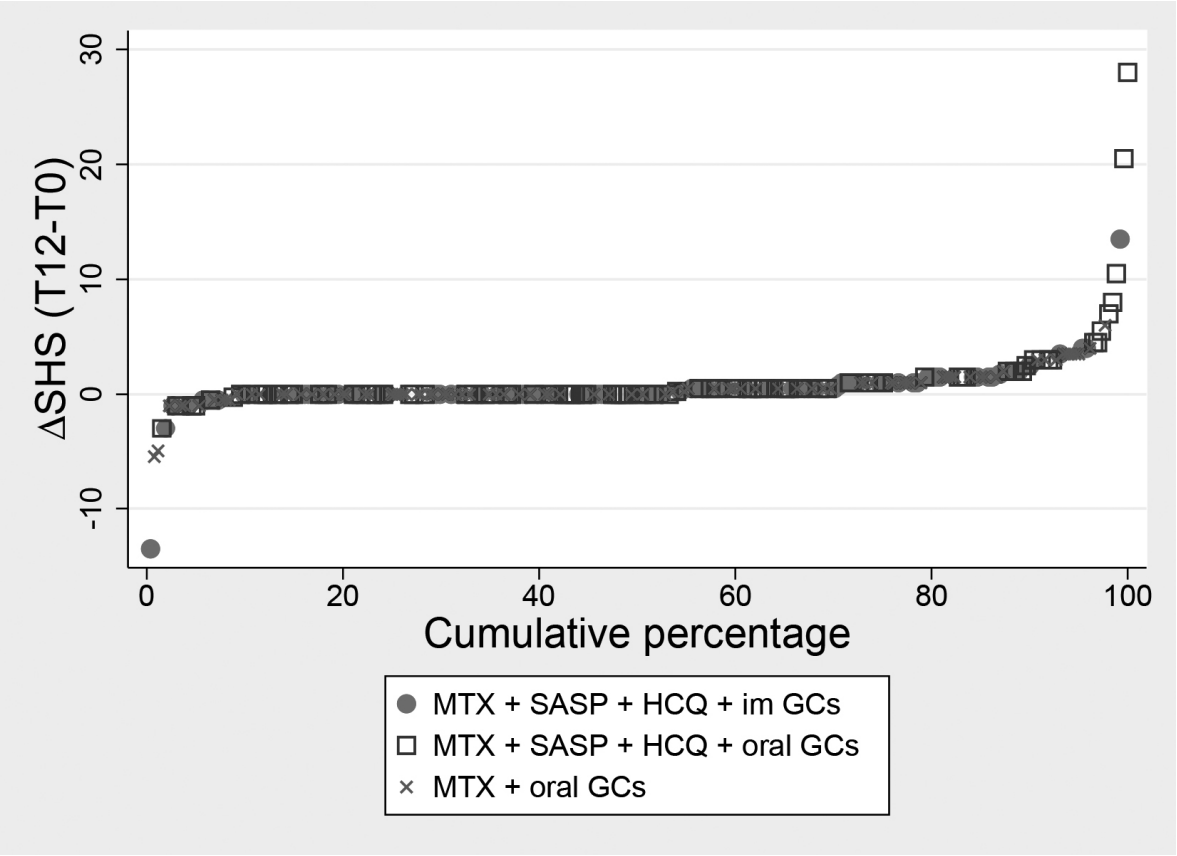
The tREACH exclusion criteria are:

1. Diagnosed with
    a. a crystal arthropathy,
    b. a (post-)infectious arthritis, or
    c. an autoimmune disorder other than RA
2. Previous DMARD therapy or glucocorticoid usage
3. Contra-indications for initial study medication, namely:
    a. chronic liver disease
    b. excessive alcohol and drug use
    c. pregnancy (wish)
    d. leucopenia $<3.0 \times 10^9$/l
    e. thrombocytopenia $<150 \times 10^9$/l
    f. aspartate aminotransferase/ alanine aminotransferase more than two times the upper normal value
    g. creatinine level >150 µmol/l.

## Appendix 2: EULAR response criteria



## Appendix 3: Cumulative probability plot for radiological progression stratified for induction therapy.




Each point on the plot represents the radiographical progression in an individual patient (score after 1 year minus score at baseline). Abbreviations: GCs, glucocorticoids; HCQ, hydroxychloroquine; im, intramuscular; MTX, methotrexate; SASP, sulfasalazine; SHS, modified Sharp/Van der Heijde score.

# Appendix 4: Subgroup analyses for patients with RA according to 2010 ACR/EULAR criteria

## Table 1: Number of participants, with RA according to 2010 ACR/EULAR criteria, at each time-point, stratified for induction therapy.

| | T0 | T3 | T6 | T9 | T12 |
|---|---|---|---|---|---|
| **A. MTX + SASP + HCQ + im GCs** | 87 | 82 | 78 | 77 | 74 |
| **B. MTX + SASP + HCQ + oral GCs** | 88 | 84 | 81 | 81 | 80 |
| **C. MTX + oral GCs** | 95 | 88 | 86 | 84 | 85 |

## Table 2: Baseline characteristics of patients with RA according to 2010 ACR/EULAR criteria, stratified for induction therapy.

| | A. MTX + SASP + HCQ + im GCs (n=87) | B. MTX + SASP + HCQ + oral GCs (n=88) | C. MTX + oral GCs (n=95) |
|---|---|---|---|
| **Demographic** | | | |
| Age (yrs), *mean (sd)* | 53 (15) | 54 (14) | 54 (14) |
| Sex, female, *no(%)* | 52 (60) | 63 (72) | 67 (71) |
| **Disease characteristics** | | | |
| Symptom duration (days), *mean (sd)** | 160 (95) | 183 (93) | 151 (81) |
| RF pos., *no(%)* | 68 (78) | 64 (72) | 65 (68) |
| ACPA pos., *no(%)* | 72 (83) | 66 (75) | 75 (79) |
| **Disease activity** | | | |
| DAS, *mean (sd)* | 3.34 (0.78) | 3.44 (1.08) | 3.40 (0.98) |
| DAS28, *mean (sd)* | 4.86 (1.09) | 4.88 (1.29) | 4.79 (1.28) |
| TJC44, *median (IQR)* | 8 (4 - 14) | 9.5 (5 – 16) | 10 (4 – 14) |
| SJC44, *median (IQR)* | 8 (5 - 12) | 8 (4 – 12) | 7 (4 – 12) |
| VAS global (0 -100mm), *median (IQR)* | 53 (37 - 70) | 55 (29 – 69) | 53 (37 – 70) |
| ESR in mm/hr, *median (IQR)* | 27 (14 – 40) | 22 (13 – 39.5) | 24 (14 – 43) |
| CRP in mg/L, *median (IQR)* | 8.5 (4 -23) | 6.4 (3.75 - 19) | 11 (5 – 26) |
| **Radiographs (hand/foot)** | | | |
| Total SHS (0 - 488 ), *median (IQR)* | 0.5 (0 – 2) | 0.5 (0 – 2) | 1 (0 - 2.5) |
| Erosion score (0 - 280), *median (IQR)* | 0 (0 – 1) | 0 (0 – 1) | 0.5 (0 – 1) |
| JSN score (0 - 168), *median (IQR)* | 0 (0 – 1) | 0 (0 – 1) | 0 (0 - 1.5) |
| Erosion, *no(%)*[1] | 17/87 (20) | 18/88 (20) | 20/93 (22) |
| **Questionnaires**[2] | | | |
| HAQ, *mean (sd)* | 0.98 (0.69) (n=80) | 0.99 (0.63) (n=82) | 1.06 (0.68) (n=90) |
| RADAI (0-10), *mean (sd)* | 4.01 (1.85) (n=78) | 4.02 (1.59) (n=78) | 4.18 (1.83) (n=85) |

[1]Erosive disease is defined as having a erosion score >1.2 (=smallest detectable difference)

[2]Not everyone filled in a (complete) questionnaire and therefore n is different for HAQ and RADAI.

*p=0.016 for B vs C.

**Table 3: Clinical response after 12 months for each induction therapy group in the subgroup of patients with RA according to 2010 criteria, intention-to-treat analysis.**

| | A. MTX + SASP + HCQ + im GCs (n=74) | B. MTX + SASP + HCQ + oral GCs (n=80) | C. MTX + oral GCs (n=85) |
|---|---|---|---|
| **Disease activity** | | | |
| DAS, *mean (sd)* | 1.40 (0.69) | 1.62 (0.88) | 1.67 (0.88) |
| ΔDAS (T12 - T0), *mean (sd)* | -1.89 (-1.00) | -1.77 (-1.16) | -1.72 (-1.28) |
| Disease state according to DAS, *no(%)* | | | |
| *moderate to high disease activity (DAS≥2.4)* | 8 (11) | 15 (19) | 18 (21) |
| *low disease activity (1.6≥DAS<2.4)* | 20 (27) | 23 (29) | 24 (28) |
| *remission (DAS<1.6)* | 46 (62) | 42 (53) | 43 (51) |
| Boolean remission criteria, *no(%)*[1] | 17 (23) | 12(15) | 14(17) |
| EULAR response criteria (T12 - T0), *no(%)*[2] | | | |
| *good* | 54 (73) | 50 (63) | 56 (66) |
| *Moderate* | 13 (18) | 18 (23) | 9 (11) |
| *none* | 7 (9) | 12 (15) | 20 (24) |
| TJC44, *median (IQR)* | 0 (0 - 2) | 0 (0 - 4) | 1 (0 - 4) |
| SJC44, *median (IQR)** | 0 (0 - 2) | 0 (0 - 1) | 0 (0 - 2) |
| VAS global (0 -100mm), *median (IQR)* | 18 (8 - 32) | 22.5 (9.5 - 37.5) | 23 (10 - 40) |
| ESR in mm/hr, *median (IQR)* | 11 (5 - 18) | 10.5 (6.5 - 20.5) | 12 (6 - 21) |
| CRP in mg/L, *median (IQR)* | 3 (1 - 5.2) | 4 (1 - 7) | 3 (1.9 - 5) |
| **Radiographs (hand/foot)** | | | |
| Total SHS (0 - 488 ), *median (IQR)* | 1.25 (0 – 3) | 1 (0 – 3) | 1.5 (0 - 3.5) |
| Erosion score (0 - 280), *median (IQR)* | 0.5 (0 - 1.25) | 0.5 (0 - 1.5) | 0.5 (0 - 1.5) |
| JSN score (0 - 168), *median (IQR)* | 0.5 (0 - 1.5) | 0 (0 - 1.5) | 0.5 (0 – 2) |
| ΔTotal SHS (T12 - T0), *median (IQR)* | 0.38 (0 – 1) | 0 (0 – 1) | 0 (0 – 1) |
| Patients with progression >0.5, *no (%)* | 25/73 (34) | 24/78 (31) | 28/82 (34) |
| Patients with progression >1.2, *no (%)* | 16/73 (22) | 20/78 (26) | 19/82 (23) |
| **Questionnaires**[3] | | | |
| HAQ, *mean (sd)* | 0.38 (0.46) (n=66) | 0.52 (0.56) (n=74) | 0.63 (0.57) (n=82) |
| ΔHAQ (T12 - T0), *mean (sd)* | -0.47 (-0.64) (n=62) | -0.43 (-0.59) (n=71) | -0.47 (-0.53) (n=80) |
| RADAI (0 - 10), *mean (sd)* | 1.45 (1.24) (n=65) | 1.83 (1.54) (n=71) | 2.15 (1.82) (n=78) |
| ΔRADAI (T12 - T0), *mean (sd)* | -2.23 (-1.70) (n=61) | -2.07 (-1.89) (n=66) | -2.12 (-1.92) (n=73) |

[1]Boolean remission criteria are defined as having a TJC44≤1, SJC44≤1, VAS global≤10mm and CRP≤10 mg/L

[2]EULAR response criteria are based on attained level and change in DAS

[3]Not everyone filled in a (complete) questionnaire and therefore n is different for HAQ and RADAI.

*p=0.044 for B vs C.

Abbreviations: CRP, C-reactive protein; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; GCs, glucocorticoids; HAQ, Health Assessment Questionnaire; HCQ, hydroxychloroquine; im, intramuscular; IQR, interquartile range; JSN, joint space narrowing; MTX, methotrexate; RADAI, Rheumatoid Arthritis Disease Activity Index questionnaire; SASP,sulfasalazine; sd, standard deviation; SHS, modified Sharp/Van der Heijde score; SJC44, swollen joint count (44 joints); TJC44, tender joint count (44 joints); VAS, visual analogue scale.

**Table 4: Medication usage after 12 months and treatment alteration over time for each induction therapy group in the subgroup of patients with RA according to 2010 criteria.**

| | A. MTX + SASP + HCQ + im GCs (n=87) | B. MTX + SASP + HCQ + oral GCs (n=88) | C. MTX + oral GCs (n=95) |
|---|---|---|---|
| **Medication after 12 months** | | | |
| MTX | 69 (79) | 68 (77) | 80 (84) |
| MTX dosage, *median (IQR)* | 15 (7.5 - 25) | 15 (7.5 - 25) | 20 (7.5 - 25) |
| SASP | 25 (29) | 25 (28) | 2 (2) |
| HCQ | 49 (56) | 54 (61) | 8 (8) |
| Biological use* | 26 (30) | 23 (26) | 41 (43) |
| *Etanercept* | 18 (21) | 12 (14) | 22 (23) |
| *Adalimumab*† | 4 (5) | 5 (6) | 16 (17) |
| *Abatacept* | 3 (3) | 5 (6) | 3 (3) |
| *Other*[1] | 1 (1) | 1 (1) | 0 (0) |
| **Tapered treatment**[2] | | | |
| Taperings‡ | 84/229 (37) | 65/242 (27) | 59/255 (23) |
| at 1 time-point | 15 (18) | 18 (20) | 15 (16) |
| at 2 time-points | 12 (13) | 10 (8) | 10 (10) |
| at 3 time-points | 15 (16) | 9 (11) | 8 (8) |
| **Flare after tapering**[3] | 6/84 (7) | 3/65 (5) | 4/59 (7) |

Results shown are a number (%) unless stated otherwise.

[1]Other biologicals are: Infliximab (A) and Rituximab (B)

[2]Treatment could be tapered after 6 months. Therefore the total amount of possible taperings is the sum of all assessments at the last three visits, per treatment arm.

[3]A flare is defined as a DAS≥2.4. The proportion is calculated by dividing the number of flares by the total amount of taperings

*p=0.016 for B vs C.

†p=0.018 for B vs C

‡p=0.022 for A vs B

Abbreviations: GCs, glucocorticoids; HCQ, hydroxychloroquine; im, intramuscular; IQR, interquartile range; MTX, methotrexate; SASP, sulfasalazine.

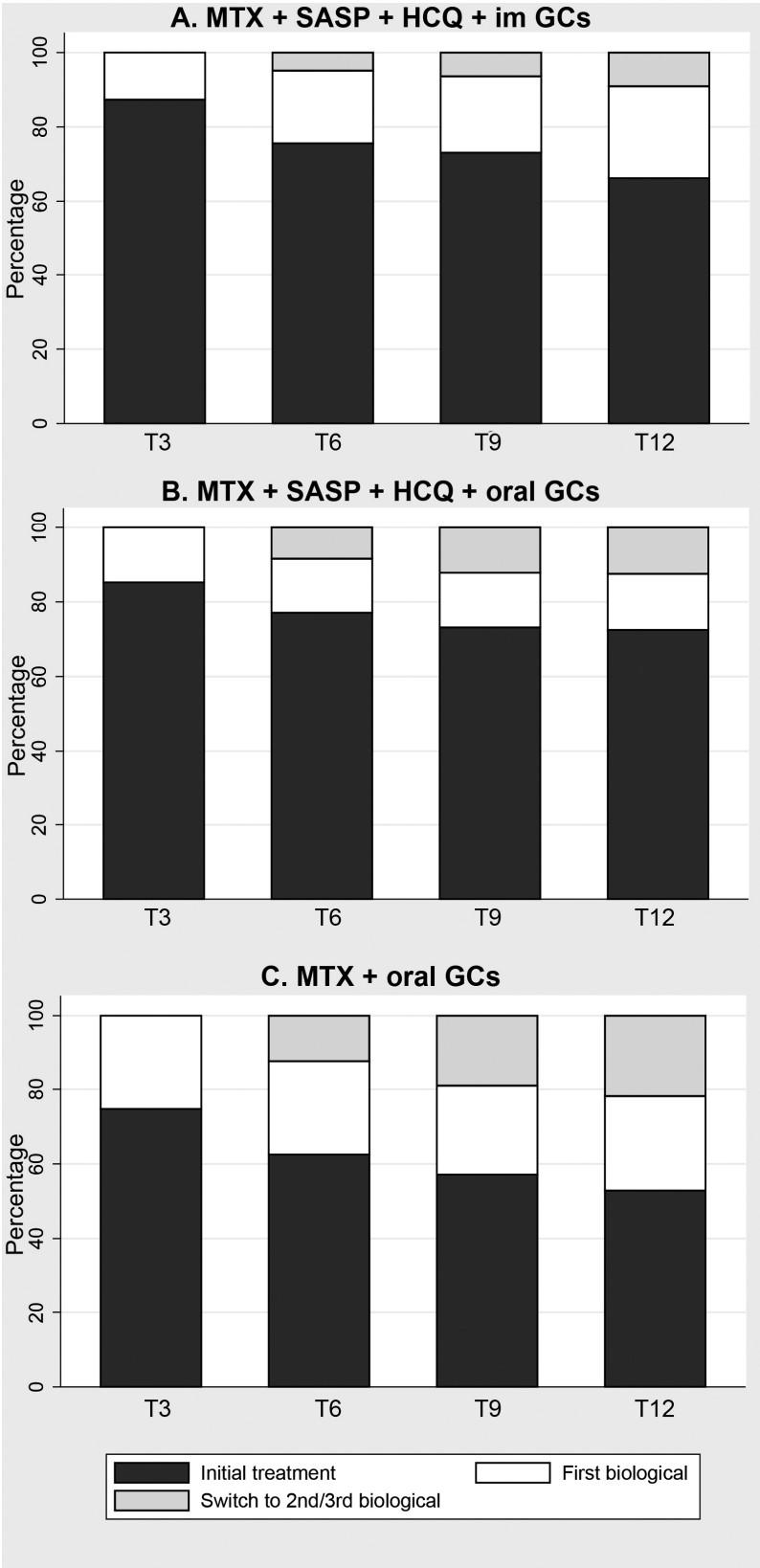
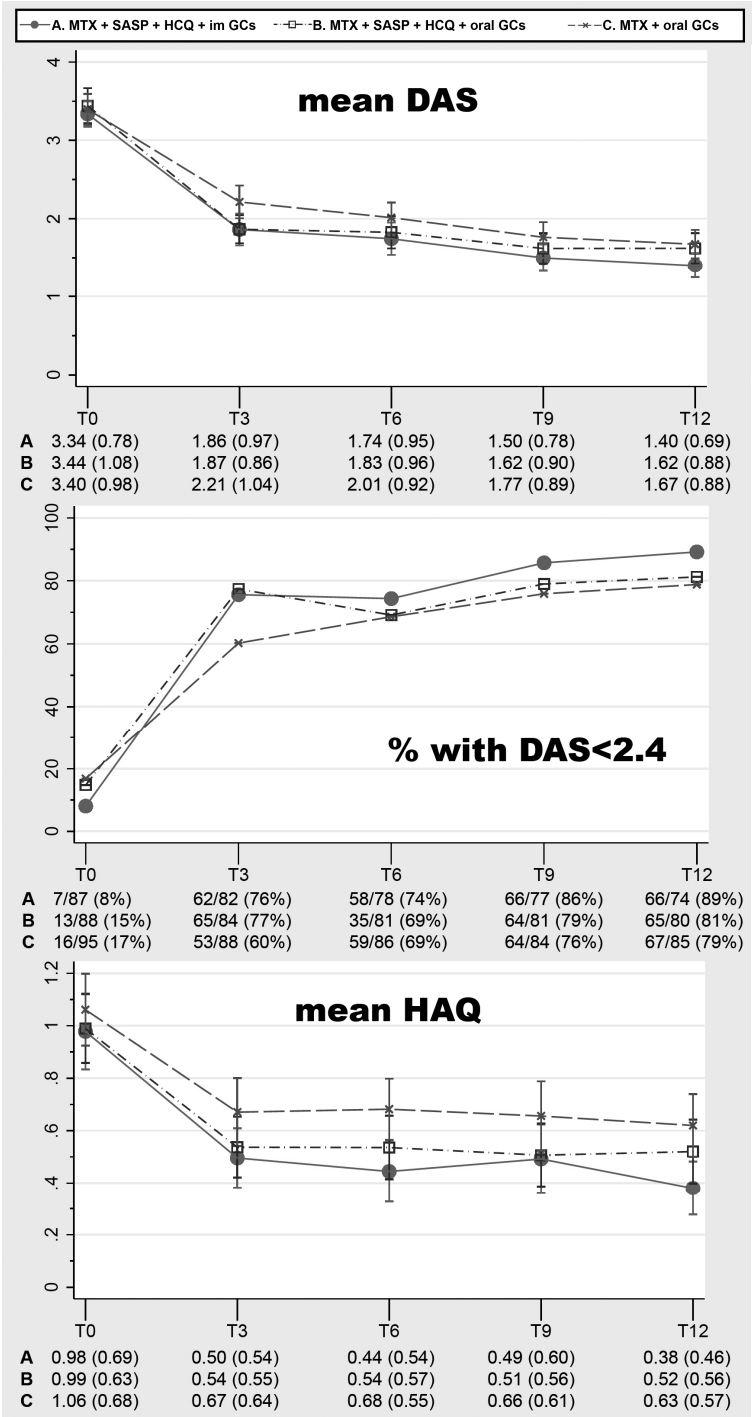



**Figure 1: Medication usage over time, stratified for induction therapy in the subgroup of patients with RA according to 2010 criteria.**

Abbreviations: GCs, glucocorticoids; HCQ, hydroxychloroquine; im, intramuscular; MTX, methotrexate; SASP, sulfasalazine.


A. MTX + SASP + HCQ + im GCs
B. MTX + SASP + HCQ + oral GCs
C. MTX + oral GCs
mean DAS
0
1
2
3
4
T0
T3
T6
T9
T12
A 3.34 (0.78) 1.86 (0.97) 1.74 (0.95) 1.50 (0.78) 1.40 (0.69)
B 3.44 (1.08) 1.87 (0.86) 1.83 (0.96) 1.62 (0.90) 1.62 (0.88)
C 3.40 (0.98) 2.21 (1.04) 2.01 (0.92) 1.77 (0.89) 1.67 (0.88)
% with DAS<2.4
0
20
40
60
80
100
T0
T3
T6
T9
T12
A 7/87 (8%) 62/82 (76%) 58/78 (74%) 66/77 (86%) 66/74 (89%)
B 13/88 (15%) 65/84 (77%) 35/81 (69%) 64/81 (79%) 65/80 (81%)
C 16/95 (17%) 53/88 (60%) 59/86 (69%) 64/84 (76%) 67/85 (79%)
mean HAQ
0
.2
.4
.6
.8
1
1.2
T0
T3
T6
T9
T12
A 0.98 (0.69) 0.50 (0.54) 0.44 (0.54) 0.49 (0.60) 0.38 (0.46)
B 0.99 (0.63) 0.54 (0.55) 0.54 (0.57) 0.51 (0.56) 0.52 (0.56)
C 1.06 (0.68) 0.67 (0.64) 0.68 (0.55) 0.66 (0.61) 0.63 (0.57)

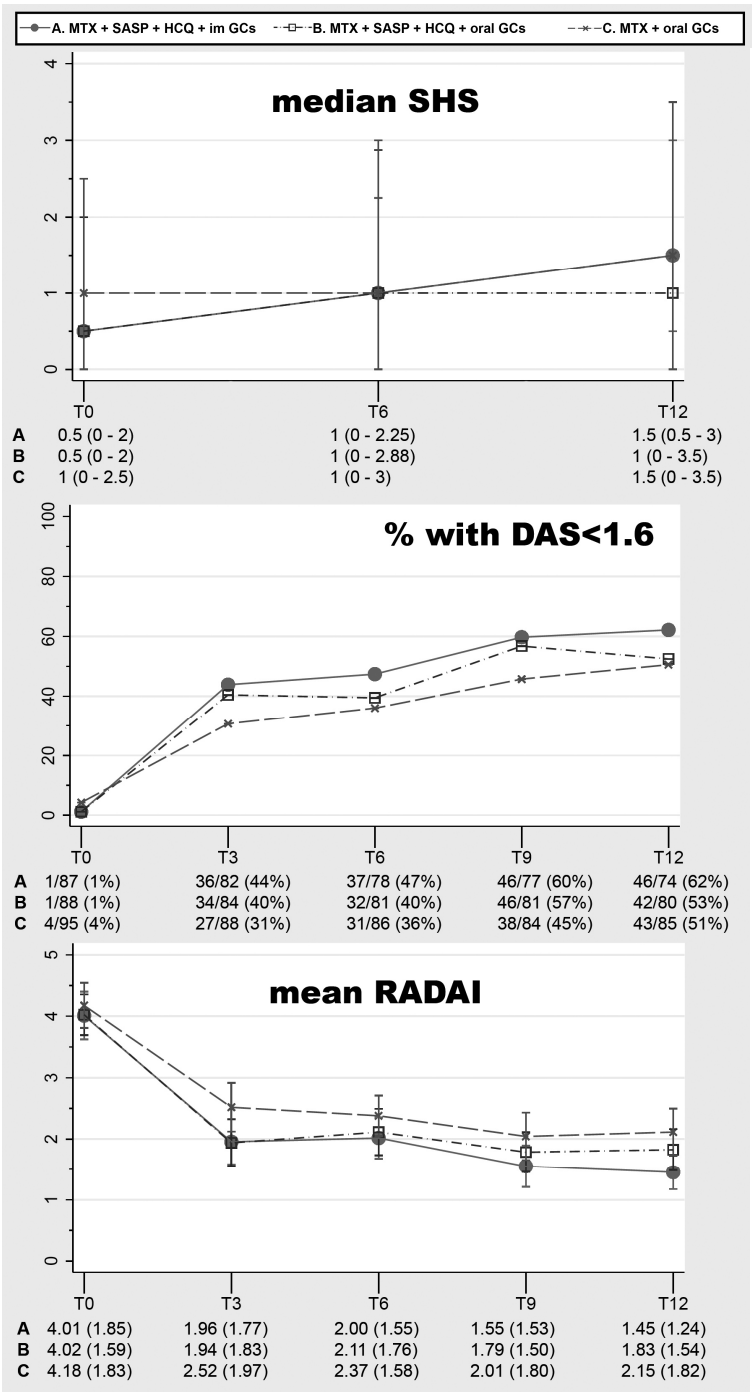



**Figure 2: (Self-assessed) disease activity, functional ability and radiographic joint damage over time, stratified for induction therapy in the subgroup of patients with RA according to 2010 criteria.**

Error bars indicate respectively 95% confidence intervals and interquartile range for given means and median.

| | A. MTX + SASP + HCQ + im GCs | B. MTX + SASP + HCQ + oral GCs | C. MTX + oral GCs |
|---|---|---|---|
| **AUC** | | | |
| DAS | 22.4 (7.3) (n=87) | 23.5 (8.4) (n=88) | 25.6 (8.4) (n=95) |
| HAQ | 6.4 (5.0) (n=80) | 7.0 (5.5) (n=82) | 8.5 (5.9) (n=90) |

Results shown are mean(SD)

# Appendix 5: Subgroup analyses for patients with RA according to 1987 ACR criteria

## Table 1: Number of participants, with RA according to 1987 ACR criteria, at each time-point, stratified for induction therapy.

| | T0 | T3 | T6 | T9 | T12 |
|---|---|---|---|---|---|
| **A. MTX + SASP + HCQ + im GCs** | 69 | 65 | 63 | 60 | 58 |
| **B. MTX + SASP + HCQ + oral GCs** | 57 | 55 | 52 | 53 | 52 |
| **C. MTX + oral GCs** | 63 | 59 | 57 | 55 | 56 |

## Table 2: Baseline characteristics of patients with RA according to 1987 ACR criteria, stratified for induction therapy.

| | A. MTX + SASP + HCQ + im GCs (n=69) | B. MTX + SASP + HCQ + oral GCs (n=57) | C. MTX + oral GCs (n=63) |
|---|---|---|---|
| **Demographic** | | | |
| Age (yrs), *mean (sd)* | 54 (16) | 55 (14) | 55 (14) |
| Sex, female, *no(%)* | 41 (59) | 39 (68) | 43 (68) |
| **Disease characteristics** | | | |
| Symptom duration (days), *mean (sd)* | 160 (94) | 174 (87) | 146 (73) |
| RF pos., *no(%)* | 55 (80) | 47 (82) | 45 (71) |
| ACPA pos., *no(%)* | 56 (81) | 40 (70) | 49 (78) |
| **Disease activity** | | | |
| DAS, *mean (sd)* | 3.43 (0.76) | 3.56 (1.06) | 3.57 (0.99) |
| DAS28, *mean (sd)* | 5.04 (0.99) | 5.13 (1.24) | 5.03 (1.22) |
| TJC44, *median (IQR)* | 9 (6 - 14) | 10 (5 – 15) | 10 (5 – 15) |
| SJC44, *median (IQR)* | 9 (6 - 12) | 11 (6 – 12) | 9 (6 – 11) |
| VAS global (0 -100mm), *median (IQR)* | 55 (37 - 69) | 58 (31 – 71) | 55 (35 – 70) |
| ESR in mm/hr, *median (IQR)* | 28 (15 – 44) | 24 (16 – 51) | 25 (20 – 44) |
| CRP in mg/L, *median (IQR)* | 9 (4 -24) | 8 (4 - 24) | 13 (5.6 – 31) |
| **Radiographs (hand/foot)** | | | |
| Total SHS (0 - 488 ), *median (IQR)* | 1 (0 – 2.5) | 1 (0 – 2.5) | 1 (0 – 3) |
| Erosion score (0 - 280), *median (IQR)* | 0.5 (0 – 1) | 0.5 (0 – 1.5) | 0.5 (0 – 1) |
| JSN score (0 - 168), *median (IQR)* | 0 (0 - 1.5) | 0 (0 - 1.5) | 0.5 (0 - 1.5) |
| Erosion, *no(%)*[1] | 15/69 (22) | 15/57 (26) | 14/62 (23) |
| **Questionnaires**[2] | | | |
| HAQ, *mean (sd)* | 1.05 (0.67) (n=64) | 0.99 (0.64) (n=53) | 1.10 (0.68) (n=60) |
| RADAI (0-10), *mean (sd)* | 4.16 (1.86) (n=63) | 4.13 (1.53) (n=51) | 4.31 (1.98) (n=57) |

[1]Erosive disease is defined as having a erosion score >1.2 (=smallest detectable difference)

[2]Not everyone filled in a (complete) questionnaire and therefore n is different for HAQ and RADAI.

Abbreviations: ACPA, anti-citrullinated protein/peptide antibodies; CRP, C-reactive protein; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; GCs, glucocorticoids; HAQ,Health Assessment Questionnaire; HCQ, hydroxychloroquine; im, intramuscular; IQR, interquartile range; JSN, joint space narrowing; MTX, methotrexate; RADAI, Rheumatoid Arthritis Disease Activity Index questionnaire; RF, rheumatoid factor; SASP,sulfasalazine; sd, standard deviation; SHS, modified Sharp/Van der Heijde score; SJC44, swollen joint count (44 joints); TJC44, tender joint count (44 joints); VAS, visual analogue scale.

**Table 3: Clinical response after 12 months for each induction therapy group in the subgroup of patients with RA according to 1987 criteria, intention-to-treat analysis.**

| | A. MTX + SASP + HCQ + im GCs (n=58) | B. MTX + SASP + HCQ + oral GCs (n=52) | C. MTX + oral GCs (n=56) |
|---|---|---|---|
| **Disease activity** | | | |
| DAS, *mean (sd)* | 1.41 (0.68) | 1.64 (0.93) | 1.64 (0.94) |
| ΔDAS (T12 - T0), *mean (sd)* | -1.97 (-1.00) | -1.93 (-1.22) | -1.92 (-1.26) |
| Disease state according to DAS, *no(%)* | | | |
| *moderate to high disease activity (DAS≥2.4)* | 6 (10) | 9 (17) | 12 (21) |
| *low disease activity (1.6≥DAS<2.4)* | 17 (29) | 15 (29) | 16 (29) |
| *remission (DAS<1.6)* | 35 (60) | 28 (54) | 28 (50) |
| Boolean remission criteria, *no(%)*[1] | 16 (28) | 10 (20) | 12 (21) |
| EULAR response criteria (T12 - T0), *no(%)*[2] | | | |
| *Good* | 43 (74) | 33 (63) | 40 (71) |
| *Moderate* | 11 (19) | 13 (25) | 6 (11) |
| *None* | 4 (7) | 6 (12) | 10 (18) |
| TJC44, *median (IQR)* | 0 (0 - 2) | 0 (0 - 4) | 0 (0 - 4) |
| SJC44, *median (IQR)* | 0 (0 - 2) | 0 (0 - 2) | 0 (0 - 2) |
| VAS global (0 -100mm), *median (IQR)* | 14 (7 - 30) | 24.5 (9 - 38) | 23 (8.5 - 42.5) |
| ESR in mm/hr, *median (IQR)* | 12 (5 - 20) | 13 (7 - 20.5) | 14.5 (5 - 22) |
| CRP in mg/L, *median (IQR)* | 3.1 (1 - 6) | 3.1 (1 - 7) | 3 (1.85 - 5.5) |
| **Radiographs (hand/foot)** | | | |
| Total SHS (0 - 488 ), *median (IQR)* | 1.5 (0.5 - 3.75) | 1.5 (0.5 - 5.5) | 2 (0 - 4) |
| Erosion score (0 - 280), *median (IQR)* | 0.5 (0 - 1.5) | 1 (0 - 3) | 0.5 (0 - 2) |
| JSN score (0 - 168), *median (IQR)* | 0.5 (0 - 1.75) | 0 (0 - 1.5) | 0.63 (0 - 2.25) |
| ΔTotal SHS (T12 - T0), *median (IQR)* | 0.38 (0 – 1) | 0.5 (0 – 2) | 0 (0 – 1.5) |
| Patients with progression >0.5, *no (%)* | 20/57 (35) | 20/51 (39) | 21/54 (39) |
| Patients with progression >1.2, *no (%)* | 14/57 (25) | 18/51 (35) | 16/54 (30) |
| **Questionnaires**[3] | | | |
| HAQ, *mean (sd)* | 0.39 (0.49) (n=53) | 0.56 (0.59) (n=49) | 0.61 (0.61) (n=55) |
| ΔHAQ (T12 - T0), *mean (sd)* | -0.55 (-0.63) (n=50) | -0.44 (-0.65) (n=47) | -0.51 (-0.49) (n=54) |
| RADAI (0 - 10), *mean (sd)* | 1.40 (1.20) (n=52) | 1.89 (1.61) (n=48) | 2.14 (1.96) (n=51) |
| ΔRADAI (T12 - T0), *mean (sd)* | -2.36 (-1.62) (n=49) | -2.12 (-2.01) (n=44) | -2.24 (-1.91) (n=49) |

[1]Boolean remission criteria are defined as having a TJC44≤1, SJC44≤1, VAS global≤10mm and CRP≤10 mg/L

[2]EULAR response criteria are based on attained level and change in DAS

[3]Not everyone filled in a (complete) questionnaire and therefore n is different for HAQ and RADAI.

Abbreviations: CRP, C-reactive protein; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; GCs, glucocorticoids; HAQ,Health Assessment Questionnaire; HCQ, hydroxychloroquine; im, intramuscular; IQR, interquartile range; JSN, joint space narrowing; MTX, methotrexate; RADAI, Rheumatoid Arthritis Disease Activity Index questionnaire; SASP,sulfasalazine; sd, standard deviation; SHS, modified Sharp/Van der Heijde score; SJC44, swollen joint count (44 joints); TJC44, tender joint count (44 joints); VAS, visual analogue scale.

**Table 4: Medication usage after 12 months and treatment alteration over time for each induction therapy group in the subgroup of patients with RA according to 1987 criteria**

| | A. MTX + SASP + HCQ + im GCs (n=69) | B. MTX + SASP + HCQ + oral GCs (n=57) | C. MTX + oral GCs (n=63) |
|---|---|---|---|
| **Medication after 12 months** | | | |
| MTX | 56 (81) | 48 (84) | 53 (84) |
| MTX dosage, *median (IQR)* | 15 (7.5 - 25) | 20 (7.5 - 25) | 20 (10 - 25) |
| SASP | 22 (32) | 17 (30) | 2 (3) |
| HCQ | 41 (59) | 37 (65) | 5 (8) |
| Biological use* | 20 (29) | 13 (23) | 25 (40) |
| *Etanercept* | 14 (20) | 8 (14) | 13 (21) |
| *Adalimumab*† | 3 (4) | 2 (4) | 10 (16) |
| *Abatacept* | 2 (3) | 3 (6) | 2 (3) |
| *Other*[1] | 1 (1) | 0 (0) | 0 (0) |
| **Tapered treatment**[2] | | | |
| Taperings | 64/181 (35) | 49/157 (31) | 46/168 (27) |
| at 1 time-point | 10 (18) | 11 (20) | 14 (16) |
| at 2 time-points | 9 (13) | 7 (8) | 7 (10) |
| at 3 time-points | 12 (16) | 8 (11) | 6 (8) |
| **Flare after tapering**[3] | 2/64 (3) | 3/49 (6) | 4/46 (9) |

Results shown are a number(%) unless stated otherwise.

[1]Other biologicals are: Infliximab (A) and Rituximab (B)

[2]Treatment could be tapered after 6 months. Therefore the total amount of possible taperings is the sum of all assessments at the last three visits, per treatment arm.

[3]A flare is defined as a DAS≥2.4. The proportion is calculated by dividing the number of flares by the total amount of taperings

*p=0.047 for B vs C.

†p=0.024 for B vs C

Abbreviations: GCs, glucocorticoids; HCQ, hydroxychloroquine; im, intramuscular; IQR, interquartile range; MTX, methotrexate; SASP, sulfasalazine.

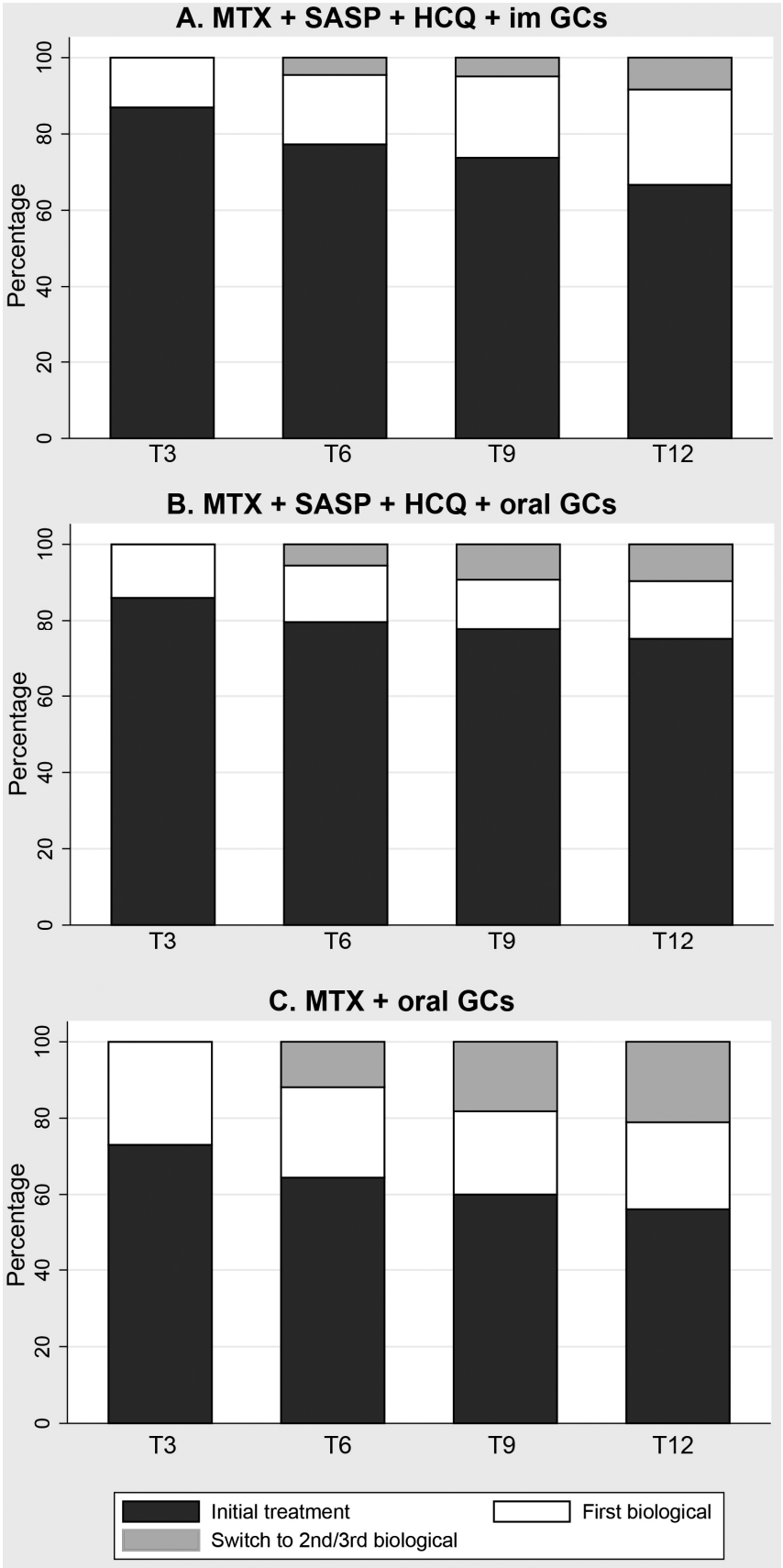
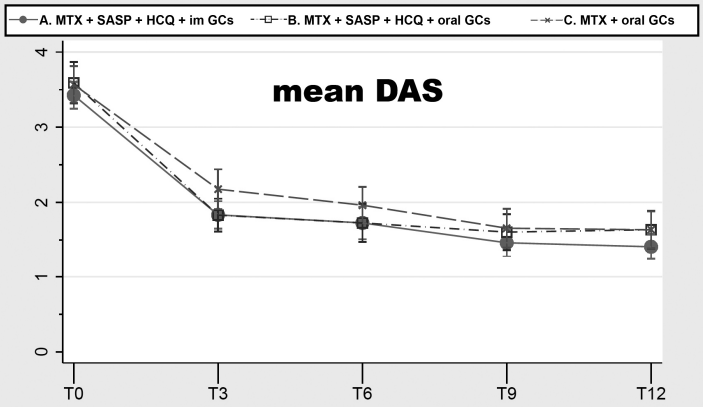
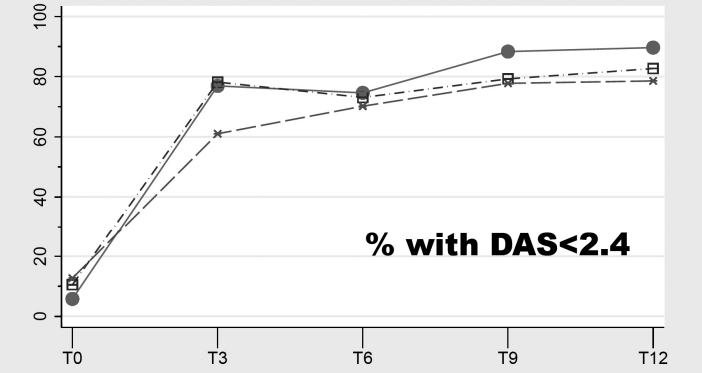



**Figure 1: Medication usage over time, stratified for induction therapy in the subgroup of patients with RA according to 1987 criteria.**

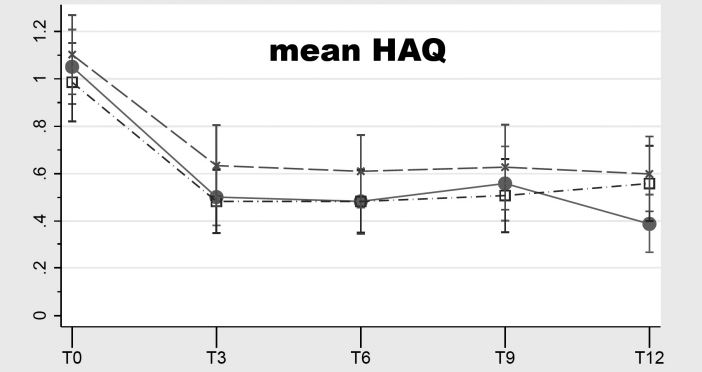
Abbreviations: GCs, glucocorticoids; HCQ, hydroxychloroquine; im, intramuscular; MTX, methotrexate; SASP, sulfasalazine.




| | T0 | T3 | T6 | T9 | T12 |
|---|---|---|---|---|---|
| **A** | 3.42 (0.76) | 1.83 (0.77) | 1.73 (0.90) | 1.46 (0.74) | 1.41 (0.68) |
| **B** | 3.59 (1.06) | 1.83 (0.84) | 1.73 (0.95) | 1.61 (0.90) | 1.64 (0.93) |
| **C** | 3.57 (0.99) | 2.18 (1.07) | 1.96 (0.95) | 1.67 (0.97) | 1.64 (0.94) |




| | T0 | T3 | T6 | T9 | T12 |
|---|---|---|---|---|---|
| **A** | 4/69 (6%) | 50/65 (77%) | 47/63 (75%) | 53/60 (88%) | 52/88 (90%) |
| **B** | 6/57 (11%) | 43/55 (78%) | 38/52 (73%) | 42/53 (79%) | 43/52 (83%) |
| **C** | 8/63 (13%) | 36/59 (61%) | 40/57 (70%) | 43/55 (78%) | 44/56 (79%) |




| | T0 | T3 | T6 | T9 | T12 |
|---|---|---|---|---|---|
| **A** | 1.05 (0.67) | 0.50 (0.51) | 0.48 (0.57) | 0.56 (0.62) | 0.39 (0.49) |
| **B** | 0.99 (0.64) | 0.48 (0.52) | 0.48 (0.49) | 0.51 (0.58) | 0.56 (0.59) |
| **C** | 1.10 (0.68) | 0.63 (0.69) | 0.61 (0.60) | 0.64 (0.67) | 0.61 (0.61) |

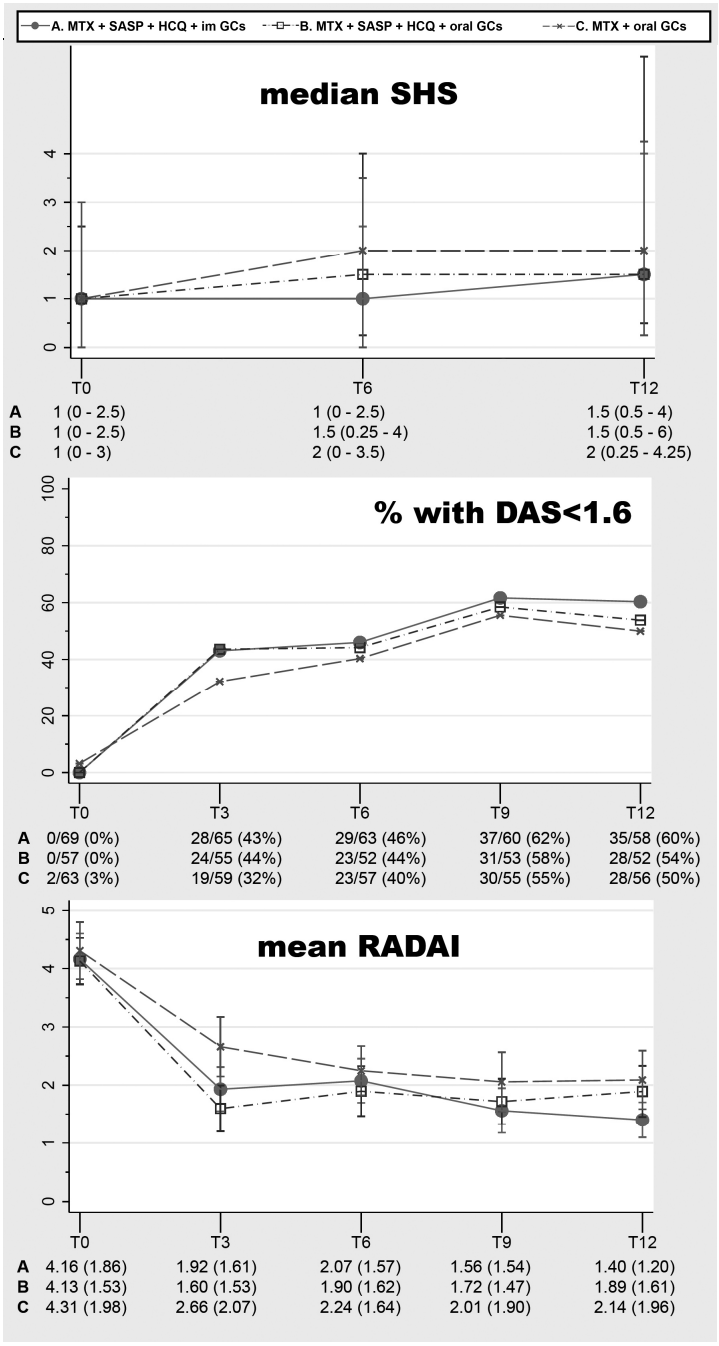



**Figure 2: (Self-assessed) disease activity, functional ability and radiographic joint damage over time, stratified for induction therapy in the subgroup of patients with RA according to 1987 criteria.**

Error bars indicate respectively 95% confidence intervals and interquartile range for given means and median.

| | A. MTX + SASP + HCQ + im GCs | B. MTX + SASP + HCQ + oral GCs | C. MTX + oral GCs |
|---|---|---|---|
| **AUC** | | | |
| DAS | 22.3 (6.3) (n=69) | 23.3 (8.3) (n=57) | 25.3 (8.8) (n=63) |
| HAQ | 6.8 (5.2) (n=64) | 6.8 (5.3) (n=53) | 8.4 (6.4) (n=60) |

Results shown are mean(SD).

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CHAPTER 4

# Best cost-effectiveness and worker productivity with initial triple DMARD therapy compared with MTX monotherapy in early rheumatoid arthritis; Cost-utility analysis of the tREACH trial.

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**Objective:**
To evaluate direct and indirect costs per Quality Adjusted Life Year (QALY) for different initial treatment strategies in very early rheumatoid arthritis.

**Methods:**
The 1-year data of the tREACH trial were used. Patients with a high probability (>70%) according to their likelihood of progressing to persistent arthritis, based on the prediction model of Visser, were randomized into one of following initial treatment strategies: (A) initial triple DMARD therapy (iTDT) with glucocorticoids (GCs) intramuscular (n=91), (B) iTDT with an oral GC tapering scheme (n=93), and (C) initial methotrexate monotherapy (iMM) with GCs similar to B (n=97). Data on QALYs, measured with Dutch EuroQol and Short Form 6D, direct and indirect cost were used. Direct costs are costs of treatment and medical consumption, whereas indirect costs are costs due to loss of productivity.

**Results:**
Average QALYs for A, B and C were respectively 0.75, 0.75 and 0.73 for Dutch EuroQol; and 0.77, 0.76 and 0.75 for Short Form 6D. Highest total costs per QALY (standard deviation) were respectively €12748 (€18767), €10380 (€15608) and €17408 (€21828) for strategy A, B and C (p=0.012, B versus C). Direct as well as indirect costs were higher with iMM (strategy C) compared with iTDT (strategy B). Higher direct costs were due to ~40% more biological usage over time. Higher indirect costs on the other hand were caused by more long-term sickness and reduction in contract hours.

**Conclusion:**
iTDT had lower costs per QALY compared with iMM. Furthermore iTDT had better worker productivity.

**Key words**

- Cost-utility; Rheumatoid Arthritis; Early Arthritis; QALY; Worker productivity; Direct and Indirect costs

## INTRODUCTION

In last two decades major paradigm changes in the management of rheumatoid arthritis (RA) have occurred. These changes are: (1) early detection of the disease, hence development of 2010 criteria for RA [1], (2) early initiation of intensive therapy, and (3) a treat-to-target approach, leading to current EULAR recommendations.[2] Complying with these recommendations result in better functional and radiological outcomes.[3-4]

Although the management of RA has underwent major changes, some important debate points still exist. A prominent discussion is about specifying most appropriate initial treatment strategy, where the emphasis is on DMARD combination therapy versus monotherapy. [2, 5] Therefore, in the treatment in the Rotterdam Early Arthritis Cohort (tREACH) trial we compared the 1-year clinical efficacy of initial triple DMARD therapy (iTDT) versus initial methotrexate (MTX) monotherapy (iMM).[6] We showed that treatment goals were attained faster and maintained with less expensive drugs with iTDT as opposed to iMM, without more serious adverse events. Considering the decreased burden of the disease over time with iTDT, we were curious whether costs differed between initial treatment regimens, especially since 20-50% of the total costs are medication costs. [7]

Furthermore, to manage the exponentially increasing health care costs health insurance companies and governments will judge the compensation of prescribed drugs by evidence based data on cost-effectiveness . Therefore, sufficient data on efficient use of expensive drugs, especially biologic agents, are needed to be able to continue optimal rheumatic care in the future. [8]

Previous cost analyses showed that a strategic approach with rapid treatment intensification to biological agents is cost-effective. [9-10] However, it is still unclear which initial treatment regimen has the best cost-effectiveness ratio. Furthermore, all previous cost-effectiveness analysis were performed in patients fulfilling 1987 classification criteria for RA.[11] Until now no data on cost-effectiveness in patients fulfilling 2010 criteria for RA are available.[1] Trials in the early phase of RA, like our tREACH trial, are needed to evaluate if aforementioned approach is also cost-effective in very early RA.

Therefore, our aim is to investigate (1) which initial treatment strategy has the lowest costs per Quality Adjusted Life Years (QALYs), with the emphasis on the comparison between iTDT and iMM and both glucocorticoid (GC) bridging therapies, and (2) whether the initial treatment regimens of the tREACH trial are cost-effective.

## PATIENTS AND METHODS

### Patients

For this study data were used of the tREACH trial (ISRCTN26791028). tREACH, a multicenter, stratified single-blinded trial, is performed in eight rheumatology centres in the Netherlands. Medical ethics committees at each participating centre approved the study protocol, and all patients gave written informed consent before inclusion.

An extended description of the tREACH had already been published.[6] Inclusion criteria for tREACH are: Age ≥18 years, arthritis in ≥1 joint, and symptom duration <1 year. Exclusion criteria are given in online supplement 1, table 1.

Eligible patients were stratified into three groups according to their likelihood of progressing to persistent arthritis based of the Visser prediction model.[12] The three strata (low, intermediate, and high) correspond with probability tertiles of developing persistent arthritis. For this analysis we included the high probability stratum.

**Design**

Patients were randomised, by an independent call centre, into one of following initial treatment strategies:

A. iTDT (MTX, sulfasalazine, and hydroxychloroquine) with GCs intramuscular
B. iTDT with an oral GC tapering scheme
C. iMM with oral GCs similar to B

Concurrent therapy with NSAIDs, and intra-articular GCs injections (maximum of two per three months) was allowed during the study.

DMARD dosages were: MTX 25 mg/week orally (dosage reached after three weeks), sulfasalazine 2 grams/day and hydroxychloroquine 400 mg/day, reduced to 200mg/day after 3 months. GCs were either given intramuscular (methylprednisolone 120mg or triamcinolone 80mg) or in an oral tapering scheme (weeks 1-4: 15 mg/day, weeks 5-6: 10 mg/day, weeks 7-8: 5 mg/day, and weeks 9-10: 2.5 mg/day). All patients received folic acid (10 mg/week) during MTX prescription. Osteoporosis prophylaxis (risedronate 35 mg/week and calcium/vitamin D combination 500/400 mg/IU/day) is given to patients in treatment arms B and C, during first 3 months.

Trained research nurses, blinded for allocated treatment arm throughout the study, examined patients and calculated the disease activity score (DAS). [13] A treat-to-target approach was used, aiming for a DAS<2.4.[13] If DAS≥2.4 medication is intensified. Intensification steps were subsequent (1) MTX + etanercept (50mg/week, subcutaneous) (2) MTX + adalimunab (40mg/ 2 weeks, subcutaneous), and (3) MTX + abatacept (500 – 1000 mg/ 4 weeks, intravenous, depending on weight). Treatment intensifications were the same for each treatment arm.

If DAS<1.6 at two consecutive visits medication was tapered. Hierarchically ordered tapering steps are: (1) biological, (2) sulfasalazine, (3) MTX, and (4) hydroxychloroquine. Biological(s), MTX and sulfasalazine were gradually discontinued, whereas hydroxychloroquine was stopped immediately. A flare during tapering, defined as DAS≥2.4, results in restarting full therapy, according to the protocol.

**Quality Adjusted Life Years (QALYs)**

QALYs express the influence of disease burden on patient's health over time. Living in perfect health for 1 year corresponds with a QALY of 1, on the other hand a QALY of 0 reflects death. [14] Patient's health was described with following questionnaires: (1) the EuroQol (EQ-5D) and (2) Short Form 36. [15-16] From these questionnaires we respectively derived the Dutch EQ-5D and Short Form 6D (SF-6D). [17-19] The EQ-5D and SF-6D were assessed every 3 months and QALYs were calculated as the area under the curve (AUC). Costs per QALY are calculated, because since 2005 coverage of prescribed drugs by Dutch health insurance companies depend on this outcome. [20] In the Netherlands a treatment (approach) with an overall expenditure ≤€ 20.000 per QALY is considered to be cost-effective.[20]

**Direct and indirect costs**

We analyzed direct and indirect costs during the first year of follow-up from a societal perspective. Direct costs are the costs of treatment and medical consumption, whereas indirect costs are costs due to loss of productivity (i.e. sick leave and unemployment). [21]

Costs of (study) medication were calculated from the dose reported in the patients' case records, valued according to the college of health insurances (see online supplement 2, table 1). [22] Reported medication costs also included costs for start-up dosages, used supplements and if necessary day-care admissions. Medication costs were calculated using following assumptions: (1) compliance was 100%, (2) treatment changes commenced immediately and (3) if patients were lost to follow-up (study) medication was stopped.

Medical consumption was recorded every 6 months by questionnaires. Duration of hospitalisations and admission diagnosis were recorded every 3 months. We used the Dutch average length of stay by diagnosis if the duration of hospitalisation was unknown. Medical consumption, including hospital admissions, was valued at Dutch standard prices, except for costs of complementary and alternative medicine, which were based upon American data (see online supplement 2, table 2). [23-24]

Indirect costs included sick leave and reduction in work time. Patients filled out questionnaires, every 3 months, about loss of productivity. Complementary to this, half-yearly questionnaires regarding work time and unemployment were filled out. The friction cost method was used to calculate the indirect costs. [25] The basic assumption of this method is that every employee is replaceable in time. The friction cost period is the time between occurrence of a job vacancy, due to long-term sick leave, and filling it. Costs due to loss of productivity are solely counted during this period, which encompasses 23 weeks (160 days) in the Netherlands. [23] Productivity costs were valued at age- and sex-dependent standard hourly costs, ranging from €9 to €39 per hour (see online supplement 2, table 3). [23] Indirect costs were calculated using following assumption: work time at baseline and after 6 months were respectively used for the calculation of the friction costs during the first and second half year.

### Statistical Analysis

Outcomes were calculated in an intention-to-treat analysis, using all available data. Statistical comparison of the baseline characteristics and outcomes (after 12 months) between iTDT and iMM (arm B versus C) and both GC bridging therapies (arm A versus B) were made by student t test, $\chi^2$ test, or Wilcoxon rank-sum test, when appropriate.

Besides a drop-out ratio of 12%, respectively 9%, 4% and 4% of the patients incompletely or didn't filled out the QALY, medical consumption and/or loss of productivity questionnaires. These missing data were equally distributed between treatment arms. Because total missing data exceeded 5% we used multiple imputations by chained equations, with 40 imputations, to deal with aforementioned missing data to overcome possible bias.[26] An imputation regression model was constructed with EQ-5D, SF-6D, medical consumption or loss of productivity as dependent variables and age, gender, treatment arm, and corresponding measures at all other time-points as the independent variables.

In addition to the comparison of average costs per QALY between treatment arms, we also calculated the incremental cost-effectiveness ratios (ICERs) and its corresponding 95% confidence intervals with the Fieller method.[27] An ICER is the ratio of the difference in costs to incremental benefits between treatment arms.

All analyses were performed for patients in the high probability stratum and two subgroups consisting of patients with RA according to 1987 and 2010 criteria. [1, 11] All statistical analyses were carried out using STATA version 12.0. A p value $<0.05$ was considered statistically significant.

## RESULTS

### Patients

In the high probability stratum 281 patients were randomly assigned to treatment arm A (n=91), B (n=93), or C (n=97). Of the 281 randomized tREACH patients 33 (12%) dropped-out within the first year of follow-up (see online supplement 1, figure 1). Patients were mostly females (68%) with an average symptom duration of 166 days (156-177 days, 95% confidence interval) (table 1). RF and/or ACPA positivity was present in 239 (85%) patients; of those, 176 (74%) were both RF and ACPA positive. At baseline, 48 (17%) patients had ≥1 erosion typical for RA. The employment-population ratio is 163/221 (74%).

**Table 1: Baseline characteristics of patients with a high probability to develop a persistent arthritis, stratified for induction therapy.**

| | A. MTX + SASP + HCQ + im GCs (n=91) | B. MTX + SASP + HCQ + oral GCs (n=93) | C. MTX + oral GCs (n=97) |
|---|---|---|---|
| **Demographic** | | | |
| Age (yrs), *mean (sd)* | 53 (15) | 54 (14) | 54 (14) |
| Sex, female, *no(%)* | 55 (60) | 67 (72) | 68 (72) |
| Paid work, *no(%)* | 53 (78) | 53 (71) | 57 (73) |
| Working hours per week, *median(IQR)** | 36 (21 – 40) | 24 (16 – 40) | 32 (24 – 40) |
| Retired, *no(%)* | 23 (25) | 18 (19) | 19 (20) |
| **Disease characteristics** | | | |
| Symptom duration (days), *mean (sd)*† | 162 (97) | 184 (92) | 154 (83) |
| RF pos., *no(%)* | 55 (60) | 51 (55) | 51 (53) |
| ACPA pos., *no(%)* | 59 (65) | 50 (54) | 56 (58) |
| Fullfillment RA criteria, *no(%)* | | | |
| *1987*‡ | 69 (76) | 57 (61) | 63 (65) |
| *2010* | 83 (91) | 80 (86) | 83 (86) |
| DAS, *mean (sd)* | 3.28 (1.06) | 3.40 (1.07) | 3.38 (0.97) |
| SJC44, *median (IQR)* | 8 (5 -12) | 7 (4 - 12) | 7 (4 - 12) |
| Erosion, *no(%)*§ | 24 (26) | 12 (13) | 12 (12) |
| **Questionnaires**[1] | | | |
| EQ-5D, *mean (sd)* | 0.60 (0.25) (n=86) | 0.65 (0.22) (n=84) | 0.61 (0.28) (n=88) |
| SF-6D, *mean (sd)* | 0.69 (0.13) (n=84) | 0.69 (0.14) (n=88) | 0.68 (0.15) (n=92) |
| HAQ, *mean (sd)* | 0.98 (0.67) (n=84) | 0.96 (0.64) (n=84) | 1.06 (0.68) (n=92) |

[1]Not everyone filled in a (complete) questionnaire and therefore n is different for HAQ and RADAI.

*p=0.027 for A vs. B ‡p=0.034 for A vs B.

†p=0.018 for B vs C. §p=0.021 for A vs B.

Abbreviations: ACPA, anti-citrullinated protein/peptide antibodies; DAS, Disease Activity Score; EQ-5D, Dutch EuroQol; GCs, glucocorticoids; HAQ,Health Assessment Questionnaire; HCQ, hydroxychloroquine; im, intramuscular; IQR, interquartile range; MTX, methotrexate; RF, rheumatoid factor; SASP,sulfasalazine; sd, standard deviation; SF-6D, Short Form 6 Dimensions; SJC44, swollen joint count (44 joints).

## Clinical outcomes and QALYs

Figure 1 shows the disease activity, functional ability and QALYs over time. Utilities, measured with EQ-5D and SF-6D did not differ at baseline (table 1) and over time (figure 1) between treatment arms. Both utility measures showed a similar pattern with the strongest improvement during the first 6 months. Average QALYs, measured with AUC, for treatment arm A, B and C were respectively 0.75, 0.75 and 0.73 for EQ-5D; and 0.77, 0.76 and 0.75 for SF-6D.

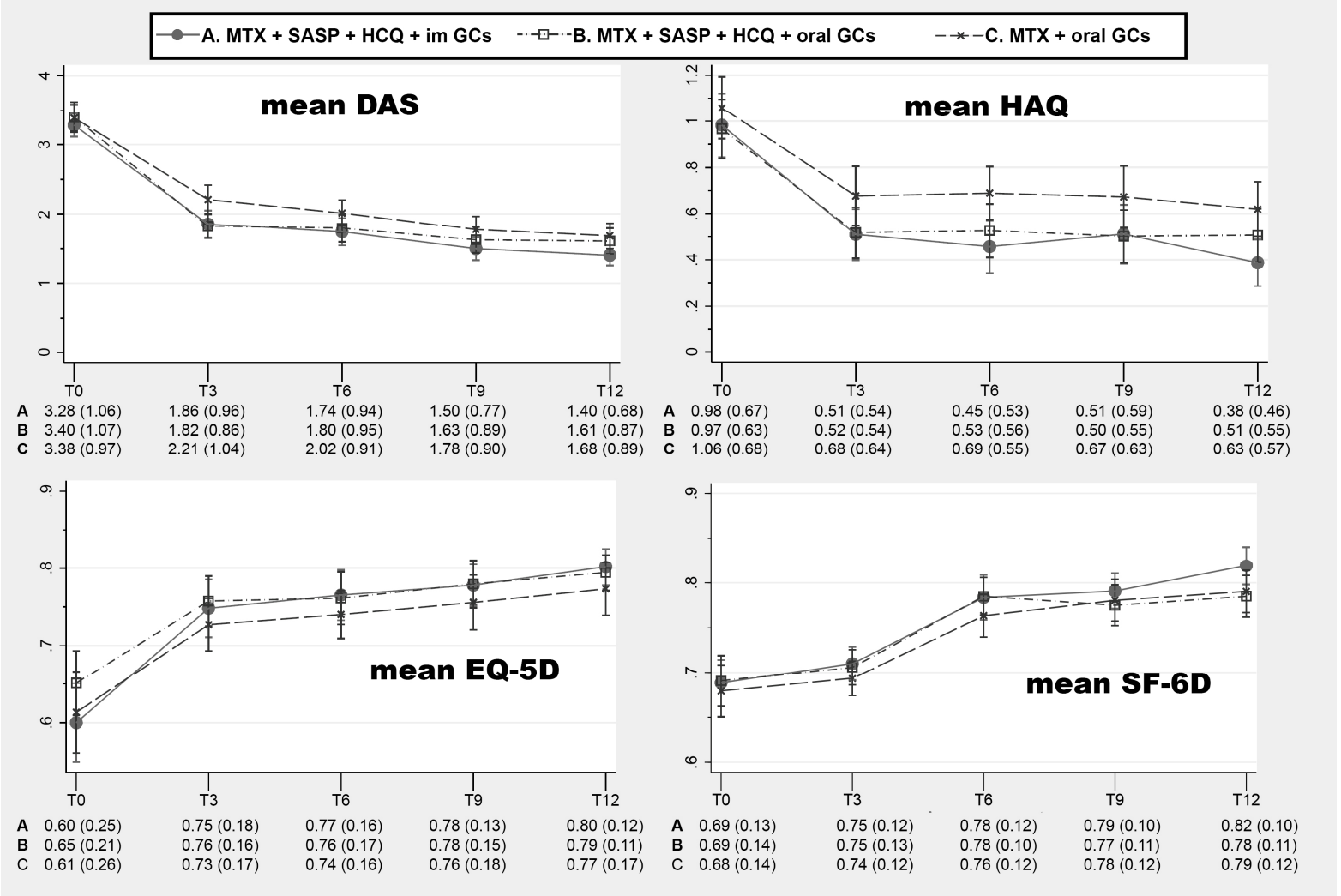


**Figure 1: Disease activity, functional ability and QALYs over time.**

Error bars indicate 95% confidence intervals. Abbreviations: DAS, Disease Activity Score; EQ-5D, Dutch EuroQol; GCs, glucocorticoids; HAQ,Health Assessment Questionnaire; HCQ, hydroxychloroquine; im, intramuscular; MTX, methotrexate; QALYs, Quality Adjusted Life Years; SASP,sulfasalazine; SF-6D, Short Form 6 Dimensions

**Direct and indirect costs**

Average direct costs (standard deviation) were respectively €3246 (4377), €3396 (4414) and €4919 (4996) for treatment arm A, B and C (p=0.027 for B versus C). Respectively 75% and 25% of the average direct costs are medication and health care utilization costs. The difference in average direct costs between iTDT (arm B) and iMM (arm C) was due to difference in the usage of expensive drugs, because no differences were found in medical consumption (table 2). After 3 months less treatment failure occurred in the iTDT group, resulting in the prescription of ~40% fewer biologicals. This difference remained over time (figure 2). Direct costs did not differ between both GC bridging therapies (arm A versus B).

Average indirect costs (standard deviation) were respectively €8913 (10593), €6207 (8130) and €10523 (10774) for treatment arm A, B and C (p=0.020 for B versus C). The sustained worker productivity in the iTDT group (arm B) caused the difference in indirect costs compared with the iMM group (arm C). After 12 months a small decrease in unemployment was seen in both iTDT groups compared to an increase in unemployment in the iMM group (table 3). Furthermore, less long term sickness, defined as sick leave >160 days, was seen with iTDT (table 3). Indirect costs did not differ between both GC bridging therapies (arm A versus B).

Total costs per QALY are given in table 4. Patients with iTDT (arm B) have lower costs per QALY compared with iMM (arm C). Total costs did not differ between both GC bridging therapies (arm A versus B). Medication, health care utilization and loss of productivity respectively determined 28-38%, 9-12% and 50-62% of the total costs.

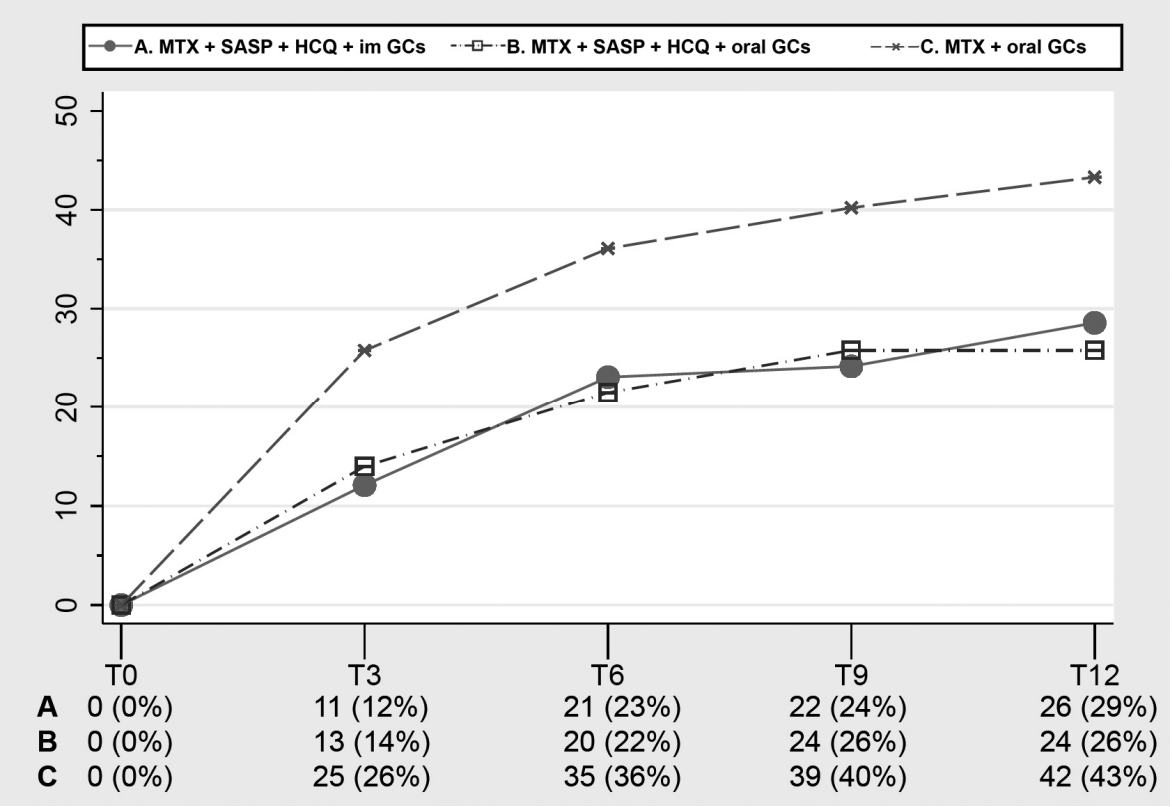


**Figure 2: Biological usage over time, stratified for induction therapy.**

## Table 2: Health care utilization and costs after 1 year of follow-up

| | A. MTX + SASP + HCQ + im GCs (n=91) | | | B. MTX + SASP + HCQ + oral GCs (n=93) | | | C. MTX + oral GCs (n=97) | | |
|---|---|---|---|---|---|---|---|---|---|
| | ***Utilization*** | ***Quantity[1]*** | ***Costs[2]*** | ***Utilization*** | ***Quantity[1]*** | ***Costs[2]*** | ***Utilization*** | ***Quantity[1]*** | ***Costs[2]*** |
| **Medication** | | | | | | | | | |
| • DMARDs | 91 (100) | - | € 195 (122) | 93 (100) | - | € 267 (234)* | 97 (100) | - | € 108 (161) |
| • Glucocorticoids | 89 (98) | - | € 7 (3) | 92 (99) | - | € 5 (2)§ | 97 (100) | - | € 7 (6) |
| • Biological | 23 (25) | - | € 2201 (4168) | 26 (28) | - | € 2221 (4110)† | 41 (42)‡ | - | € 3609 (4660) |
| • Analgesia | 26 (29) | - | € 15 (29) | 23 (25) | - | € 24 (63) | 29 (30) | - | € 15 (27) |
| • Other | 91 (100) | - | € 4 (5) | 92 (99) | - | € 16 (3)** | 97 (100) | - | € 18 (8) |
| **Medical consumption** | | | | | | | | | |
| Hospitalisation | 4 (4) | 4.5 (8) | € 86 (516) | 6 (6) | 2.5 (8 ) | € 122 (539) | 8 (8) | 4 (33) | € 298 (1974) |
| Standard health care | | | | | | | | | |
| • Primary care physician | 34 (38) | 3 (11) | € 40 (70) | 38 (41) | 2.5 (12) | € 41 (74) | 38 (39) | 3 (12) | € 44 (77) |
| • Specialist | 91 (100) | 7 (14) | € 514 (266) | 93 (100) | 7 (13) | € 536 (248) | 97 (100) | 8 (20) | € 566 (271) |
| • Nurse practitioner/physician assistant | 62 (68) | 3 (9) | € 68 (66) | 65 (70) | 3 (28) | € 73 (117) | 66 (68) | 3 ( 64) | € 75 (199) |
| • Paramedical care | | | | | | | | | |
| o Physical therapy | 24 (26) | 9 (35) | € 110 (264) | 20 (22) | 8 (48) | € 91 (262) | 21 (22) | 11 (90) | € 161 (472) |
| o Podology | 3 (3) | 3 (3) | € 5 (30) | 1 (1) | 1 (1) | € 1 (6) | 1 (1) | 4 (4) | € 2 (23) |
| o Occupational therapy | 0 (0) | - | € 0 (0) | 0 (0) | - | € 0 (0) | 2 (2) | 4.5 (5) | € 2 (14) |
| Complementary medicine | | | | | | | | | |
| • Alternative medical systems | 1 (1) | 2 (2) | € 1 (7) | 1 (1) | 1 (1) | € 0 (3) | 2 (2) | 4 (5) | € 3 (18) |

Results shown are respectively number (%) for utilization, median (maximum) for quantity and mean (standard deviation) for costs.

[1]Quantity reflects respectively the median(maximum) length of stay (in days) of the patients who are hospitalized and number of visits/sessions of the patients who utilize standard health care and/or complementary medicine.

[2]Reporterd costs are the average costs for all patients in corresponding treatment arm

*p=0,01 and p<0.0001 for respectively A vs. B and B vs. C. §p=0.002 and p=0.009 for respectively A vs. B and B vs. C.

†p=0.031 for B vs. C. ‡p=0.039 for B vs. C.

**p<0,0001 and p<0.002 for respectively A vs. B and B vs. C.

Abbreviations: GCs, glucocorticoids; HCQ, hydroxychloroquine; im, intramuscular; MTX, methotrexate and SASP,sulfasalazine.

## Table 3: Loss of productivity and costs, stratified for induction therapy.

| | A. MTX + SASP + HCQ + im GCs (n=91) | B. MTX + SASP + HCQ + oral GCs (n=93) | C. MTX + oral GCs (n=97) |
|---|---|---|---|
| **Employment after 12 months** | | | |
| Paid work | 54 (79) | 57 (76) | 51 (65) |
| Unemployment* | -1 (-2) | -4 (-8) | +6 (+11) |
| Working hours per week, *median(IQR)* | 32 (4 – 40) | 24 (12 – 40) | 25 (4 – 36) |
| **Loss of productivity** | | | |
| Sick leave | | | |
| • Occurrence | 47 (89) | 43 (81) | 46 (81) |
| • Long term sickness[1]† | 10 (19) | 5 (9) | 17 (30) |
| • Days absent, *median(IQR)* | 3 (1 – 8) | 5 (2 – 11) | 4 (1 – 8) |
| Contract hours | | | |
| • Reduction | | | |
| o Occurrence | 17 (32) | 20 (38) | 22 (39) |
| o Decrease, *median(IQR)*‡ | 18 (4 – 37) | 5 (1 – 11) | 29 (10 – 36) |
| • Increase | | | |
| o Occurrence | 8 (15) | 7 (13) | 9 (16) |
| o Increase, *median(IQR)* | 8 (4 – 11) | 10 (2 – 17) | 10 (4 – 20) |
| Total productivity loss in days, *median(IQR)* | 17 (3 – 100) | 14 (4 - 51) | 28 (4 - 179) |
| **Indirect costs, *mean(sd)*§** | € 8913 (10593) | € 6207 (8130) | € 10523 (10774) |

Results shown are number (%) unless stated otherwise.

[1]Long term sickness is defined as absence from work longer than 160 days (Dutch friction period)

*p=0.015 for B vs. C. ‡p=0.0007 for B vs. C. †p=0.0076 for B vs. C. §p=0.020 for B vs. C.

## Table 4: QALYs and (specified) average cost per QALY after 1 year of follow-up

| | A. MTX + SASP + HCQ + im GCs (n=91) | B. MTX + SASP + HCQ + oral GCs (n=93) | C. MTX + oral GCs (n=97) |
|---|---|---|---|
| **QALYs (AUC)** | | | |
| EQ-5D | 0.75 (0.12) | 0.75 (0.10) | 0.73 (0.13) |
| SF-6D | 0.77 (0.08) | 0.76 (0.09) | 0.75 (0.10) |
| **Costs per QALY using EQ-5D** | | | |
| Total direct costs* | € 4855 (7245) | € 5105 (7154) | € 7991 (10350) |
| • *Medication* | € 3686 (6774) | € 3876 (6496) | € 6177 (9650) |
| • *Medical consumption* | € 1025 (693) | € 1014 (625) | € 1302 (1265) |
| • *Hospitalization* | € 144 (884) | € 215 (1002) | € 512 (3446) |
| Total indirect costs‡ | € 7893 (15371) | € 5276 (11624) | € 9416 (15140) |
| Total costs§ | € 12748 (18767) | € 10380 (15608) | € 17408 (21828) |
| **Costs per QALY using SF-6D** | | | |
| Total direct costs* | € 4409 (6102) | € 4809 (6465) | € 6983 (7478) |
| • *Medication* | € 3309 (5748) | € 3632 (5953) | € 5373 (7018) |
| • *Medical consumption* | € 970 (625) | € 997 (621) | € 1208 (1090) |
| • *Hospitalization* | € 131 (792) | € 180 (812) | € 401 (2541) |
| Total indirect costs‡ | € 7250 (13230) | € 4847 (9682) | € 8807 (14022) |
| Total costs§ | € 11659 (15366) | € 9656 (12695) | € 15790 (17870) |

Results shown are mean(sd).

***EQ-5D:*** *p=0.027 for B vs C. ‡p=0.036 for B vs C. §p=0.012 for B vs C.

***SF-6D:*** *p=0.034 for B vs C. ‡p=0.025 for B vs C. §p=0.007 for B vs C.

Abbreviations: AUC, area under the curve; EQ-5D, Dutch EuroQol; GCs, glucocorticoids; HCQ, hydroxychloroquine; im, intramuscular; MTX, methotrexate; QALYs, Quality Adjusted Life Years; SASP,sulfasalazine; sd, standard deviation; SF-6D, Short Form 6 Dimensions.

The ICERs (95% confidence interval) between iTDT and iMM (arm B vs. C), using both EQ-5D and SF-6D, are respectively -€157232 (-€310061 to -€4404) and -€587547 (-€1740584 to €565491). Between both GC bridging therapies (arm A vs. B) the ICERs are -€188280 (-€771164 to €394604) and €152304 (-€235583 to €540190) making respectively use of the EQ-5D and SF-6D.

All above-mentioned analyses, in the results section, were also performed in both subgroups, namely RA according to 1987 and 2010 criteria, which produced similar results (see online supplement 3 and 4).

## DISCUSSION

In this study, we showed that iTDT had lower costs per QALY compared with iMM. Direct as well as indirect costs were lower in the iTDT group compared with the iMM group. The difference in direct costs was due to ~40% more biological usage over time in the iMM group. Less unemployment, long-term sickness and reduction in contract hours on the other hand caused the difference in indirect costs, favouring iTDT. Besides lower costs, patients with iTDT had better worker productivity. No differences in direct, indirect and total costs between both GC bridging therapies were seen. Noticeable is the fact that the total costs of all treatment arms are less than €20.000 per QALY, which is the limit for cost-effectiveness, according to Dutch policy makers.

This study was designed to compare initial intensive treatment strategies in early RA. At the time of writing the protocol the 2010 criteria for RA still had to be developed. Therefore, we based our design on the Visser model, which predicts the likelihood of progressing to persistent arthritis.[12] Interestingly, the Visser algorithm and 2010 criteria for RA have similar discriminative ability to identify patients at risk of persistent arthritis at 1 year.[28] The tREACH trial is, therefore, one of the first studies conducted in RA patients fulfilling 2010 criteria.

Because treatment is initiated in a very early phase of the disease the influence of disease burden on patient's health over time, expressed by QALYs, is less in comparison with previous trials (0.75 vs. 0.69, first year QALYs, measured with EQ-5D, of respectively the tREACH trial, arm B and BeSt trial, group 3). [10, 29-30] An explanation for this difference might be that, first, due to diagnosing RA in an earlier phase patients have less severe disease characteristics without irreversible joint destruction. For example, our baseline DAS was lower compared with the BeSt trial (3.4 vs. 4.5) and less erosive disease was seen (respectively 15% vs. 70%). [6, 31] Second, the intensive treatment strategy contributed to aforementioned difference, which is reflected by the higher proportion of patients reaching the predefined treatment goal (i.e. low disease activity 82% in tREACH, arm B versus 65% in BeSt, group 3 after 1 year). Important differences in iTDT between tREACH and BeSt were MTX dosage (respectively 25 versus 7.5 mg/week), and addition of hydroxychloroquine. This underlines the importance of initiating intensive DMARD therapy in an earlier phase of RA.

Less burden of the disease not only led to higher QALYs over time, but also less health care utilisation and loss of productivity, leading to lower costs, in comparison with previous cost-effectiveness analyses. [10, 29-30] Within our trial the difference in disease burden between iTDT and iMM also led to difference in medication usage and worker productivity. Especially, the difference in worker productivity is remarkable. This difference was caused by a higher job retainment rate with iTDT, which reinforces the importance of choosing the right initial treatment strategy.

Our study had certain limitations. Foremost, baseline imbalances occurred, despite randomisation, which were in favour of iMM, because of less severe disease characteristics. Thus, differences in cost per QALY between treatment arms may even be higher if the groups were more homogeneous.

Furthermore, the time-frame in our cost-utility analysis was the 1st year of follow-up. During this 1st year, however, not all patients had attained or maintained the predefined treatment goals. Additionally, medication is tapered in patients with sustained remission. Hence, medication usage and indirectly medical consumption were still fluctuating, which might influence the longterm results of economic evaluations. However, the longterm economic conclusions will, in our case, possibly favour iTDT, because of better maintenance of predefined treatment goals and more frequent tapering of medication.

Also, a recall bias could not be ruled out, because patients with a more active disease might have recollect the amount of sick leave better. Since patients with iTDT have less disease burden compared with iMM, they possibly underreport the amount of sick leave, which might have led to an underestimation of the indirect costs. On the other hand, we did not include reduced productivity due to the act of attending work while sick (presenteeism) in our indirect cost analysis. Indirect costs would be higher if presenteeism was taken into account, whereby the raise in indirect cost would probably be less in patients with iTDT compared with iMM, because of less burden of the disease.

At last, generalizability of these data could be cumbersome, because of differences in legislation and regulations between countries. In the Netherlands discharging employees is relatively difficult due to legislation. Therefore, the Dutch labor market is characterized by low job mobility and high average duration of unemployment for older jobseekers.[32] On the other hand working part-time is more common in the Netherlands in comparison with other countries. [33] This reduces the workload allowing people to retain their work productivity longer. Likewise, accessibility, affordability, efficiency and quality of health care differs between countries. [34] Despite aforementioned differences between countries, the fact that iTDT had lower cost per QALY than iMM is generalizable.

In conclusion, iTDT had lower costs per QALY compared with iMM. Costs did not differ between both GC bridging therapies. Interestingly, all initial treatment regimens of the tREACH trial are cost-effective, according to the definition of Dutch policy makers. Besides lower costs, patients treated with iTDT also had better worker productivity compared with iMM. In line with the clinical effectiveness, aforementioned results underline again why iTDT instead of iMM, is preferred as first choice in very early RA.

## Supplement 1: Study design and flow tREACH

### Table 1: Exclusion criteria tREACH trial

Exclusion criteria are:

1. Following diagnoses:
    - a crystal arthropathy
    - (post-)infectious arthritis
    - autoimmune disorder other than RA;
2. Receiving DMARD therapy or glucocorticoids prior to randomisation
3. Presence of contra-indications for initial study medication, namely:
    - chronic liver disease
    - excessive alcohol and drug use
    - pregnancy (wish)
    - leucopenia $< 3.0 \times 10^9$/l
    - thrombocytopenia $< 150 \times 10^9$/l
    - aspartate aminotransferase/ alanine aminotransferase more than two times the upper normal value
    - creatinine level > 150 µmol/l.

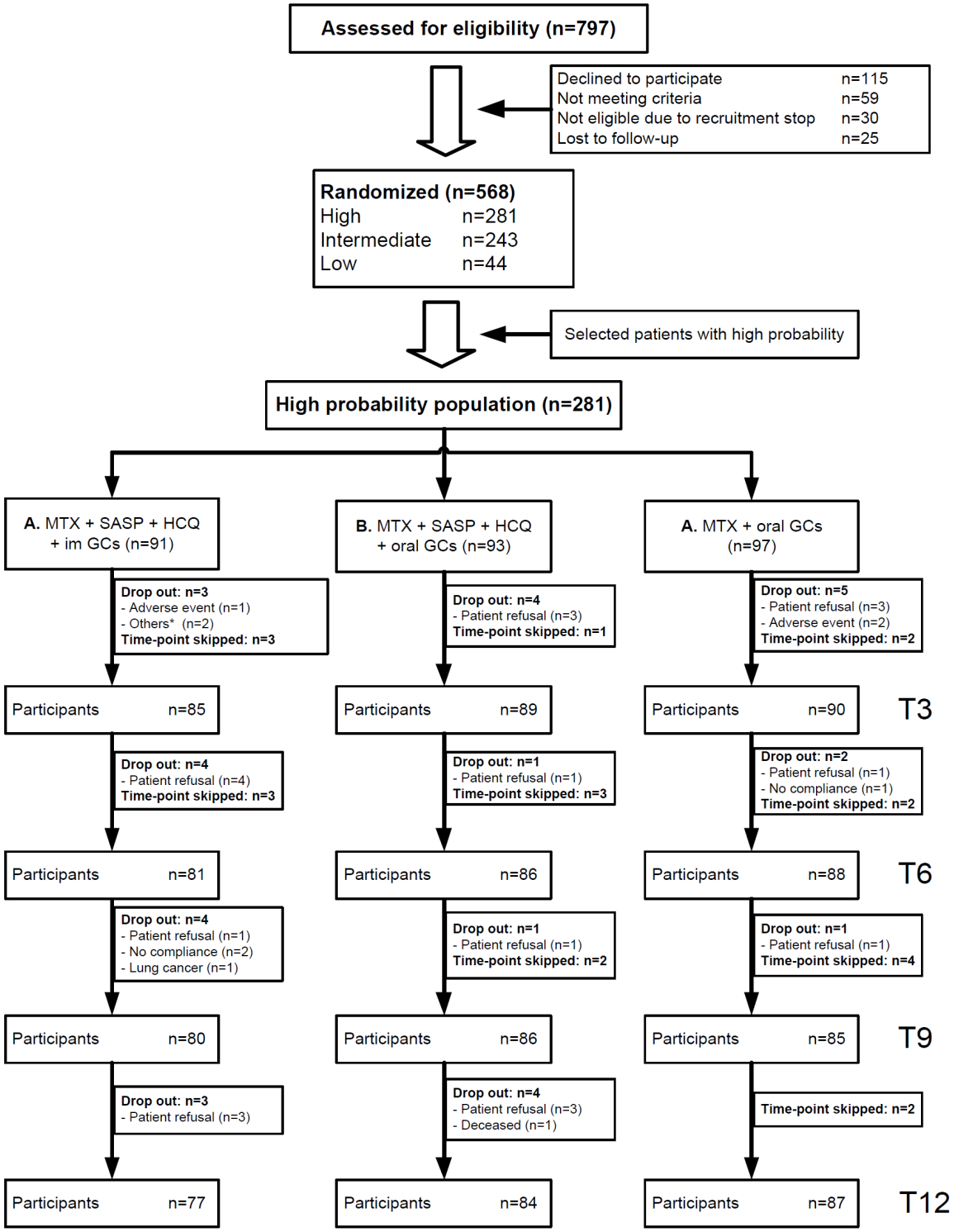


**Figure 1: Trial profile.**

Other reasons for dropping out were incorrect randomisation and problems with communication. Abbreviations: GCs, glucocorticoids; HCQ, hydroxychloroquine; im, intramuscular; MTX, methotrexate; SASP, sulfasalazine.

# Supplement 2: Reference prices for cost-utility analyses tREACH

## Table 1: Medication costs in the Netherlands.

| Generic name | Calculation base | Costs |
|---|---|---|
| **DMARDs** | | |
| Methotrexate | | |
| • Oral | 2.5mg tablet | € 0.13 |
| • Subcutaneous | | |
| o 2.5 tot 10mg | per piece | € 16.30 |
| o 12.5 tot 20 mg | per piece | € 17.78 |
| o 22.5 tot 25mg | per piece | € 20.74 |
| Sulphasalazine (oral) | 500mg tablet | € 0.07 |
| Hydroxychloroquine (oral) | 200mg tablet | € 0.13 |
| Leflunomide (oral) | | |
| • 20mg tablet | per piece | € 1.32 |
| • 10mg tablet | per piece | € 1.16 |
| **Glucocorticoids** | | |
| Prednisone (oral) | | |
| • Oral | 5mg tablet | € 0.05 |
| • Total tapering scheme | | € 4.94 |
| Triamcinolone (i.m.) | 80mg | € 10.88** |
| Methylprednisolone (i.m.) | 120mg | € 6.12** |
| **Biologicals** | | |
| Etanercept (s.c.) | | |
| • 25mg | per piece | € 138.03 |
| • 50mg | per piece | € 283.26 |
| Adalimunab (40mg s.c.) | per piece | € 571.91 |
| Infliximab (i.v.) | 100mg flask | € 646.77 |
| Abatacept (i.v.) | 250mg flask | € 382.44 |
| Rituximab (i.v.) | 500mg flask | € 1536.15 |
| **Analgesia** | | |
| Paracetamol | 500mg tablet | € 0.02 |
| NSAIDs (average) | per month | € 7.99 |
| COX-2 inhibitor (average) | per month | € 27.08 |
| **Other** | | |
| Folic acid (oral) | 5mg tablet | € 0.03 |
| Risedronate (oral) | 35mg tablet | € 0.16 |
| Calcium carbonate/colecalciferol (oral) | 500mg/400IE tablet | € 0.12 |
| Proton-pump inhibitors (average) | per month | € 23.45 |

* Total cost of prednisone's gradual discontinuation scheme.

** Costs for 1 intramuscular administration of methylprednisolone

**Table 2: Reference prices for direct costs within the standard and complementary healthcare sector.**

| | Reference price |
|---|---|
| **Standard healthcare** | |
| Inpatient day | |
| • General hospital (day) | € 435 |
| • University hospital (day) | € 575 |
| Intensive care unit (day) | € 2183 |
| Daycare treatment (day) | € 251 |
| Outpatient visit | |
| • Specialist | |
| o General hospital | € 64 |
| o University hospital | € 129 |
| • Nurse practitioner/physician assistent | € 30 |
| Emergency room visit | € 151 |
| Primary care physician | € 28 |
| Paramedical care | |
| • Physical therapy | € 36 |
| • Podology | € 56 |
| • Exercise therapy | € 35 |
| • Speech therapy | € 33 |
| • Occupational therapy (hour) | € 22 |
| • Dietary advice (hour) | € 27 |
| Mental healthcare | |
| • Social worker | € 65 |
| • Independent psychiatrist | € 103 |
| • Independent psychotherapist | € 77 |
| | |
| **Complementary medicine** | |
| Alternative medical systems | € 31 |
| • Acupuncture | € 37 |
| • Homeopathic treatment | € 25 |
| • Naturopathy | € 49 |
| • Traditional healers | € 15 |
| Manipulative and body-based therapies | € 23 |
| • Chiropractic or osteopathic manipulation | € 17 |
| • Massage | € 36 |
| • Movement therapies | € 4 |
| Energy-healing therapy | € 22 |

Results are shown as costs per session unless stated otherwise

**Table 3: Average productivity costs per hour, stratified for sex and age**

| Age (years) | Total | Men | Women |
|---|---|---|---|
| 15 to 19 | € 9.27 | € 9.65 | € 8.76 |
| 20 to 24 | € 17.51 | € 17.75 | € 17.18 |
| 25 to 29 | € 23.93 | € 24.19 | € 23.62 |
| 30 to 35 | € 28.80 | € 29.65 | € 27.54 |
| 35 to 40 | € 32.25 | € 34.03 | € 29.25 |
| 40 to 45 | € 33.92 | € 36.67 | € 29.06 |
| 45 to 50 | € 34.87 | € 38.32 | € 28.91 |
| 50 to 55 | € 35.61 | € 39.06 | € 29.25 |
| 55 to 60 | € 36.37 | € 39.38 | € 29.50 |
| 60 to 65 | € 36.41 | € 39.13 | € 28.67 |
| *Average* | *€ 30.02* | *€ 32.49* | *€ 25.94* |

# Supplement 3: Subgroup analyses for patients with RA according to 2010 ACR/EULAR criteria

## Table 1: Number of participants, with RA according to 2010 ACR/EULAR criteria, at each time-point, stratified for induction therapy

| | T0 | T3 | T6 | T9 | T12 |
|---|---|---|---|---|---|
| **A. MTX + SASP + HCQ + im GCs** | 87 | 82 | 78 | 77 | 74 |
| **B. MTX + SASP + HCQ + oral GCs** | 88 | 84 | 81 | 81 | 80 |
| **C. MTX + oral GCs** | 95 | 88 | 86 | 84 | 85 |

## Table 2: Baseline characteristics of patients with RA according to 2010 ACR/EULAR criteria, stratified for induction therapy.

| | A. MTX + SASP + HCQ + im GCs (n=87) | B. MTX + SASP + HCQ + oral GCs (n=88) | C. MTX + oral GCs (n=95) |
|---|---|---|---|
| **Demographic** | | | |
| Age (yrs), *mean (sd)* | 53 (15) | 54 (14) | 54 (14) |
| Sex, female, *no(%)* | 52 (60) | 63 (72) | 67 (71) |
| Paid work, *no(%)* | 50 (77) | 49 (70) | 55 (72) |
| Working hours / week, *median(IQR)** | 36 (20 – 40) | 24 (13 – 40) | 32 (20 – 40) |
| Retired, *no(%)* | 22 (25) | 18 (20) | 19 (20) |
| **Disease characteristics** | | | |
| Symptom duration (days), *mean (sd)*† | 160 (95) | 183 (93) | 151 (81) |
| RF pos., *no(%)* | 68 (78) | 64 (72) | 65 (68) |
| ACPA pos., *no(%)* | 72 (83) | 66 (75) | 75 (79) |
| DAS, *mean (sd)* | 3.34 (0.78) | 3.44 (1.08) | 3.40 (0.98) |
| SJC44, *median (IQR)* | 8 (5 - 12) | 8 (4 – 12) | 7 (4 – 12) |
| Erosion, *no(%)* | 24 (28) | 12 (14) | 12 (13) |
| **Questionnaires**[1] | | | |
| EQ-5D, *mean (sd)* | 0.59 (0.26) (n=82) | 0.64 (0.22) (n=81) | 0.61 (0.28) (n=86) |
| SF-6D, *mean (sd)* | 0.69 (0.13) (n=80) | 0.69 (0.14) (n=84) | 0.68 (0.15) (n=90) |
| HAQ, *mean (sd)* | 0.98 (0.69) (n=80) | 0.99 (0.63) (n=82) | 1.06 (0.68) (n=90) |

[1]Not everyone filled in a (complete) questionnaire and therefore n is different for HAQ and RADAI.

*p=0.044 for A vs. B.

†p=0.016 for B vs C.

‡p=0.023 for A vs B .

Abbreviations: ACPA, anti-citrullinated protein/peptide antibodies; DAS, Disease Activity Score; EQ-5D, Dutch EuroQol; GCs, glucocorticoids; HAQ,Health Assessment Questionnaire; HCQ, hydroxychloroquine; im, intramuscular; IQR, interquartile range; MTX, methotrexate; RF, rheumatoid factor; SASP,sulfasalazine; sd, standard deviation; SF-6D, Short Form 6 Dimensions; SJC44, swollen joint count (44 joints)

**Table 3: Health care utilization and costs in patients with RA according to 2010 criteria, stratified for induction therapy.**

| | A. MTX + SASP + HCQ + im GCs (n=87) | | | B. MTX + SASP + HCQ + oral GCs (n=88) | | | C. MTX + oral GCs (n=95) | | |
|---|---|---|---|---|---|---|---|---|---|
| | ***Utilization*** | ***Quantity[1]*** | ***Costs[2]*** | ***Utilization*** | ***Quantity[1]*** | ***Costs[2]*** | ***Utilization*** | ***Quantity[1]*** | ***Costs[2]*** |
| **Medication** | | | | | | | | | |
| • DMARDs | 87 (100) | - | € 197 (124) | 88 (100) | - | € 272 (240)* | 95 (100) | - | € 109 (162) |
| • Glucocorticoids | 85 (98) | - | € 7 (3) | 87 (99) | - | € 5 (2)† | 95 (100) | - | € 7 (6) |
| • Biological usage | 23 (26) | - | € 2303 (4236) | 25 (28) | - | € 2269 (4170) | 40 (42)§ | - | € 3540 (4575) |
| • Analgesia usage | 24 (28) | - | € 16 (30) | 22 (25) | - | € 25 (65) | 28 (29) | - | € 15 (28) |
| • Other | 87 (100) | - | € 4 (5) | 87 (99) | - | € 16 (3)‡ | 95 (100) | - | € 18 (8) |
| **Medical consumption** | | | | | | | | | |
| Hospitalisation | 4 (5) | 4.5 (8) | € 90 (527) | 5 (6) | 1 (8) | € 109 (525) | 8 (8) | 4 (33) | € 304 (1994) |
| Standard health care | | | | | | | | | |
| • Primary care physician | 31 (36) | 3 (11) | € 37 (68) | 36 (41) | 2 (12) | € 40 (74) | 38 (40) | 3 (12) | € 45 (78) |
| • Specialist | 87 (100) | 7 (14) | € 508 (266) | 88 (100) | 7 (13) | € 529 (248) | 95 (100) | 8 (20) | € 569 (273) |
| • Nurse practitioner/physician assistant | 60 (69) | 3 (9) | € 69 (67) | 61 (69) | 3 (28) | € 73 (120) | 65 (68) | 3 (64) | € 87 (201) |
| • Paramedical care | | | | | | | | | |
| o Physical therapy | 22 (25) | 9 (35) | € 104 (261) | 19 (22) | 8 (48) | € 96 (269) | 20 (21) | 14 (90) | € 160 (476) |
| o Podology | 3 (3) | 3 (3) | € 6 (31) | 1 (1) | 1 (1) | € 1 (6) | 1 (1) | 4 (4) | € 2 (23) |
| o Occupational therapy | 0 (0) | - | € 0 (0) | 0 (0) | - | € 0 (0) | 2 (2) | 4.5 (5) | € 2 (14) |
| Complementary medicine | | | | | | | | | |
| • Alternative medical systems | 1 (1) | 2 (2) | € 1 (7) | 1 (1) | 1 (1) | € 0 (3) | 2 (2) | 4 (5) | € 3 (18) |

Results shown are respectively number (%) for utilization, median (maximum) for quantity and mean (standard deviation) for costs.

[1]Quantity reflects respectively the median(maximum) length of stay (in days) of the patients who are hospitalized and number of visits/sessions of the patients who utilize standard health care and/or complementary medicine.

[2]Reporterd costs are the average costs for all patients in corresponding treatment arm

*p=0,01 and p<0.0001 for respectively A vs. B and B vs. C.

†p=0.003 and p=0.011 for respectively A vs. B and B vs. C.

‡p<0,0001; and p<0.002 for respectively A vs. B and B vs. C.

Abbreviations: GCs, glucocorticoids; HCQ, hydroxychloroquine; im, intramuscular; MTX, methotrexate and SASP,sulfasalazine.

**Table 4: Loss of productivity and costs in patients with RA according to 2010 ACR/EULAR criteria, stratified for induction therapy.**

| | A. MTX + SASP + HCQ + im GCs (n=87) | B. MTX + SASP + HCQ + oral GCs (n=88) | C. MTX + oral GCs (n=95) |
|---|---|---|---|
| **Employment after 12 months** | | | |
| Paid work | 51 (78) | 53 (76) | 49 (64) |
| Unemployment* | -1 (-2) | -4 (-8) | +6 (+11) |
| Working hours per week, *median(IQR)* | 30 (4 – 40) | 24 (10 – 40) | 25 (4 – 36) |
| **Loss of productivity** | | | |
| Sick leave | | | |
| • Occurrence | 44 (88) | 39 (80) | 44 (80) |
| • Long term sickness[1]† | 9 (18) | 5 (10) | 17 (31) |
| • Days absent, *median(IQR)* | 3 (1 – 8) | 4 (1 – 9) | 4 (1 – 9) |
| Contract hours | | | |
| • Reduction | | | |
| o Occurrence | 17 (34) | 20 (41) | 22 (40) |
| o Decrease, *median(IQR)*‡ | 18 (4 – 37) | 5 (1 – 11) | 29 (10 – 36) |
| • Increase | | | |
| o Occurrence | 8 (16) | 6 (12) | 8 (15) |
| o Increase, *median(IQR)* | 8 (4 – 11) | 7 (2 – 17) | 11 (3 – 24) |
| Total productivity loss in days, *median(IQR)* | 21 (3 – 100) | 14 (4 – 51) | 32 (3 – 182) |
| **Indirect costs*, mean(sd)*§** | € 8724 (10183) | € 6157 (8372) | € 10787 (10869) |

Results shown are number (%) unless stated otherwise.

[1]Long term sickness is defined as absence from work longer than 160 days (Dutch friction period)

*p=0.009 for B vs. C. †p=0.010 for B vs C. ‡p=0.0007 for B vs. C. §p=0.018 for B vs. C.

**Table 5: QALYs and (specified) average cost per QALY after 1 year of follow-up for patients with RA according to 2010 ACR/EULAR criteria.**

| | A. MTX + SASP + HCQ + im GCs (n=87) | B. MTX + SASP + HCQ + oral GCs (n=88) | C. MTX + oral GCs (n=95) |
|---|---|---|---|
| **QALYs (AUC)** | | | |
| EQ-5D | 0.75 (0.12) | 0.75 (0.11) | 0.73 (0.13) |
| SF-6D | 0.77 (0.08) | 0.76 (0.09) | 0.75 (0.10) |
| **Costs per QALY using EQ-5D** | | | |
| Total direct costs* | € 5001 (7377) | € 5176 (7236) | € 7821 (10148) |
| • *Medication* | € 3844 (6887) | € 3965 (6595) | € 5992 (9420) |
| • *Medical consumption* | € 1006 (689) | € 1014 (635) | € 1306 (1276) |
| • *Hospitalization* | € 151 (904) | € 197 (996) | € 523 (3481) |
| Total indirect costs† | € 7573 (14757) | € 5186 (11870) | € 9475 (15274) |
| Total costs‡ | € 12574 (18420) | € 10362 (15994) | € 17296 (21835) |
| **Costs per QALY using SF-6D** | | | |
| Total direct costs | € 4538 (6211) | € 4892 (6559) | € 6903 (7394) |
| • *Medication* | € 3450 (5841) | € 3729 (6055) | € 5278 (6914) |
| • *Medical consumption* | € 951 (622) | € 997 (631) | € 1216 (1099) |
| • *Hospitalization* | € 137 (810) | € 166 (807) | € 410 (2567) |
| Total indirect costs* | € 6987 (12704) | € 4708 (9819) | € 8896 (14148) |
| Total costs† | € 11526 (15019) | € 9599 (12982) | € 15799 (17952) |

Results shown are mean (standard deviation).

***EQ-5D*** *p=0.045 for B vs. C. †p=0.036 for B vs C ‡p=0.016 for B vs. C.

***SF-6D*** *p=0.022 for B vs. C. †p=0.009 for B vs. C.

**Table 6: ICERs between treatment arms for patients with RA according to 2010 ACR/EULAR criteria.**

| | EQ-5D | SF-6D |
|---|---|---|
| **ICERs between** | | |
| • iTDT and iMM (arm B and C) | -€ 192077 (101689) | -€ 851341 (1420466) |
| • Both GC bridging therapies (arm A and B) | -€ 243319 (442781) | € 123778 (155164) |

Results shown are mean (sd).

Abbreviations: EQ-5D, Dutch EuroQol; GCs, glucocorticoids; ICER, incremental cost-effectiveness ratio; iMM, initial Methotrexate monotherapy; iTDT, initial triple DMARD therapy; SF-6D, Short Form 6 Dimensions.

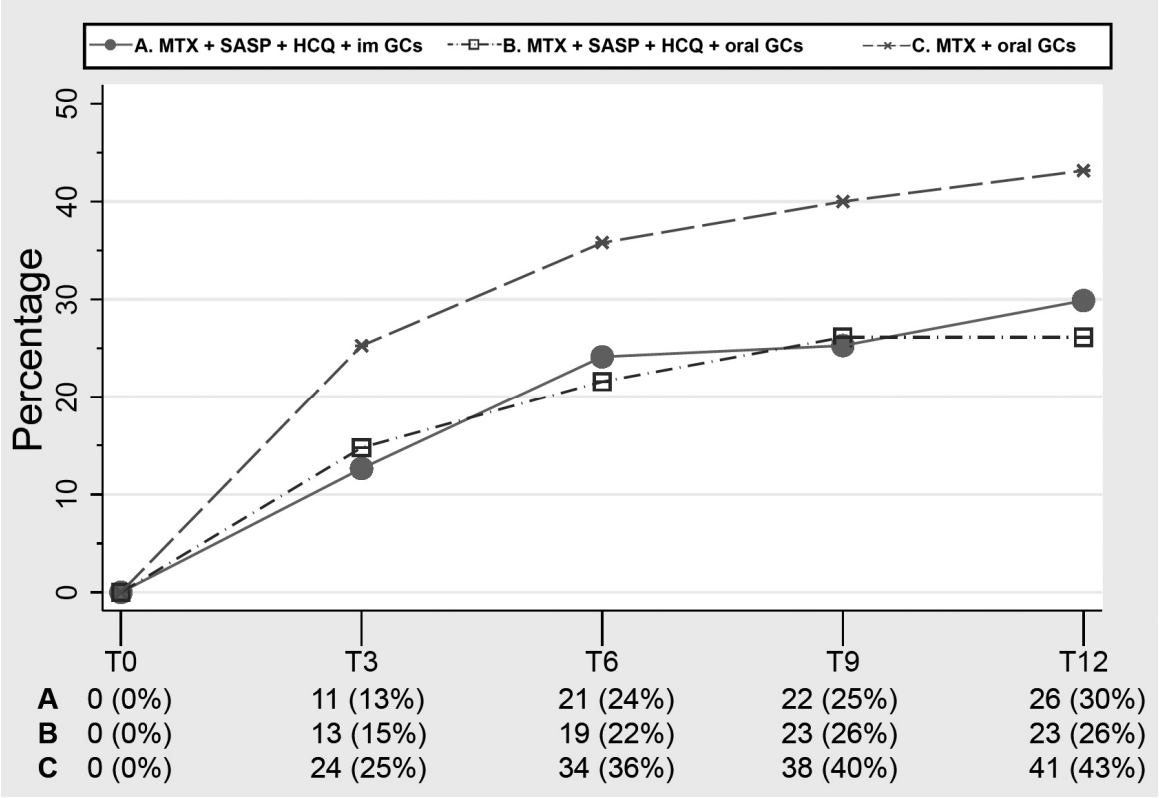


**Figure 1: Biological usage over time in patients with RA according to 2010 ACR/EULAR criteria, stratified for induction therapy.**

Abbreviations: GCs, glucocorticoids; HCQ, hydroxychloroquine; im, intramuscular; MTX, methotrexate; SASP, sulfasalazine.

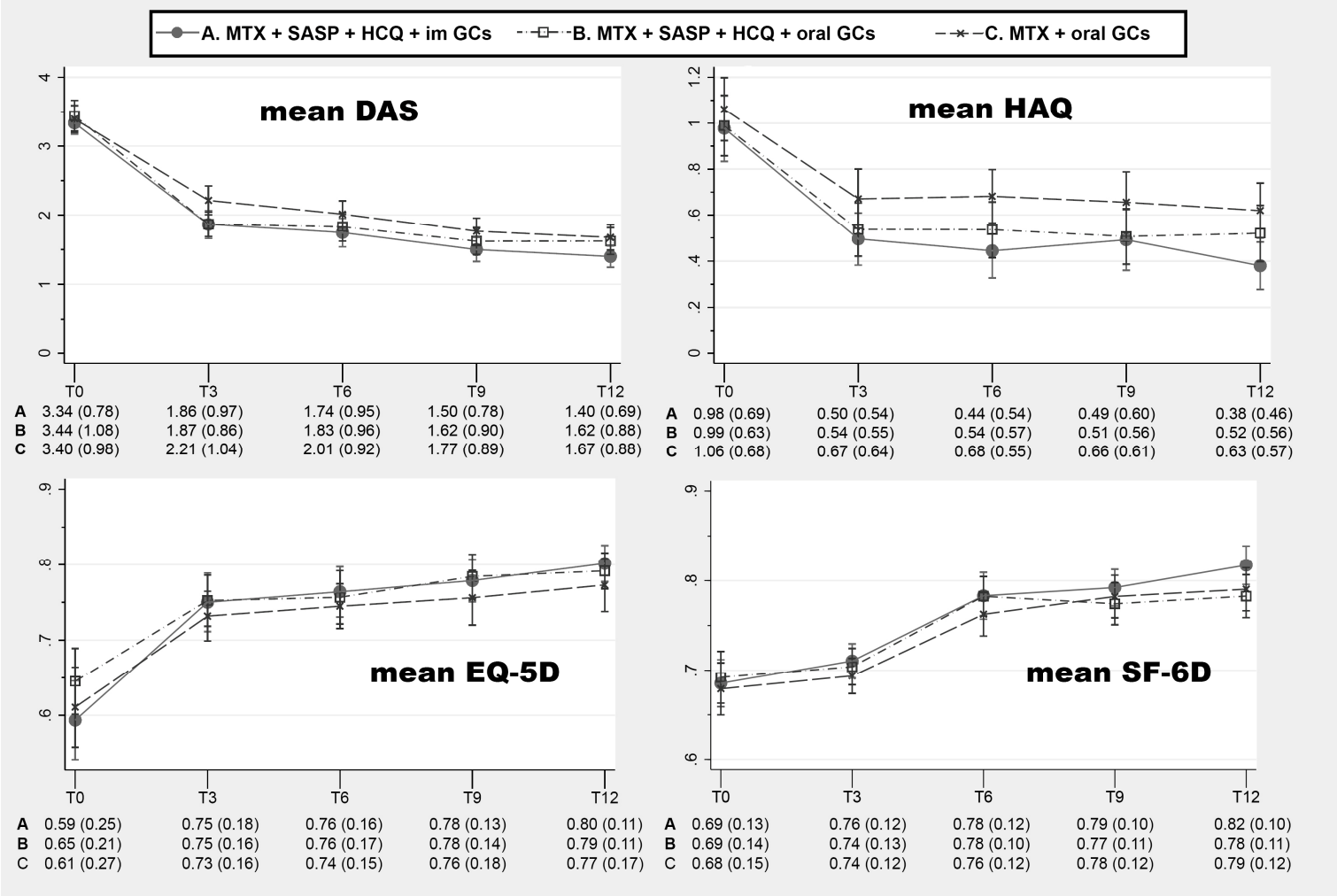


**Figure 2: Disease activity, functional ability and QALYs over time for patients with RA according to 2010 ACR/EULAR criteria.**

Error bars indicate 95% confidence intervals. Abbreviations: DAS, Disease Activity Score; EQ-5D, Dutch EuroQol; GCs, glucocorticoids; HAQ,Health Assessment Questionnaire; HCQ, hydroxychloroquine; im, intramuscular; MTX, methotrexate; QALYs, Quality Adjusted Life Years; SASP,sulfasalazine; SF-6D, Short Form 6 Dimensions

# Supplement 4: Subgroup analyses for patients with RA according to 1987 ACR criteria

## Table 1: Number of participants, with RA according to 1987 ACR criteria, at each time-point, stratified for induction therapy.

| | T0 | T3 | T6 | T9 | T12 |
|---|---|---|---|---|---|
| A. MTX + SASP + HCQ + im GCs | 69 | 65 | 63 | 60 | 58 |
| B. MTX + SASP + HCQ + oral GCs | 57 | 55 | 52 | 53 | 52 |
| C. MTX + oral GCs | 63 | 59 | 57 | 55 | 56 |

## Table 2: Baseline characteristics of patients with RA according to 1987 ACR criteria, stratified for induction therapy.

| | A. MTX + SASP + HCQ + im GCs (n=69) | B. MTX + SASP + HCQ + oral GCs (n=57) | C. MTX + oral GCs (n=63) |
|---|---|---|---|
| **Demographic** | | | |
| Age (yrs), *mean (sd)* | 54 (16) | 55 (14) | 55 (14) |
| Sex, female, *no(%)* | 41 (59) | 39 (68) | 43 (68) |
| Paid work, *no(%)* | 35 (73) | 26 (59) | 34 (71) |
| Working hours/week, *median(IQR)** | 36 (20 – 40) | 24 (15.5 – 36) | 32 (24 – 40) |
| Retired, *no(%)* | 21 (30) | 13 (23) | 15 (24) |
| **Disease characteristics** | | | |
| Symptom duration (days), *mean (sd)* | 160 (94) | 174 (87) | 146 (73) |
| RF pos., *no(%)* | 55 (80) | 47 (82) | 45 (71) |
| ACPA pos., *no(%)* | 56 (81) | 40 (70) | 49 (78) |
| DAS, *mean (sd)* | 3.43 (0.76) | 3.56 (1.06) | 3.57 (0.99) |
| SJC44, *median (IQR)* | 9 (6 - 12) | 11 (6 – 12) | 9 (6 – 11) |
| Erosion, *no(%)* | 23 (33) | 11 (19) | 9 (14) |
| **Questionnaires[1]** | | | |
| EQ-5D, *mean (sd)* | 0.57 (0.26) (n=65) | 0.63 (0.23) (n=54) | 0.57 (0.29) (n=57) |
| SF-6D, *mean (sd)* | 0.68 (0.13) (n=64) | 0.68 (0.15) (n=55) | 0.68 (0.16) (n=60) |
| HAQ, *mean (sd)* | 1.05 (0.67) (n=64) | 0.99 (0.64) (n=53) | 1.10 (0.68) (n=60) |

[1]Not everyone filled in a (complete) questionnaire and therefore n is different for HAQ and RADAI.

*p=0.034 for A vs. B

Abbreviations: ACPA, anti-citrullinated protein/peptide antibodies; DAS, Disease Activity Score; EQ-5D, Dutch EuroQol; GCs, glucocorticoids; HAQ,Health Assessment Questionnaire; HCQ, hydroxychloroquine; im, intramuscular; IQR, interquartile range; MTX, methotrexate; RF, rheumatoid factor; SASP,sulfasalazine; sd, standard deviation; SF-6D, Short Form 6 Dimensions; SJC44, swollen joint count (44 joints).

**Table 3: Health care utilization and costs in patients with RA according to 1987 ACR criteria, stratified for induction therapy.**

| | A. MTX + SASP + HCQ + im GCs (n=69) | | | B. MTX + SASP + HCQ + oral GCs (n=57) | | | C. MTX + oral GCs (n=63) | | |
|---|---|---|---|---|---|---|---|---|---|
| | ***Utilization*** | ***Quantity[1]*** | ***Costs[2]*** | ***Utilization*** | ***Quantity[1]*** | ***Costs[2]*** | ***Utilization*** | ***Quantity[1]*** | ***Costs[2]*** |
| **Medication** | | | | | | | | | |
| • DMARDs | 69 (100) | - | € 184 (102) | 57 (100) | - | € 273 (243)* | 63 (100) | - | € 100 (144) |
| • Glucocorticoids | 68 (99) | - | € 7 (3) | 56 (98) | - | € 6 (2)† | 63 (100) | - | € 8 (7) |
| • Biological usage | 18 (26) | - | € 2231 (4149) | 14 (25) | - | € 1986 (4053) | 24 (38) | - | € 3552 (4864) |
| • Analgesia usage | 18 (26) | - | € 18 (33) | 12 (21) | - | € 29 (73) | 18 (29) | - | € 14 (27) |
| • Other | 69 (100) | - | € 4 (6) | 56 (98) | - | € 15 (3)‡ | 63 (100) | - | € 19 (9) |
| **Medical consumption** | | | | | | | | | |
| Hospitalisation | 4 (6) | 4.5 (8) | € 113 (591) | 3 (5) | 1 (1) | € 62 (325) | 7 (11) | 3 (33) | € 404 (2411) |
| Standard health care | | | | | | | | | |
| • Primary care physician | 26 (38) | 3 (10) | € 38 (66) | 22 (39) | 2 (12) | € 39 (76) | 25 (40) | 3 (10) | € 38 (67) |
| • Specialist | 69 (100) | 7 (14) | € 504 (243) | 57 (100) | 7 (12) | € 509 (222) | 63 (100) | 8 (14) | € 538 (257) |
| • Nurse practitioner/physician assistant | 51 (74) | 4 (9) | € 78 (69) | 40 (70) | 3 (28) | € 73 (117) | 42 (67) | 3 (64) | € 97 (243) |
| • Paramedical care | | | | | | | | | |
| o Physical therapy | 17 (25) | 10 (28) | € 96 (233) | 10 (18) | 6 (48) | € 69 (259) | 10 (16) | 14 (60) | € 111 (361) |
| o Podology | 3 (4) | 3 (3) | € 7 (35) | 1 (2) | 1 (1) | € 1 (7) | 1 (2) | 4 (4) | € 4 (28) |
| o Occupational therapy | 0 (0) | - | € 0 (0) | 0 (0) | - | € 0 (0) | 1 (2) | 4 (4) | € 1 (11) |
| Complementary medicine | | | | | | | | | |
| • Alternative medical systems | 0 (0) | - | € 0 (0) | 1 (2) | 1 (1) | € 1 (4) | 0 (0) | - | € 0 (0) |

Results shown are respectively number (%) for utilization, median (maximum) for quantity and mean (standard deviation) for costs.

[1]Quantity reflects respectively the median(maximum) length of stay (in days) of the patients who are hospitalized and number of visits/sessions of the patients who utilize standard health care and/or complementary medicine.

[2]Reporterd costs are the average costs for all patients in corresponding treatment arm

*p=0,007 and p<0.0001 for respectively A vs. B and B vs. C.

†p=0.016 and p=0.019 for respectively A vs. B and B vs. C.

‡p<0,0001 and p<0.002 for respectively A vs. B and B vs. C.

Abbreviations: GCs, glucocorticoids; HCQ, hydroxychloroquine; im, intramuscular; MTX, methotrexate and SASP,sulfasalazine.

**Table 4: Loss of productivity and costs in patients with RA according to 1987 ACR criteria, stratified for induction therapy.**

| | A. MTX + SASP + HCQ + im GCs (n=69) | B. MTX + SASP + HCQ + oral GCs (n=57) | C. MTX + oral GCs (n=63) |
|---|---|---|---|
| **Employment after 12 months** | | | |
| Paid work | 35 (73) | 31 (70) | 30 (63) |
| Unemployment* | 0 (0) | -5 (19) | +4 (12) |
| Working hours per week, *median(IQR)* | 28 (4 – 40) | 24 (10 – 38) | 24 (3 – 32) |
| **Loss of productivity** | | | |
| Sick leave | | | |
| • Occurrence | 33 (94) | 22 (85) | 27 (79) |
| • Long term sickness[1] | 8 (23) | 3 (12) | 11 (32) |
| • Days absent, *median(IQR)* | 3 (1 – 7) | 4 (1 – 6) | 3 (1 – 8) |
| Contract hours | | | |
| • Reduction | | | |
| o Occurrence | 13 (37) | 11 (42) | 17 (50) |
| o Decrease, *median(IQR)*† | 19 (4 – 37) | 6 (0 – 12) | 27 (4 – 36) |
| • Increase | | | |
| o Occurrence | 6 (17) | 4 (15) | 4 (12) |
| o Increase, *median(IQR)* | 8 (2 – 12) | 7 (3 – 38) | 17 (9 – 28) |
| Total productivity loss in days, *median(IQR)* | 26 ( 3 – 117) | 10 (3 – 51) | 34 (4 – 182) |
| **Indirect costs*, mean(sd)*‡** | € 10390 (11260) | € 5201 (6478) | € 10332 (9960) |

Results shown are number (%) unless stated otherwise.

[1]Long term sickness is defined as absence from work longer than 160 days (Dutch friction period)

*p=0.014 and p=0.035 for respectively A vs B and B vs C. †p=0.027 for B vs C. ‡p=0.026 for B vs C

**Table 5: QALYs and (specified) average cost per QALY after 1 year of follow-up for patients with RA according to 1987 ACR criteria**

| | A. MTX + SASP + HCQ + im GCs (n=69) | B. MTX + SASP + HCQ + oral GCs (n=57) | C. MTX + oral GCs (n=63) |
|---|---|---|---|
| **QALYs (AUC)** | | | |
| EQ-5D | 0.74 (0.12) | 0.76 (0.11) | 0.74 (0.13) |
| SF-6D | 0.77 (0.08) | 0.76 (0.09) | 0.76 (0.10) |
| **Costs per QALY using EQ-5D** | | | |
| Total direct costs* | € 4949 (7437) | € 4524 (6397) | € 8202 (11618) |
| • *Medication* | € 3745 (6913) | € 3432 (5798) | € 6299 (10758) |
| • *Medical consumption* | € 1014 (669) | € 940 (555) | € 1192 (1129) |
| • *Hospitalization* | € 190 (1013) | € 152 (929) | € 711 (4230) |
| Total indirect costs† | € 8118 (16114) | € 3582 (8113) | € 8663 (14639) |
| Total costs‡ | € 13067 (20010) | € 8106 (11404) | € 16865 (23286) |
| **Costs per QALY using SF-6D** | | | |
| Total direct costs* | € 4464 (6129) | € 4351 (6184) | € 6994 (8066) |
| • *Medication* | € 3334 (5748) | € 3320 (5782) | € 5367 (7518) |
| • *Medical consumption* | € 958 (594) | € 933 (588) | € 1085 (850) |
| • *Hospitalization* | € 173 (907) | € 97 (532) | € 542 (3096) |
| Total indirect costs† | € 7415 (13776) | € 3261 (7023) | € 7857 (12801) |
| Total costs‡ | € 11880 (16134) | € 7612 (9717) | € 14851 (17655) |

Results shown are mean (standard deviation).

***EQ-5D*** *p=0.036 for B vs. C. †p=0.022 for B vs. C. ‡p=0.011 for B vs. C.

***SF-6D*** *p=0.048 for B vs. C. †p=0.018 for B vs. C. ‡p=0.007 for B vs. C.

**Table 6: ICERs between treatment arms for patients with RA according to 1987 ACR criteria.**

| | EQ-5D | SF-6D |
|---|---|---|
| **ICERs between** | | |
| • iTDT and iMM (arm B and C) | -€ 249749 (237858) | € 2243771 (6410625) |
| • Both GC bridging therapies (arm A and B) | -€ 196360 (216701) | € 709911 (1350450) |

Results shown are mean (sd).

Abbreviations: EQ-5D, Dutch EuroQol; GCs, glucocorticoids; ICER, incremental cost-effectiveness ratio; iMM, initial Methotrexate monotherapy; iTDT, initial triple DMARD therapy; SF-6D, Short Form 6 Dimensions.

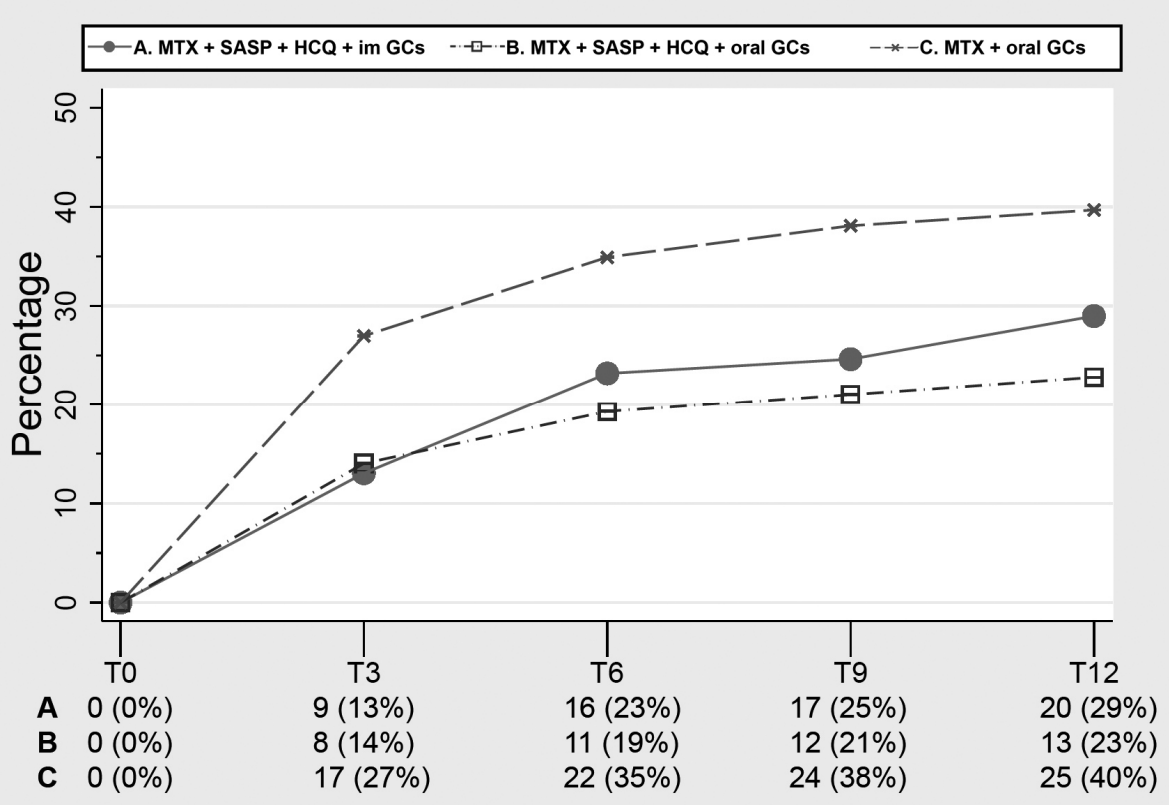


**Figure 1: Biological usage over time in patients with RA according to 1987 ACR criteria, stratified for induction therapy.**

Abbreviations: GCs, glucocorticoids; HCQ, hydroxychloroquine; im, intramuscular; MTX, methotrexate; SASP, sulfasalazine.

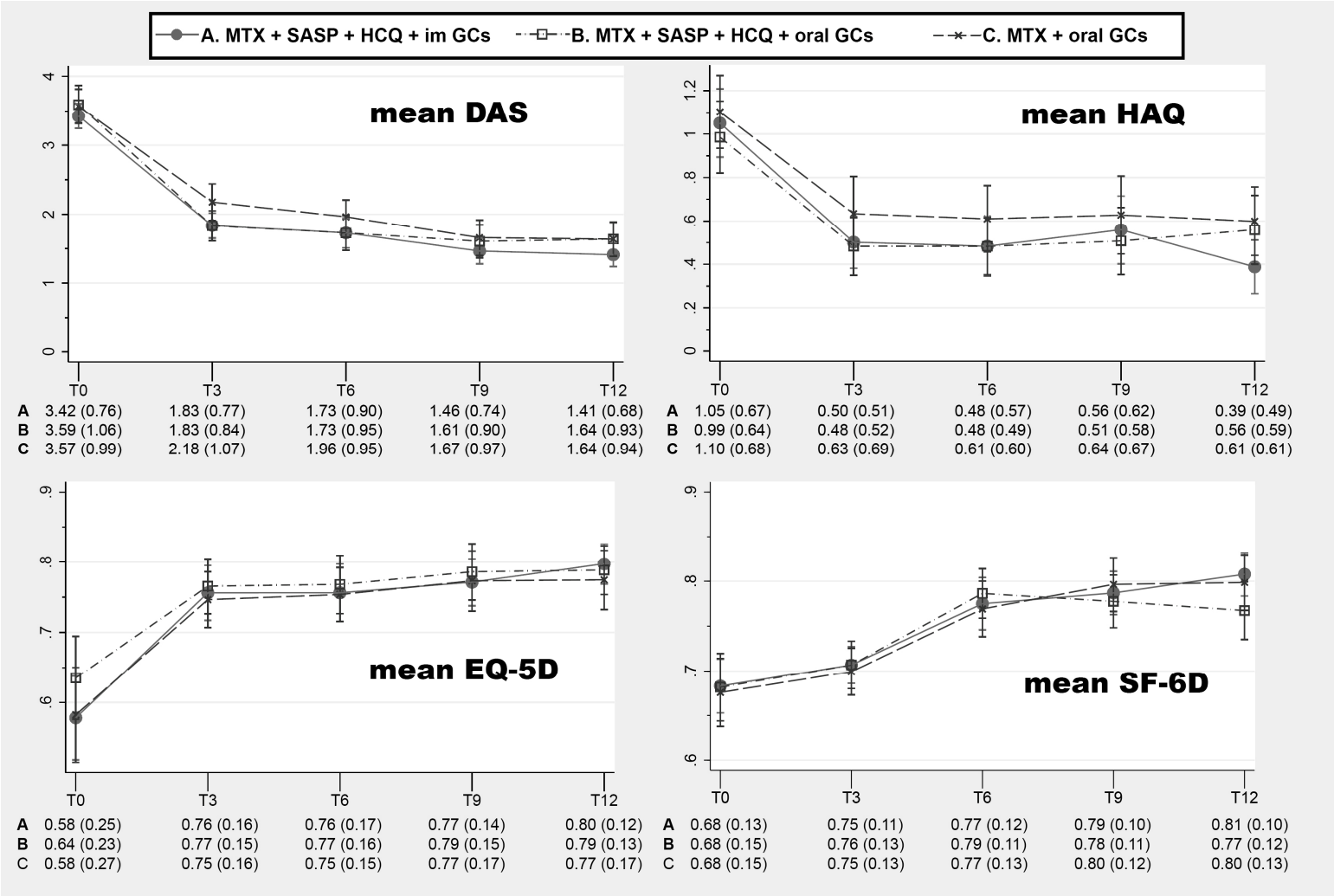


**Figure 2: Disease activity, functional ability and QALYs over time for patients with RA according to 1987 ACR criteria.**

Error bars indicate 95% confidence intervals.Abbreviations: DAS, Disease Activity Score; EQ-5D, Dutch EuroQol; GCs, glucocorticoids; HAQ,Health Assessment Questionnaire; HCQ, hydroxychloroquine; im, intramuscular; MTX, methotrexate; QALYs, Quality Adjusted Life Years; SASP,sulfasalazine; SF-6D, Short Form 6 Dimensions

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CHAPTER 5

# Treatment decisions and related costs differ significantly depending on the choice of a disease activity index in rheumatoid arthritis, according to 1987 and 2010 classification criteria.

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**Objective**
To evaluate the therapeutic and economic consequences of various disease activity indices (DAIs) in rheumatoid arthritis (RA ) according to 1987 and 2010 criteria.

**Methods**
Data on disease activity states from all sustained visits were assessed from all patients who participated in the treatment in the Rotterdam Early Arthritis Cohort (tREACH) study, a stratified randomized trial to evaluate different treatment strategies in patients with a symptom duration of <1 year. Frequencies of treatment adaptations, based upon exclusive thresholds of various DAIs, were visualized in reclassification tables. The Stuart-Maxwell test was applied to analyze any significant differences between treatment decisions according to the different DAIs. Simulated annual median medication costs were estimated using the tREACH medication protocol with standard national costs.

**Results**
DAIs perform similar in RA according to 1987 and 2010 criteria. A total of 1104 disease activity scores per DAI were available from 296 patients. DAIs differ significantly, compared with the original disease activity score (DAS), in classifying a patient's disease state. Consequently, treatment intensifications occur more frequently with simplified disease activity index (SDAI), clinical disease activity index (CDAI) and DAS28 usage, compared with DAS. Tapering treatment occurs less frequently with SDAI and CDAI and more frequently with DAS28. Simulated annual median medication costs are significantly higher with DAS28, SDAI and CDAI usage compared with DAS usage.

**Conclusion**
Usage of various DAIs in a single patient leads to inconsistent disease state categorizations. Consequently, these inconsistencies significantly influence therapeutic decisions and accompanying costs. As DAI usage is imperative to uphold current European League Against Rheumatology (EULAR) treatment recommendations, rheumatologists should consider these therapeutic and economic consequences before choosing a particular DAI.

**Key message**

- Usage of various DAIs in early RA leads to inconsistent disease state categorizations.
- Inconsistencies between DAIs significantly influence therapeutic decisions and accompanying costs in early RA.
- In early RA, therapeutic and economic consequences should also be considered for DAI selection.

**Key words**

- Rheumatoid Arthritis; Disease Activity

## INTRODUCTION

In order to obtain better functional and radiological outcomes, in rheumatoid arthritis (RA), the recently published European League Against Rheumatology (EULAR) treatment guideline recommends treatment strategies that are targeted to achieve remission, or at least low disease activity.[1-3] To achieve this goal within 3 months, and definitely within 6 months, patients should be monitored strictly ('tight control') with a disease activity index (DAI) and abide by intensifying medication.[4] Consequently, intensifying treatment will be more expensive since most international guidelines recommend starting expensive biologicals after failing on two conventional DMARDs in an optimal dosage for 3 months.[3, 5] Tight controlled intensive treatment also has an increased remission rate compared with routine care.[6] Therefore, in the near future, DAI usage might expand to giving guidance in tapering treatment in case of sustained remission.[2-3]

There are various DAIs available: Disease Activity Score (DAS), DAS with substituting a constant for the patient's global health (DAS (3var)), DAS with C-reactive protein (CRP) instead of erythrocyte sedimentation rate (ESR) (DAS-CRP), DAS with both previous mentioned modifications (DAS (CRP/3var)), same combinations for DAS with 28 joints (DAS28), Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI).[7-10] A DAI is a pooled index that involves the incorporation of various parameters into a formula to obtain a numerical indicator of disease activity. The following core set parameters were identified: tender and swollen joint counts, acute-phase reactants, general health, physician's and patient's global assessment of disease activity (EGA and PGA, respectively).[11] All DAIs have their own thresholds for remission, low, moderate and high disease activity.[10] There is no DAI recommended by the guideline developers, apart from that it should include a swollen and tender joint count.[2-3]

Previous studies showed good correlation (range 0.85-0.99) between various DAIs.[12-15] A good correlation between DAIs implies that disease activity values have similar trends, but it gives no information on similarity of the state of the disease (i.e remission, low and moderate-to-high disease activity) of the various DAIs. Therefore, even with a good correlation of two DAIs, depending on the DAIs thresholds, patients could be classified into different disease activity states. Unfortunately, no data are presented on the discordance of disease state categorizations between DAIs. Since treatment adjustments are based on these thresholds, differences in disease state categorizations might have both therapeutic and economic consequences.

The current EULAR treatment guideline for RA[2-3] is adopted for patients who fulfill the 2010 classification criteria for RA.[16] The introduction of the 2010 classification criteria for RA leads to another challenge in the valid interpretation of DAIs. Interestingly, although all DAIs have been developed in cohorts comprising patients with RA according to the 1987 criteria[17], DAIs already have been used in undifferentiated arthritis[18-20], since validation is lacking in this early population.

Therefore, our objectives were: (1) to estimate differences in treatment decisions based upon thresholds of various DAIs, using the original DAS as a reference standard; (2) to estimate annual median medication costs of various DAIs; and (3) to describe the characteristics of DAIs. All three objectives were accomplished in RA according to the 2010 classification criteria and a subgroup, consisting of patients with RA according to the 1987 criteria.

## PATIENTS AND METHODS

### Patients

For this study, data of a currently ongoing clinical trial (ISRCTN26791028), namely the treatment in the Rotterdam Early Arthritis Cohort (tREACH) were used.[21] The tREACH study, a multicenter, stratified single-blinded trial to evaluate different treatment strategies in early RA, is performed in eight rheumatology centers in the southwestern part of The Netherlands. The study was approved by the Ethics Committee of the Erasmus Medical Center and CCMO (Dutch abbreviation for Central Committee on Research Involving Human Subjects). In all participating centres, the local ethics committee judged the protocol for local workability. The local ethics committees who judged the study protocol were the ethics committee of the Maasstad Hospital, Sint Franciscus Gasthuis, Vlietland Hospital, Albert Schweitzer Hospital, Admiraal de Ruyter Hospital and Zorgsaam Zeeuws-Vlaanderen. All patients gave written informed consent, according to the declaration of Helsinki, before inclusion.

Inclusion criteria for the tREACH study are age ≥18 years, arthritis ≥1 joint, symptom duration <1 year, no overexertion or trauma. Patients are excluded if their arthritis was due to (post-) infectious arthritis, crystal arthropathy or another autoimmune rheumatic disorder.

Eligible patients were stratified into three groups according to their likelihood of progressing to persistent arthritis based of the prediction model of Visser *et al*.[22] The three strata (low, intermediate and high) correspond with probability tertiles of developing persistent arthritis according to the Visser model. For the present analysis we selected those patients who had a randomization date before 1 December 2010 and fulfilled the classification criteria for RA according to the 2010 ACR/EULAR criteria.[16]

In each probability stratum, patients are randomly assigned to three treatment strategies. Allocated treatment strategies in the high probability stratum are: (A) Combination therapy (methotrexate (MTX), sulfasalazine (SSZ) and hydroxychloroquine(HCQ)) with glucocorticoids (GCs) intramuscular, (B) Combination therapy with an oral GC tapering scheme and (C) MTX with an oral GC tapering scheme. Treatment strategies in the intermediate group comprise: (A) MTX, (B) an oral GC tapering scheme (C) HCQ. The low probability group has following induction therapies: (A) NSAID, (B) GCs intramuscular and (C) HCQ. DMARD dosages were MTX 25 mg/week

oral or subcutaneous, SSZ 2 g/day and HCQ 400 mg/day. GCs were either given intramuscular (methylprednisolone 120mg or triamcinolone 80mg) or in an oral tapering scheme (weeks 1-4: 15 mg/day, weeks 5-6: 10 mg/day, weeks 7-8: 5 mg/day, and weeks 9-10: 2.5 mg/day). All patients received folic acid (10 mg/week) during MTX prescription. Osteoporosis prophylaxis (risedronate 35 mg/week and calcium/vitamin D combination 500/400 mg/IU per day) is given to patients allocated to treatment arms with combination therapy and oral GCs (High B and C).

Treatment strategies are tightly controlled, with patients being examined every 3 months and treatment decisions are based upon the original DAS thresholds.[21] In case of treatment failure, defined as DAS≥2.4, medication is intensified according to the protocol. The intensifications steps in the protocol are: (1) Combination therapy, (2) MTX + etanercept, (3) MTX + adalimunab and (4) MTX + abatacept.

In case of sustained remission, defined as DAS<1.6 at two consecutive visits, medication is tapered, which depends on the given therapy. The hierarchical ordered tapering steps are: (1) biological(s), (2) SSZ, (3) MTX, (4) HCQ. Anti-TNF agents, MTX, SSZ and oral GCs are gradually discontinued and all other medications were stopped immediately. A flare during tapering, defined as DAS≥2.4, results in restarting full therapy, according to the stage in the protocol.

**Methods**

Demographic and clinical characteristics of each patient were recorded at baseline. At each 3-monthly visit the following disease activity core set variables were assessed: a 44-joint count for swelling, a graded 53-joint count for tenderness[23], general health (GH), PGA and acute phase reactants (ESR and CRP). Since we did not collect the EGA[24], we used the value of the PGA for the EGA. Using the value of the PGA for the EGA is a good estimation, because the ratio of the mean EGA and PGA is ~1; data adapted from Smolen *et al*.[25] However, we also used more conservative estimated values of respectively 0.5 and 0.75 of the PGA for the EGA in our analysis.

The following DAIs are calculated: DAS, DAS (3var), DAS-CRP, DAS (CRP/3var), same combinations for DAS28, SDAI and CDAI.[7-10] Thresholds for remission and moderate to high disease activity for DAS (modifications), DAS28 (modifications), SDAI and CDAI are respectively <1.6 and ≥2.4, <2.6 and ≥3.2, ≤3.30 and >11, and ≤2.80 and >10.[7-10] Appendix 1 shows the mathematical formulas and thresholds for given DAIs.

Median medication costs per year for each DAI were estimated by simulating treatment decisions in the tREACH medication protocol using the various DAIs with their exclusive thresholds for remission and moderate disease activity. For this simulation we used 124 patients, using data of their first year of follow-up, of whom frequencies of 3-monthly treatment switches and evolved medication costs were analyzed. So at each visit (four in total) treatment could be continued, intensified or tapered. The amount of treatment intensifications and taperings for each patient were analyzed. Thereafter the medication costs simulation was performed, which had

following assumptions: (1) there were no protocol violations, (2) compliance was 100% and no side-effects occurred, and (3) treatment changes commenced immediately. As patients are their own controls in this post hoc analysis only the medication and not the other costs will differ. Appendix 2 gives an overview of the monthly medication costs in the Netherlands for used drugs at a maximum dosage.

**Statistical analyses**

To measure agreement between DAIs in disease state categorizations, the quadratic weighted kappa statistic[26-27] was applied. Rule of thumb for the strength of agreement is: $\kappa$ >0.8 'almost perfect',0.61-0.8 'substantial', 0.41–0.6 'moderate', 0.21–0.4 ', 'fair' and <0.2 'slight' agreement.[28] The Stuart-Maxwell test was used to assess agreement between disease state categorizations. A statistically significant Stuart-Maxwell test indicates a large disagreement in disease activity states classification between two DAIs.[29] Spearman rank correlations, using all available data, were also calculated. Discordance between indices was graphically represented with scatter plots.

Reclassification tables give insight in the possible difference in the frequency of treatment intensifications and taperings between DAS usage and other DAIs. Over- and underrating were defined as intensifying or tapering treatment more and less frequently, respectively, than the DAS. Proportions of discordance with DAS usage were given and the Stuart-Maxwell test was applied to assess the strength of discordance. To demonstrate a difference in estimated median annual medication costs between DAS and all other DAIs a Wilcoxon rank-sum test was applied.

All analyses were performed for patients fulfilling the 2010 classification criteria for RA[16] and a subgroup, consisting of patients with RA according to ACR 1987 criteria.[17] All statistical analyses were carried out using STATA version 11.1. A $p<0.05$ was considered statistically significant.

## RESULTS

**Baseline characteristics**

Table 1 shows the baseline characteristics of the 296 tREACH patients who fulfilled the 2010 ACR/EULAR classification criteria for RA. Patients were mostly females (68%) with an average symptom duration of 156 days (146 – 166 days, 95% confidence interval (CI)). Rheumatoid factor (RF) and/or Anti-citrullinated protein antibodies (ACPA) positivity was present in 199 patients (67%); of those, 142 (71%) were both RF and ACPA positive. At baseline, 47 patients (16%) had erosions. Active disease was found in 96 - 126 patients (32% - 43%), depending on the DAI used. Combination DMARD therapy was provided to 68% of the patients, while, respectively, 21% and 11% of the patients used a single DMARD and steroids as initial protocolised treatment. The subgroup description of those patients fulfilling the ACR 1987 RA criteria showed higher DAI scores, more swollen joints and were more often RF and ACPA positive (resp. 79% and 70%) compared with the total population.

**Table 1: Baseline characteristics of RA patients according to the 2010 and/or 1987 classification criteria.**

| | Total population (n=296) | Fullfillment of 1987 criteria for RA(n=168) | Fullfillment of 2010, but not 1987 criteria for RA (n=128) |
|---|---|---|---|
| Age (yrs), *mean (95% CI)* | 54 (52 - 55) | 55 (53 - 57) | 52 (49 - 54) |
| Sex, female, *no(%)* | 200 (68) | 110 (65) | 90 (70) |
| Symptom duration (days),*mean (95%CI)* | 156 (146 - 166) | 152 (140 - 165) | 161 (143 - 178) |
| Initial treatment, *no(%)* | | | |
| • *Combination therapy* | 116 (68) | 145 (86) | 57 (45) |
| • *Single DMARD* | 61 (21) | 13 (8) | 48 (37) |
| • *Steroids* | 33 (11) | 10 (6) | 23 (18) |
| RF pos., *no(%)* | 171 (58) | 133 (79) | 38 (30) |
| ACPA pos., *no(%)* | 170 (57) | 118 (70) | 52 (41) |
| Erosion, *no(%)* | 47 (16) | 38 (23) | 9 (7) |
| Morning stiffness >1hr., *no(%)* | 242 (82) | 145 (86) | 97 (76) |
| Tender joints, *median (IQR)* | | | |
| • *44 joints* | 10 (5 - 15.5) | 10 (5 - 16) | 11 (5 - 15) |
| • *28 joints* | 6 (3 - 10) | 6 (3 - 10) | 6 (2.5 - 10) |
| Ritchi Articular Index (RAI), *median(IQR)* | 7 (4 - 11) | 7 (4 - 10.5) | 8 (4.5 - 11) |
| Swollen joints, *median (IQR)* | | | |
| • *44 joints* | 8 (4 - 12) | 10 (6.5 - 13) | 4 (2 - 11) |
| • *28 joints* | 6 (3 - 10) | 7 (5 - 11.5) | 3 (1 - 8.5) |
| General Health, *median (IQR)* | 53 (30 - 68) | 54 (30 - 70) | 51 (32 - 65.5) |
| PGA, *median (IQR)* | 6 (4 - 8) | 7 (4 - 8) | 4 (6 - 10) |
| ESR (mm/hr), *median (IQR)* | 22 (12 - 39) | 25 (15 - 44) | 16 (9 - 35) |
| CRP (mg/dl), *median (IQR)* | 7 (4 - 19) | 10 (5 - 24.5) | 5 (3 - 12) |
| DAS, *mean (95% CI)* | 3.41 (3.30 - 3.52) | 3.54 (3.40 - 3.68) | 3.23 (3.06 - 3.40) |
| DAS (3var), *mean (95% CI)* | 3.27 (3.17 - 3.37) | 3.39 (3.27 - 3.52) | 3.10 (2.94 - 3.26) |
| DAS (CRP), *mean (95% CI)* | 3.26 (3.15 - 3.36) | 3.36 (3.22 - 3.50) | 3.12 (2.95 - 3.28) |
| DAS (CRP/3var), *mean (95% CI)* | 3.09 (3.00 - 3.19) | 3.19 (3.07 - 3.31) | 2.96 (2.81 - 3.11) |
| DAS28, *mean (95% CI)* | 4.85 (4.71 - 4.99) | 5.11 (4.93 - 5.28) | 4.51 (4.29 - 4.73) |
| DAS28 (3var), *mean (95% CI)* | 4.64 (4.50 - 4.77) | 4.90 (4.74 - 5.06) | 4.29 (4.06 - 4.51) |
| DAS28 (CRP), *mean (95% CI)* | 4.53 (4.41 - 4.66) | 4.73 (4.57 - 4.89) | 4.27 (4.09 - 4.45) |
| DAS28 (CRP/3var), *mean (95% CI)* | 4.31 (4.19 - 4.42) | 4.51 (4.36 - 4.66) | 4.03 (3.85 - 4.22) |
| SDAI, *mean (95% CI)* | 27.74 (26.30 - 29.19) | 29.67 (27.78 - 31.55) | 25.18 (22.98 - 27.38) |
| CDAI, *mean (95% CI)* | 26.06 (24.70 - 27.41) | 27.67 (25.92 - 29.42) | 23.90 (21.80 - 26.01) |

Abbreviations: ACP, Anti-citrullinated protein/peptide antibodies; CDAI, Clinical Disease Activity Index; CI, Confidence Interval; CRP, C-reactive protein; DAS, Disease Activity Score; DAS(3var), DAS without GH; DAS(CRP), DAS with CRP instead of ESR; DAS(CRP/3var), DAS with CRP and without GH; DAS28, DAS using a 28 joint count; EGA, Evaluator's Global Assessment; ESR, Erythrocyte Sedimentation Rate; GH, general health; IQR, Interquartile range; PGA, Patient's Global Assessment; RF,Rheumatoid Factor; sd, standard deviation and SDAI, Simplified Disease Activity Index.

### Disease state(s) agreement measures

In total 1104 disease activity scores per DAI were available from 296 patients. Correlation between the DAIs (table 2), using all available data, ranged from 0.76 for CDAI with DAS28(3var) to 0.99 comparing DAS with DAS(3var) and SDAI with CDAI. The lowest weighted quadratic kappa statistic was 0.57 for DAS28(3var) versus SDAI or CDAI (table 2). Intercorrelations of DAI scores within patients declined as the time period between assessments were longer. Intercorrelations of DAIs ranged from ±0.65 for assessments with a 3-month interval to ±0.25 between visits with a time window of 1 year. All correlation coefficients and kappa statistics had $p<0.0001$. Similar results were found in patients who fulfilled 1987 classification criteria for RA (data not presented).

**Table 2: Quadratic weighted kappa statistics and correlation coefficients in RA according to 2010 classification criteria.**

| | DAS | DAS (CRP) | DAS (3var) | DAS (CRP/3var) | DAS28 | DAS28 (CRP) | DAS28 (3var) | DAS28 (CRP/3var) | SDAI | CDAI |
|---|---|---|---|---|---|---|---|---|---|---|
| **DAS** | | 0.91 (87) | 0.96 (94) | 0.89 (84) | 0.83 (82) | 0.83 (78) | 0.80 (75) | 0.81 (76) | 0.65 (65) | 0.65 (65) |
| **DAS (CRP)** | 0.97 | | 0.90 (86) | 0.95 (93) | 0.75 (74) | 0.86 (80) | 0.72 (68) | 0.84 (79) | 0.68 (66) | 0.68 (66) |
| **DAS (3var)** | 0.99 | 0.95 | | 0.90 (86) | 0.81 (79) | 0.81 (75) | 0.81 (75) | 0.82 (77) | 0.63 (64) | 0.63 (64) |
| **DAS (CRP/3var)** | 0.96 | 0.99 | 0.96 | | 0.73 (71) | 0.83 (77) | 0.73 (67) | 0.85 (78) | 0.65 (64) | 0.65 (63) |
| **DAS28** | 0.93 | 0.86 | 0.92 | 0.85 | | 0.82 (81) | 0.92 (90) | 0.79 (79) | 0.63 (41) | 0.63 (67) |
| **DAS28 (CRP)** | 0.91 | 0.95 | 0.89 | 0.92 | 0.91 | | 0.76 (74) | 0.91 (87) | 0.71 (71) | 0.70 (69) |
| **DAS28 (3var)** | 0.90 | 0.81 | 0.91 | 0.82 | 0.98 | 0.87 | | 0.80 (75) | 0.57 (62) | 0.57 (61) |
| **DAS28 (CRP/3var)** | 0.87 | 0.90 | 0.88 | 0.92 | 0.89 | 0.97 | 0.88 | | 0.66 (67) | 0.65 (66) |
| **SDAI** | 0.83 | 0.86 | 0.81 | 0.84 | 0.82 | 0.89 | 0.77 | 0.86 | | 0.99 (97) |
| **CDAI** | 0.83 | 0.86 | 0.81 | 0.83 | 0.81 | 0.87 | 0.76 | 0.84 | 0.99 | |

Above the diagonal the quadratic weighted kappa statistics (percentage agreement within parentheses) are given. Below the diagonal the Spearman's correlation coefficients are shown. All correlation coefficients and kappa statistics have p-values <0.0001.

Abbreviations: CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS , Disease Activity Score; DAS(3var), DAS without GH; DAS(CRP), DAS with CRP instead of ESR; DAS(CRP/3var), DAS with CRP and without GH; DAS28, DAS using a 28 joint count; ESR, erythrocyte sedimentation rate; GH, general health and SDAI, Simplified Disease Activity Index.

**Table 3: DMARD and biologic usage in the tREACH trial for each time-point in patients with RA, according to the 2010 criteria, and 1 year follow-up (n=124).**

| | Baseline | 3 months | 6 months | 9 months | 12 months |
|---|---|---|---|---|---|
| MTX | 40 (32) | 18 (15) | 14 (11) | 13 (10) | 13 (10) |
| Combination therapy* | 53 (43) | 64 (52) | 56 (45) | 49 (40) | 45 (36) |
| MTX + Etanercept | 0 (0) | 26 (21) | 26 (21) | 25 (20) | 25 (20) |
| MTX + Adalimunab | 0 (0) | 0 (0) | 16 (13) | 17 (14) | 13 (10) |
| MTX + Abatacept | 0 (0) | 0 (0) | 0 (0) | 9 (7) | 18 (15) |
| Other medication† | 31 (25) | 16 (13) | 12 (10) | 11 (9) | 10 (8) |

Results shown are a number (%)

*Combination therapy comprises methotrexate, sulfasalazine and hydroxychloroquine.

†Other medication comprises hydroxychloroquine, glucocorticoids and/or NSAIDs

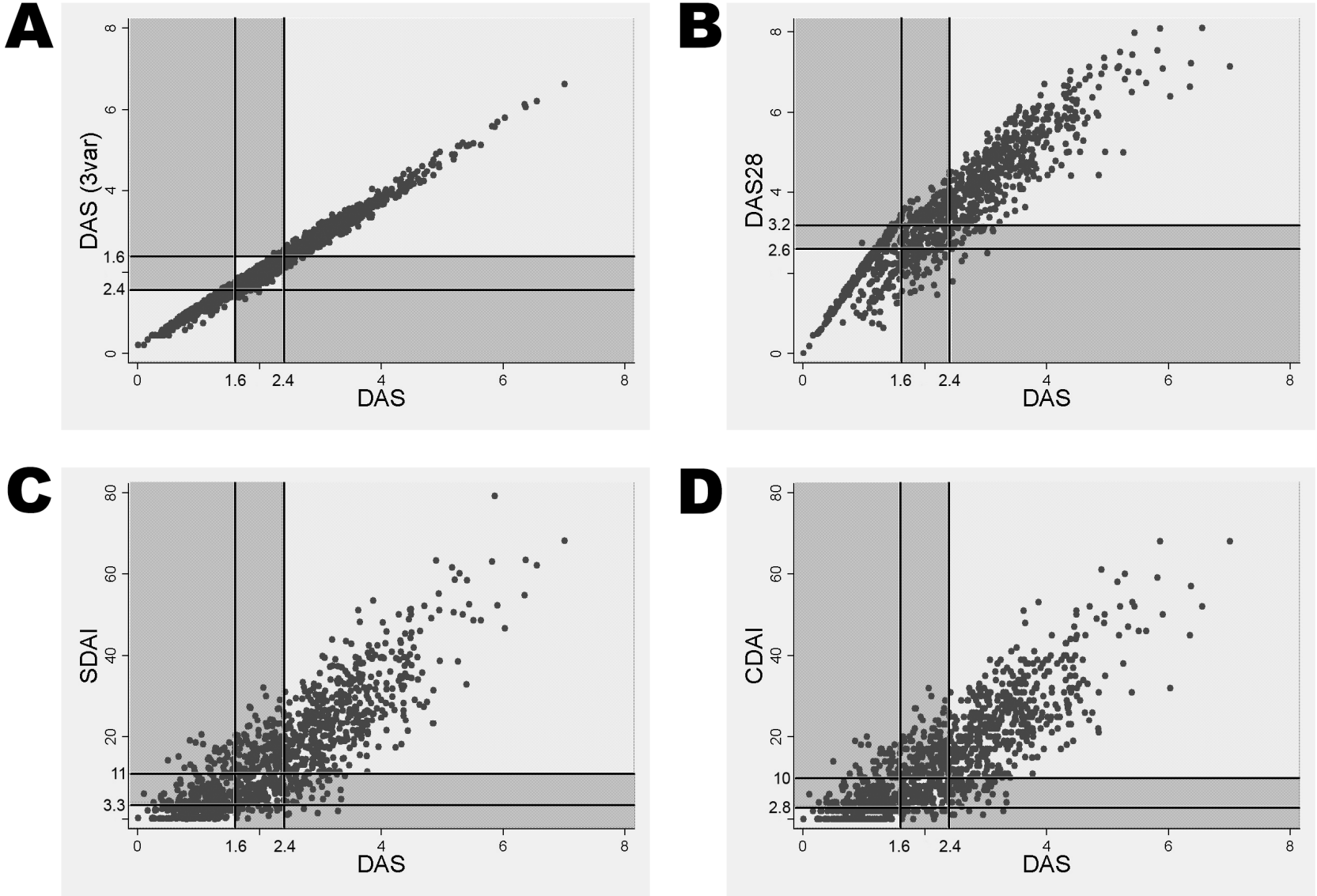
Abbreviations: MTX, methotrexate (oral).

The percentages of agreement on classifying patients into a particular disease state, however, varied widely (range 41%-97%). Discordance and concordance between disease activity states are graphically represented by scatter plots (figure 1). Scatter plots for DAS versus DAS(3var), DAS28, SDAI and CDAI, respectively, are shown (figure 1A, 1B, 1C, 1D respectively). All DAIs were significantly discordant with the original DAS regarding disease state classification. Patients were more often classified into a higher disease state (figure 1) if the DAS28, DAS28(CRP), DAS28 (3var), SDAI and CDAI were applied compared with DAS. Fewer patients were regarded as having active disease if the DAS(CRP), DAS(3var), DAS(CRP/3var) and DAS28(CRP/3var) were used. Similar results were found in patients who fulfilled 1987 classification criteria for RA (data not presented).

**Therapeutic and economic consequences**

In 124 patients with a follow-up ≥1 year, frequencies of 3-monthly treatment switches and evolved medication costs were analyzed using data of the first year of follow-up. Figure 2 shows the reclassification tables for DAS versus DAS28, CDAI and SDAI over 1 year of treatment. On the diagonal the number of patients who receive a similar number of treatment intensifications and taperings, independently on the DAI used, are presented. Under the diagonal are patients who switched treatment more frequently, whereas patients above the diagonal switched less often when compared with the DAS. Proportions of over- and underrating for treatment intensifications and taperings compared with the DAS are shown in figure 2. At least 35% of the patients had more frequent treatment intensifications with DAS28, SDAI and CDAI usage compared with the DAS. Remission was less often achieved with SDAI and CDAI usage, leading to fewer treatment taperings. However, remission is achieved 2.3 times more frequently if the DAS28 is used, leading to more frequent treatment taperings compared with DAS usage. In the subgroup, RA according to 1987 criteria, similar results were found. (data not shown)

Median medication costs per year for each DAI were estimated by simulating treatment decisions in the tREACH medication protocol using the various DAIs with their exclusive thresholds for remission and moderate disease activity. Table 3 gives an overview of biological and DMARD usage in the tREACH trial. For all other DAIs biologic and DMARD usage was simulated for each time-point. Combining this information with standard national costs and following assumptions: (1) there were no protocol violations, (2) compliance was 100% and no side-effects occurred, and (3) treatment changes commenced immediately, we performed the medication cost simulation and estimated annual median medication costs. Resulting in €318 (interquartiel range: €189 - €7733) as annual median medication costs per patient for the DAS. Simulated medication costs for all other DAIs ranged between €298 and €7658 for respectively, the DAS(CRP) and the SDAI (table 4). Compared with the DAS the estimated median cost increase for the DAS28 were €4958, for SDAI €7340 and for CDAI €6732. These differences were even larger when the simulation was applied to ACR 1987 RA patients only (data not presented).


A
DAS (3var)
0
1.6
2.4
4
6
8
DAS
B
DAS28
3.2
2.6
C
SDAI
11
3.3
20
40
60
80
D
CDAI
10
2.8

**E**

| | | |
|---|---|---|
| A | B | C |
| D | E | F |
| G | H | I |

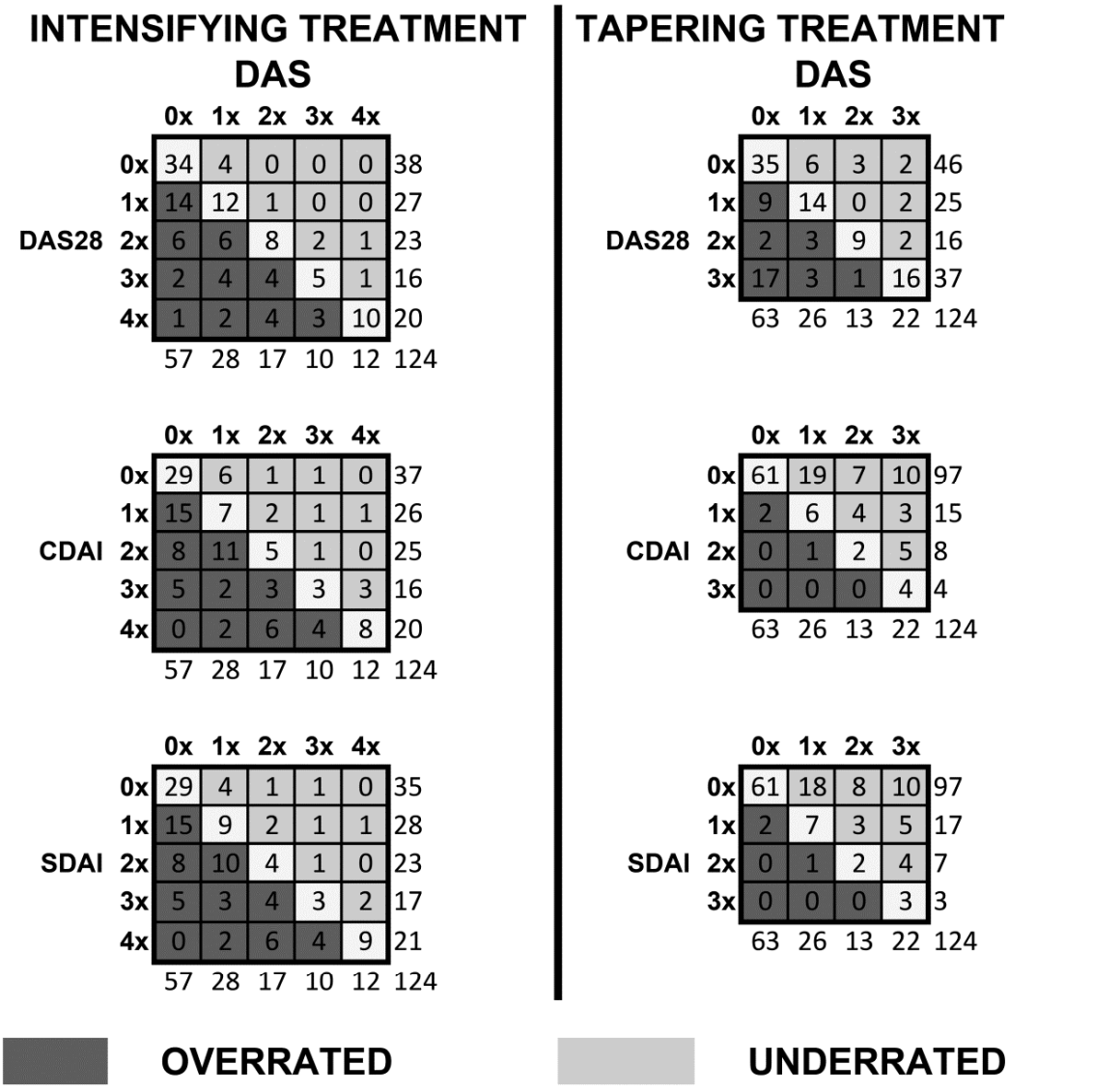
**F**

| | A | B | C | D | E | F | G | H | I | Stuart-Maxwell test |
|---|---|---|---|---|---|---|---|---|---|---|
| DAS (CRP) | 0 (0) | 26 (2) | 443 (40) | 30 (3) | 206 (19) | 50 (5) | 315 (29) | 34 (3) | 0 (0) | P=0.02 |
| DAS (3var) | 0 (0) | 11 (1) | 469 (42) | 14 (1) | 234 (21) | 24 (2) | 331 (30) | 21 (2) | 0 (0) | P=0.05 |
| DAS (CRP/3var) | 0 (0) | 24 (2) | 421 (38) | 36 (3) | 199 (18) | 72 (7) | 309 (28) | 43 (4) | 0 (0) | P<0.0000 |
| DAS28 | 8 (1) | 115 (10) | 467 (42) | 46 (4) | 89 (8) | 22 (2) | 291 (26) | 62 (6) | 4 (0) | P<0.0000 |
| DAS28 (CRP) | 1 (0) | 101 (9) | 452 (41) | 42 (4) | 103 (9) | 26 (2) | 302 (27) | 62 (6) | 15 (1) | P<0.0000 |
| DAS28 (3var) | 7 (1) | 92 (8) | 452 (41) | 56 (5) | 89 (8) | 26 (2) | 282 (26) | 85 (8) | 15 (1) | P<0.0000 |
| DAS28 (CRP/3var) | 1 (0) | 76 (7) | 430 (39) | 44 (4) | 112 (10) | 40 (4) | 300 (27) | 78 (7) | 23 (2) | P<0.0000 |
| SDAI | 42 (4) | 136 (12) | 440 (40) | 138 (13) | 111 (10) | 48 (4) | 165 (15) | 19 (2) | 5 (0) | P<0.0000 |
| CDAI | 40 (4) | 134 (12) | 433 (39) | 140 (13) | 115 (10) | 55 (5) | 165 (15) | 17 (2) | 5 (0) | P<0.0000 |

**Figure 1: Concordance between DAIs in RA, according to 2010 classification criteria.**

Scatter plots for DAS vs DAS(3var), DAS-28, SDAI and CDAI are given (respectively, A, B, C and D). DAIs are concordant and discordant in the light grey and dark grey surfaces, respectively. The vertical and horizontal lines represent thresholds for corresponding DAIs on the x and y-axis, respectively. These threshold lines divide the graph into nine rectangles. (E) A schematic diagram of a graph divided into nine rectangles, in which each rectangle is identifiable by a letter. (F) The number of patients (percentage) for each rectangle per DAI vs the DAS. Rectangles A +B+D and F +H+ I give the number or percentage of patients who are classified into a more and less active disease state, respectively, by a particular DAI compared with the DAS.

Abbreviations: CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS , Disease Activity Score; DAS(3var), DAS without GH; DAS(CRP), DAS with CRP instead of ESR; DAS(CRP/3var), DAS with CRP and without GH; DAS28, DAS using a 28 joint count; ESR, erythrocyte sedimentation rate; GH, general health and SDAI, Simplified Disease Activity Index.




| | TREATMENT INTENSIFICATION | | | TREATMENT TAPERING | | |
|---|---|---|---|---|---|---|
| | Agreement | Overrated | Underrated | Agreement | Overrated | Underrated |
| DAS (CRP) | 94 (76) | 11 (9) | 19 (15) | 99 (80) | 16 (13) | 9 (7) |
| DAS (3var) | 108 (87) | 6 (5) | 10 (8) | 118 (95) | 1 (1) | 5 (4) |
| DAS (CRP/3var) | 91 (73) | 12 (10) | 21 (17) | 98 (79) | 16 (13) | 10 (8) |
| DAS28 | 69 (56)* | 46 (37) | 9 (7) | 74 (60)* | 35 (28) | 15 (12) |
| DAS28 (CRP) | 76 (61)* | 37 (30) | 11 (9) | 85 (69) | 24 (19) | 15 (12) |
| DAS28 (3var) | 71 (57)* | 40 (32) | 13 (10) | 87 (70) | 19 (15) | 18 (15) |
| DAS28 (CRP/3var) | 76 (61) | 30 (24) | 18 (15) | 79 (64) | 16 (13) | 29 (23) |
| SDAI | 54 (44)* | 57 (46) | 13 (10) | 73 (59)* | 3 (2) | 48 (39) |
| CDAI | 52 (42)* | 56 (45) | 16 (13) | 73 (59)* | 3 (2) | 48 (39) |

**Figure 2: Simulated treatment reclassifications, using patients with RA, according to the 2010 criteria, and 1 year follow-up.**

Reclassification tables for DAS vs DAS28, SDAI and CDAI, respectively, are given. DAIs are concordant in the white areas. Patients are overrated (dark grey areas) and underrated (light grey areas) if treatment intensification or taperings, respectively, would have occured more and less frequently than when the DAS was used. The total number of patients (percentage) who are in agreement, overrated and underrated for treatment intensifications and taperings for each fictive use of DAI vs the DAS are shown in the table. The Stuart-Maxwell test (intensifications and taperings investigated seperately): $p<0.05$ compared with the DAS (indicated by an asterisk).

**Table 4: Simulation of annual medication costs per DAI in patients with RA, according to the 2010 criteria, and 1 year follow-up.**

| DAI | Median | Interquartile range |
|---|---|---|
| DAS | € 318.24 | € 188.78 - € 7732.97 |
| DAS (CRP) | € 298.49 | € 188.66 - € 7702.16 |
| DAS (3var) | € 318.24 | € 188.78 - € 7759.66 |
| DAS (CRP/3var)[1] | € 298.49 | € 188.66 - € 7709.72 |
| DAS28[3] | € 5267.65 | € 214.35 - € 8953.94 |
| DAS28 (CRP)[2] | € 2740.06 | € 207.72 - € 8828.27 |
| DAS28 (3var)[1] | € 2784.82 | € 192.74 - € 8853.37 |
| DAS28 (CRP/3var) | € 349.144 | € 188.66 - € 7767.27 |
| SDAI[3] | € 7657.85 | € 298.88 - € 10233.20 |
| CDAI[3] | € 7050.65 | € 298.49 - € 10214.00 |

Abbreviations: CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAI, Disease Activity Index; DAS , Disease Activity Score; DAS(3var), DAS without GH; DAS(CRP), DAS with CRP instead of ESR; DAS(CRP/3var), DAS with CRP and without GH; DAS28, DAS using a 28 joint count; ESR, erythrocyte sedimentation rate; GH, general health and SDAI, Simplified Disease Activity Index.

[1]P<0.05 [2]P<0.01 [3]P<0.0001

## DISCUSSION

In this study we compared the characteristics of DAIs in RA according to the 2010 and 1987 classification criteria.[16-17] The performance of the disease activity measures in patients fulfilling the new RA 2010 classification criteria was comparable to those with RA according to 1987 criteria, although lower levels of disease activity were seen for patients that only fulfilled the 2010 criteria. We found that DAS28, SDAI and CDAI overrate disease activity and classify patients into higher disease activity states compared with the DAS, potentially leading to more treatment intensifications and associated medication costs. However, the consequence of using different DAIs on functional impairment and joint damage over time is not known and has still to be investigated.

The 2010 classification criteria are aimed at identifying RA earlier in the disease course than the 1987 criteria.[30] This may explain the lower levels of disease activity shown in our study. A previous study by Fransen *et al*[31] showed good performance of the DAS in undifferentiated arthritis, suggesting that DAIs could be used in the new patient group fulfilling the 2010 RA criteria. This is helpful, as DAIs are imperative to uphold current EULAR recommendations for treating RA.[2-3]

In daily practice usage of the original DAS takes too much time and rheumatologists would probably prefer a DAI that is faster and easy-to-do. Although we and others found strong correlation coefficients, the overall agreement measures were just acceptable between the DAS and the other measures of disease activity.[12-15] This discrepancy is due to the fact that the correlation reflects the direction of a linear relationship between DAIs, but not the slope of that relationship (figure 1). Therefore, more important is the classification of patients into the disease states 'remission', 'low' or 'moderate to severe', which showed substantial variation. Considerable

reclassification was shown for the 28 joint DAIs (DAS28, SDAI and CDAI) compared with the DAS. One explanation for this might be that of all DAI formulas, the DAS and its modifications are less influenced by swollen joint counts (alterations). Due to the reclassification patients would have received more treatment intensifications, resulting in a substantial increase of medication cost. However, it is unclear if the various DAIs under- or overestimate the disease activity, which will lead to different patient outcomes as there are no head-to-head comparisons available.

In our simulation study we compared the disease state distribution at 1 year for 2 groups of patients: (1) Patients who were congruent in disease state on the DAIs at 3 months and (2) patients who had a DAS-defined disease state at 3 months that differed from any other DAI. At 1 year there were no differences in the disease state distributions. Although the treatment decisions, in reality, were based on the DAS, these data suggest we did not undertreated those patients who were incongruent at 3 months. Therefore, for the selection of a DAI, besides that it is easy to use, therapeutic and economic consequences should also be considered.

The choice of a DAI for usage in daily practice is cumbersome, because head-to-head comparisons between DAIs are lacking. However, if a particular DAI is chosen to assess disease activity in a patient with RA, that same DAI should be used during the entire follow-up of that patient. Our DAI preference for daily practice is the DAS28, because, first, it is easy to use and, secondly, its ability to detect active disease, which results in treatment intensifications and higher medication costs, is in between the other DAIs. The DAS28 is more conservative compared with the SDAI and CDAI and more liberal compared with the DAS in detecting active disease. Remission rates, however, are much higher with DAS28 compared with other DAIs. We advise that the decision to taper treatment should not only depend on measuring sustained remission with DAS28, but also on the absence of forefeet arthritis and radiographic progression.

Our study had certain limititations. First, we did not assess the EGA.[24] To be able to use the SDAI/CDAI we substituted the value of the EGA with the value of the PGA, based on the SDAI development cohort[25], wherein the mean EGA and PGA are similar. However, Sokka *et al*[32] have reported a ratio of 0.5 between the median values of EGA and PGA. Estimating the EGA with making use of the PGA has biased our results. Therefore, we conducted a sensitivity analyses with different EGA estimations to evaluate how much these different estimations would influence our results. We performed our sensitivity analysis with imputed values of the EGA, which were 0.5 and 0.75 times the PGA. This resulted in similar high correlations and substantial reclassification (Appendix 3). The weakness of our sensitivity analysis is the unknown relationship between EGA and PGA, which may be influenced by other components of the DAI and the physician's perspective. Therefore, the real differences in disease state categorizations and annual median medication cost between SDAI/CDAI and DAS are probably within the extreme limits of our EGA estimations (respectively 0.5 and 1 times the PGA).

Second, for the cost analysis we had to simulate the consequences of the various DAIs, as our trial was tightly controlled by the DAS. A wrongful accumulation of treatment adaptations may have occured, as explained in the following example: If the DAS measured a low disease activity state and the SDAI measured a moderate to high disease activity state at a particular time-point, the DAS was followed and thus treatment was not adjusted. Consequently, at a following time point the effect of what would have happened if the SDAI was followed could not be measured. As patients were their own controls, only medication costs were used for our simulation. Other direct and indirect costs, like sick leave and medical consumption, could not be analysed in our simulation. To solve this problem in future research the outcome of treatment strategies using different DAIs could be compared.

In conclusion, DAIs perform similar in RA according to 2010 and 1987 criteria. Knowing that DAIs are essential in guiding treatment decisions, choosing a particular DAI could be cumbersome, because usage of various DAIs in a single patient leads to inconsistent disease state categorizations. Consequently, these inconsistencies significantly influence therapeutic decisions and accompanying costs. Therefore, for the selection of a DAI, the therapeutic and economic consequences should be considered.

## APPENDIX 1: Formulas and thresholds for disease activity indices (DAIs).

| DAI | Formula | Thresholds |
|---|---|---|
| DAS | 0.53938√(RAI) + 0.06465(SJC44) + 0.33ln(ESR) + 0.00722(GH) | <1.6/<2.4/<3.7 |
| DAS (3var) | 0.53938√(RAI) + 0.06465(SJC44) + 0.33ln(ESR) + 0.224 | |
| DAS (CRP) | 0.53938√(RAI) + 0.06465(SJC44) + 0.17ln(CRP+1) + 0.00722(GH) + 0.45 | |
| DAS (CRP/3var) | 0.53938√(RAI) + 0.06465(SJC44) + 0.17ln(CRP+1) + 0.65 | |
| DAS28 | 0.56√(TJC28) + 0.28√(SJC28) + 0.70ln (ESR) + 0.014(GH) | <2.6/<3.2/<5.1 |
| DAS28 (3var) | (0.56√(TJC28) + 0.28√(SJC28) + 0.70ln (ESR))1.08 + 0.16 | |
| DAS28 (CRP) | 0.56√(TJC28) + 0.28√(SJC28) + 0.36ln (CRP+1) + 0.014(GH) + 0.96 | |
| DAS28 (CRP/3var) | (0.56√(TJC28) + 0.28√(SJC28) + 0.36ln (CRP+1))*1.10 + 1.15 | |
| SDAI | SJC28 + TJC28 + PGA + EGA + CRP | ≤3.3/≤11/≤26 |
| CDAI | SJC28 + TJC28 + PGA + EGA | ≤2.8/≤10/≤22 |

*Abbreviations:* CDAI, Clinical Disease Activity Index; CRP, C-reactive protein (DAS→ *mg/l* & SDAI → *mg/dl*); DAS , Disease Activity Score; DAS(3var), DAS without GH*;* DAS(CRP), DAS with CRP instead of ESR*;* DAS(CRP/3var), DAS with CRP and without GH*;* DAS28, DAS using a 28 joint count*;* EGA= Evaluator Global Assessment of disease activity (VAS of *10cm*); ESR, Erythrocyte Sedimentation Rate (mm/hr); GH, General Health (Visual Analogue Scale (VAS) of 100mm); PGA, Patient Global Assessment of disease activity (VAS of *10cm*); RAI, Ritchie Articular Index (53 joints in 26 units, graded for tenderness); SDAI, Simplified Disease Activity Index*;* SJC, Swollen Joint Count and TJC, Tender Joint Count.

## APPENDIX 2: Monthly medication cost, in the Netherlands, for used drugs at a maximum dosage.

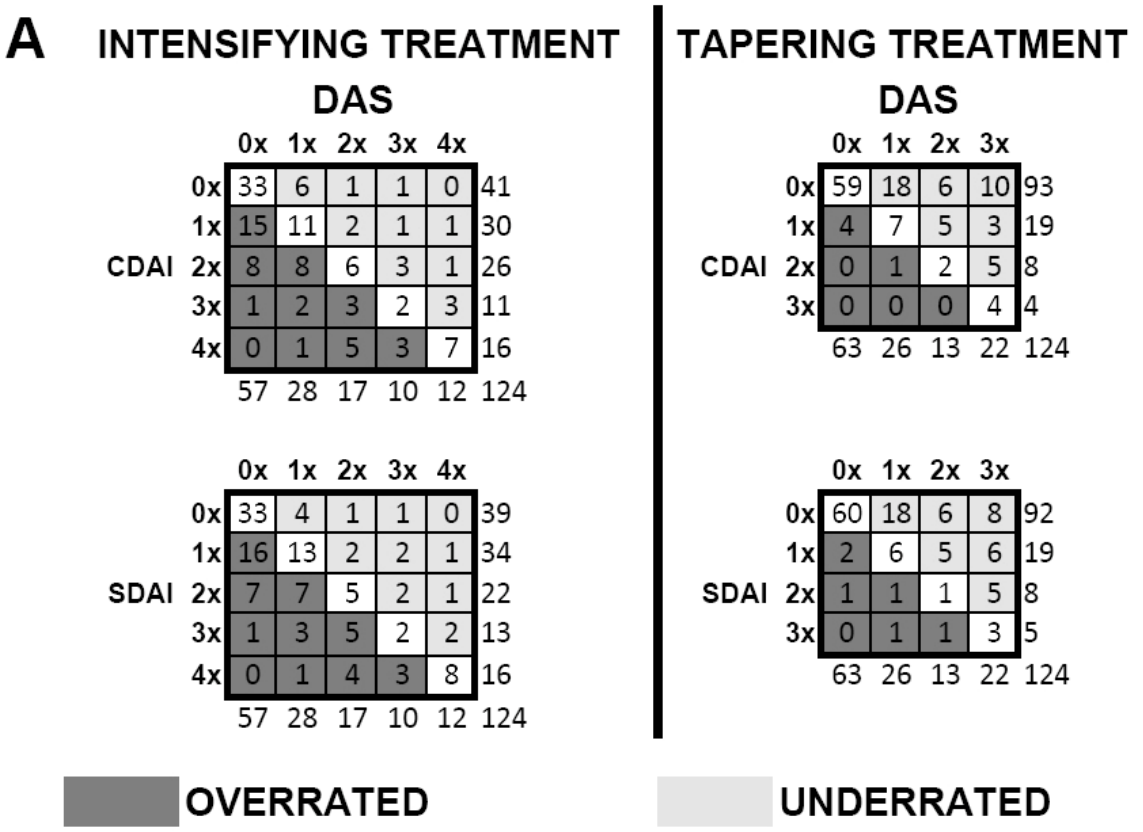
| Generic name | Calculation base | Monthly costs |
|---|---|---|
| Methotrexate (oral) | 25mg/week | € 7.30 |
| Sulfasalazine (oral) | 2000mg/day | € 8.83 |
| Hydroxychloroquine (oral) | 400mg/day | € 7.28 |
| Prednisone (oral) | 10mg/day | € 4.94* |
| Methylprednisolone (im) | 120mg | € 6.12** |
| Etanercept (sc) | 50mg/week | € 1,044.06 |
| Adalimunab (sc) | 40mg/2 weeks | € 1,064.87 |
| Abatacept (iv) | 750mg/4 weeks | € 1,132.82 |
| Naproxen (oral) | 1000mg/day | € 4.32 |
| Folic acid (oral) | 10mg/week | € 1.50 |
| Risedronate (oral) | 35mg/week | € 26.03 |
| Calcium carbonate/colecalciferol (oral) | 500mg/400IE/day | € 7.81 |

Abbreviations: im, intramuscular; iv, intravenous and sc,subcutaneous.

* Total cost of prednisone's gradual discontinuation scheme.

** Costs for 1 intramuscular administration of methylprednisolone

**A**




**B**

| | TREATMENT INTENSIFICATION | | | TREATMENT TAPERING | | |
|---|---|---|---|---|---|---|
| | Agreement | Overrated | Underrated | Agreement | Overrated | Underrated |
| SDAI | 59 (48)* | 46 (37) | 19 (15) | 72 (58)* | 5 (4) | 47 (38) |
| CDAI | 61 (49)* | 47 (40) | 16 (13) | 70 (56)* | 6 (5) | 48 (39) |

| C | Median | Interquartile range |
|---|---|---|
| SDAI† | € 5242.69 | € 264.15 - € 10193.07 |
| CDAI† | € 5226.24 | € 268.87 - € 10193.07 |

## Appendix 3: Simulated treatment reclassifications and annual medication costs for SDAI and CDAI with an EGA=0.5xPGA in RA, according to 2010 criteria.

Reclassification tables for DAS versus respectively SDAI and CDAI are given (fig. 3A). DAIs are concordant in the white areas. Patients are over- (dark-grey areas) and underrated (light-grey areas) if treatment intensification or taperings respectively would have occured more and less frequent than when the DAS was used. The total number of patients (%) who are respectively in agreement, overrated and underrated for treatment intensifications and taperings for each fictive use of SDAI and CDAI versus the use of the DAS are shown in table 3B. Table 3C showns the annual median medication costs for SDAI and CDAI.

*Stuart-Maxwell test (intensifications and taperings investigated seperately): $p<0.05$ compared with DAS.

† SDAI and CDAI differed significantly compared with the DAS (p values <0.0001).

*Abbreviations:* CDAI, Clinical Disease Activity Index; DAS , Disease Activity Score and SDAI, Simplified Disease Activity Index.

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CHAPTER 6

# Response to glucocorticoids at 2 weeks predicts the effectiveness of DMARD induction therapy at 3 months: post hoc analyses from the tREACH study.

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**Objective**
To investigate if a glucocorticoid (GC) response at 2 weeks, defined with EULAR response criteria, can predict active disease (Disease Activity Index (DAS)≥2.4) at 3 months.

**Methods**
For this study data of the treatment in the Rotterdam Ealy Arthritis Cohort study (tREACH), an ongoing clinical trial that evaluates different induction therapies in early rheumatoid arthritis, were used. We selected the patients who had a high probability of progressing to persistent arthritis (>70% based on the prediction model of Visser). All patients within the high probability stratum, who had a baseline DAS>2.2 and a DAS assessment at 2 weeks after randomisation, were included (n=120). Besides GC response at 2 weeks, we investigated which other factors were associated with having active disease (DAS≥2.4) after 3 months of disease-modifying antirheumatic drug (DMARD) treatment. All variables with a p≤0.25 were assessed in our logistic regression model with backward selection. Variables were eliminated until all remaining variables had a significant association (p<0.05).

**Results**
Patients who did not respond to GC bridging therapy at 2 weeks had an overall OR of having active disease at 3 months of 10.29 (95% confidence interval (CI): 3.34 to 31.64; p<0.001) in comparison with responders. The corrected OR was 14.00 (95% CI: 3.31 to 59.21; p<0.001). Our final model predicting response at 3 months included the following variables: gender, GC response, induction therapy arms and baseline DAS, which had an explained variance of 39%.

**Conclusion**
GC response at 2 weeks is a useful tool for recognising those patients who will probably have active disease (DAS≥2.4) after 3 months of DMARD treatment.

**Key words**
- Early Rheumatoid Arthritis; Disease Activity; Treatment; Glucocorticoids

## INTRODUCTION

The EULAR treatment guideline recommends that rheumatologists should strive, in patients with newly diagnosed rheumatoid arthritis (RA), for remission or at least low disease activity within 3 months in order to obtain better functional and radiological outcomes.[1,2] Since the time span for the optimal effect of disease-modifying antirheumatic drugs (DMARDs) is at least 6-12 weeks,[3] the right choice of the initial DMARD has an important role in obtaining recommended treatment goals. The guideline recommends methotrexate (MTX) as anchor drug, but studies show that only about 70% of patients will respond sufficiently to the initial therapy.[4,5] Moreover, we recently showed that a combination of DMARDs shows better remission rates than MTX monotherapy in the early phase of RA.[5] Therefore, it would be helpful to be able to predict treatment response to the initial DMARD treatment as early as possible, ultimately leading to a 'tailor-made' treatment approach.

The huge body of prognostic research till now has mainly focused on predicting long-term destructive and disabling disease in order to guide the initial choice of treatment.[6] In contrast, studies evaluating prediction of treatment response are sparse. Aletaha *et al*[7] demonstrated that high disease activity during the first 3 months of treatment are significantly related to high disease activity at 1 year, which subsequently leads to more destructive and disabling disease. Besides some possible pharmacogenetic markers (eg TYMS polymorphisms affect efficacy of MTX in RA), a clinical applicable predictor for treatment response to classical DMARDs in a very early stage, is unknown.[8]

In line with studies performed in polymyalgia rheumatica a clinical applicable predictor for treatment response in a very early stage might be the initial response to glucocorticoids (GCs).[9] It is well known that GCs have a rapid anti-inflammatory effect, and, therefore, are often used as bridging therapy to treat active disease in the period between initiation of DMARD treatment and onset of their therapeutic effect.[10] However, in RA clinical responses to GCs differ between patients. Sliwinska-Stanczyk *et al*[11] showed that steroid sensitivity of peripheral blood mononuclear cells of RA patients is related to their own observed clinical response to GCs. However, clinical data linking the early effect of GCs to DMARD response in RA are missing. Therefore, our objective was to investigate whether the GC response at 2 weeks, defined according to the EULAR response criteria,[12] predicts DMARD response at 3 months.

## PATIENTS AND METHODS

### Patients

For this study data were used from a current clinical trial (ISRCTN26791028), treatment in the Rotterdam Early Arthritis Cohort (tREACH).[13] The tREACH study, a multicenter, stratified single blinded trial to evaluate different induction treatment strategies in early RA, is being carried out in eight rheumatology centers in the Netherlands. The medical ethics committee at each participating center approved the study protocol, and all patients gave written informed consent before inclusion.

An extended description of the material and methods section of the tREACH study has already been published.[13] Inclusion criteria for the tREACH study are: age ≥18 years, arthritis ≥1 joint and symptom duration <1 year. Eligible patients were stratified into three groups according to their likelihood of progressing to persistent arthritis based on the prediction model of Visser.[14] The three strata (low, intermediate and high) correspond to probability tertiles of developing persistent arthritis according to the Visser model. The Visser algorithm and 2010 criteria for RA have similar discriminative abilities to identify patients at risk of persistent arthritis at 1 year.[15]

For our analysis we selected all patients who had a high probability of developing persistent arthritis and a Disease Activity Score (DAS) assessment at 2 weeks after randomisation. Not all patients in the high-probability stratum had a DAS assessment at 2 weeks, because this assessment was part of a substudy, primarily evaluating differences in GC sensitivity, embedded in the tREACH. Furthermore, patients with a DAS≤2.2 and/or DAS28≤3.3 were excluded, because the EULAR response criteria are only valid in patients having a baseline DAS>2.2 (DAS28>3.3).[12]

### Methods

Patients were randomised, using variable block randomisation stratified for centre, into one of three initial treatment strategies (later referred to as 'induction therapy arms'):

A. Combination therapy (methotrexate (MTX), Sulfasalazine(SSZ) and hydroxychloroquine (HCQ)) with GCs intramuscularly)
B. Combination therapy with an oral GC tapering scheme
C. MTX with an oral GC tapering scheme

DMARD dosages were: MTX 25 mg/week orally or subcutaneously (starting dose 10mg/week, maximum dosage reached after 3 weeks), SSZ first week 1 g/day thereafter 2 g/day and HCQ 400 mg/day. GCs were either given a single intramuscular dose at randomisation (methylprednisolone 120mg or triamcinolone 80mg) or prednisolone in an oral tapering scheme (weeks 1-4: 15 mg/day, weeks 5-6: 10 mg/day, weeks 7-8: 5 mg/day and weeks 9-10: 2.5 mg/day).

We used a treat-to-target approach, with patients being examined every 3 months. Treatment decisions were based, every 3 months, upon the DAS thresholds for low disease activity.[16] When *'treatment failure'* occurred, defined as DAS≥2.4, medication was intensified to MTX with etanercept (50mg/week). Treatment intensifications were the same in each stratum for each treatment arm.

Demographic and disease characteristics of each patient were recorded at baseline. After 2 weeks and 3 months the following variables were assessed: a 44-joint count for swelling, a graded 53-joint count for tenderness,[17] general health and erythrocyte sedimentation rate, which we used to calculate the DAS and 28-joint count DAS (DAS28). At 2 weeks we also determined the EULAR response criteria.[12] EULAR response criteria are based on attained level and change in DAS.

**Statistical analyses**

First, we investigated whether a GC response at 2 weeks, defined according to EULAR response criteria, was associated with DMARD response at 3 months of treatment. Active disease at 3 months was defined as DAS≥2.4. The discriminative ability of GC response at 2 weeks for identifying active disease at 3 months was expressed by sensitivity and specificity. To overcome confounding by medication we also carried out a stratified analysis for induction therapy arms. All analysis were also performed for the DAS28; active disease was defined as DAS28≥3.2.[18]

Furthermore, we determined which other factors were associated with active disease at 3 months by comparing the baseline characteristics of patients with and without active disease after 3 months of DMARD induction therapy. Statistical comparison between baseline characteristics was made by the student t test, $\chi^2$ test, or the Wilcoxon rank-sum test, as appropriate. All variables with a $p \leq 0.25$ together with known prognostic factors (age, gender, disease duration, rheumatoid factor (RF), anti-citrullinated peptide antibodies (ACPA) and baseline DAS) were analysed using univariate and multivariate logistic regression (with backward selection). In our backward selection procedure the variable with the highest p value was eliminated from the model, until all variables in the model had a significant association ($p<0.05$).

All statistical analyses were carried out using STATA V.11.1. A $p<0.05$ was considered statistically significant.

## RESULTS

Of the 281 tREACH patients within the high-probability stratum, 132 patients (47%) had a DAS assessment at 2 weeks after randomisation. Of those patients 12 (9%) were excluded because of a baseline DAS≤2.2. All those patients had a DAS<2.4 at 3 months of follow-up. Table 1 shows the baseline characteristics of the 120 patients. Patients were more often female (65%) and had a median symptom duration of 161 days (97 – 210 days, interquartile range). RF and/or ACPA positivity was present in 92 patients (77%), of those 70 (76%) were both RF and ACPA positive. At baseline 20 patients (17%) had ≥1 erosion typical for RA. Active disease (DAS≥2.4) was found in 113 patients (94%).

**Table 1: Baseline characteristics for patients with a DAS>2.2**

| | **Total population (n=120)** |
|---|---|
| Age (yrs), *median (IQR)* | 54 (44 – 63) |
| Sex, female, *no(%)* | 78 (65) |
| Symptom duration (days), *median (IQR)* | 161 (97 – 210) |
| RF pos., *no(%)* | 78 (65) |
| ACPA pos., *no(%)* | 84 (70) |
| Morning stiffness >1hr., *no(%)* | 93 (78) |
| Erosion, *no(%)* | 20 (17) |
| Fulfillment RA criteria, *no(%)* | |
| • *1987* | 82 (68) |
| • *2010* | 114 (95) |
| DAS, *mean (95% CI)* | 3.43 (3.28 – 3.57) |
| TJC44, *median (IQR)* | 10 (5 – 15) |
| SJC44, *median (IQR)* | 8 (4 – 12) |
| ESR (mm/hr), *median (IQR)* | 22 (13 – 39) |
| General Health (0-100mm), *median (IQR)* | 53 (37 – 66) |
| Treatment, *no (%)* | |
| *A. MTX+SSZ+HCQ+GCs im* | 43 (36) |
| *B. MTX+SSZ+HCQ+GCs oral* | 39 (33) |
| *C. MTX+GCs oral* | 38 (32) |

Abbreviations: ACPA, anti-citrullinated peptide antibodies; CI, confidence interval; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; GCs, glucocorticoids; HCQ, hydroxychloroquine; im, intramuscular; IQR, interquartile range; MTX, methotrexate; RA, rheumatoid arthritis; RF, rheumatoid factor; SJC44, swollen joint count (44 joints); SSZ, sulfasalazine; TJC44, tender joint count (44 joints).

The relation between GC response at 2 weeks, defined according to the EULAR response criteria, and having active disease after 3 months of induction DMARD treatment is shown in table 2A. A total of 39 out of 78 patients with a DAS<2.4 after 3 months of DMARD treatment (50%), were classified as good GC responders, whereas this was only the case for 6 out of 42 patients(14%) who still had active disease (DAS≥2.4). Vice versa, in patients with a DAS<2.4 only 12 of 78 patients (15%) did not respond initially to GC bridging therapy as distinct from 19 of 42 patients (45%) who had an active disease who were GC non-responders. Patients who do not respond to GC bridging therapy at 2 weeks had an overall odds ratio (OR) of having active disease at 3 months of 10.29 (95% CI: 3.34 to 31.64;p<0.001) in comparison with responders.

Table 2B demonstrates the relationship between GC response and disease activity states stratified for induction therapy arms. The OR (95% CI) for active disease of being a non-GC responder relative to a good-GC responder for treatment arms (A), (B) and (C) is, respectively, 4.2 (0.75 to 23.18); 10.7 (0.98 to 115.7) and infinite. In treatment arm C, which is current recommended induction therapy, all GC none-responders have active disease at 3 months. The same analysis was performed for DAS28 instead of DAS, and showed similar results (see supplementary tables S1 and S2).

**Table 2: Overall relationship between active disease (DAS≥2.4) after 3 months of induction DMARD therapy and response to GCs at 2 weeks (A) and also stratified for induction therapy arms (B).**

**A.**

| | **Active disease** | |
|---|---|---|
| **Response to GCs at 2 weeks** | YES (n=42) | NO (n=78) |
| • Good, *no(%)* | 6 (13) | 39 (87) |
| • Moderate, *no(%)* | 17 (39) | 27 (61) |
| • None, *no(%)* | 19 (61) | 12 (39) |

**B.**

| | **Active disease** | |
|---|---|---|
| **Response to GCs at 2 weeks** | YES (n=42) | NO (n=78) |
| A. MTX+SSZ+HCQ+GCs im, *no(%)* | | |
| • *Good* | 3 (17) | 15 (83) |
| • *Moderate* | 3 (21) | 11 (79) |
| • *None* | 5 (45) | 6 (55) |
| B. MTX+SSZ+HCQ+GCs oral, *no(%)* | | |
| • *Good* | 1 (6) | 16 (94) |
| • *Moderate* | 5 (42) | 7 (58) |
| • *None* | 4 (40) | 6 (60) |
| C. MTX+GCs oral, *no(%)* | | |
| • *Good* | 2 (20) | 8 (80) |
| • *Moderate* | 9 (50) | 9 (50) |
| • *None* | 10 (100) | 0 (0) |

Abbreviations: DAS, Disease Activity Score; DMARDs, disease-modifying antirheumatic drugs; GCs, glucocorticoids; HCQ, hydroxychloroquine; im, intramuscular; MTX, methotrexate, SSZ, sulfasalazine.

To determine the discriminative ability of GC response at 2 weeks for identifying active disease at 3 months, the following two cut-offs were used: (1) being a non-responder to GC or not and (2) being a non-responder or moderate responder to GC or not. The sensitivity (95% CI) and specificity (95% CI) of GC response to identify active disease, using the first cut-off point, were ,respectively, 45% (30% to 61%) and 85% (75% to 92%). For the second cut-off point the calculated sensitivity (95% CI) and specificity (95% CI) were, respectively, 86% (72% to 95%) and 50% (39% to 62%).

Second, we investigated which other factors were associated with having active disease after 3 months of DMARD treatment (table 3). Besides known prognostic factors (age, gender, disease duration, RF, ACPA and baseline DAS), other possible variables associated with active disease after 3 months of DMARD treatment are type of induction therapy (treatment arm (A), (B) or (C)), presence of erosions and the components of the baseline DAS, except swollen joint count. Table 4 shows the univariate logistic regression (4A) and final multivariate model (4B), after backward selection, for the prediction of active disease after 3 months of DMARD induction therapy. The final model had an explained variance of 39%. The same analysis was performed for DAS28 instead of DAS, which showed similar results (see supplementary table S3).

**Table 3: Comparing baseline characteristics of patients with and without active disease (DAS≥2.4) after 3 months of induction DMARD treatment.**

| | **Active disease** | | **p value** |
|---|---|---|---|
| | YES (n=42) | NO (n=78) | |
| Age (yrs), *median (IQR)* | 55 (45 – 63) | 54 (43 – 64) | 0.69 |
| Sex, female, *no(%)* | 35 (83) | 43 (55) | 0.002 |
| Symptom duration (days), *median (IQR)* | 139 (92 – 208) | 164 (116 – 214) | 0.30 |
| RF pos., *no(%)* | 24 (57) | 54 (69) | 0.19 |
| ACPA pos., *no(%)* | 27 (64) | 57 (73) | 0.31 |
| Morning stiffness >1hr., *no(%)* | 33 (79) | 60 (77) | 0.84 |
| Erosion, *no(%)* | 4 (10) | 16 (21) | 0.12 |
| Fulfillment RA criteria, *no(%)* | | | |
| • *1987* | 28 (67) | 54 (69) | 0.77 |
| • *2010* | 42 (100) | 72 (92) | 0.07 |
| DAS, *mean (95% CI)* | 3.89 (3.65 – 4.14) | 3.17 (3.02 – 3.34) | <0.0001 |
| TJC44, *median (IQR)* | 14 (10 – 21) | 7 (3 – 14) | <0.0001 |
| SJC44, *median (IQR)* | 8.5 (4 – 12) | 8 (4 – 12) | 0.95 |
| ESR (mm/hr), *median (IQR)* | 29 (17 – 45) | 20 (12 – 34) | 0.03 |
| General Health (0-100mm), *median (IQR)* | 54 (50 – 70) | 51.5 (30 – 65) | 0.02 |
| Treatment, *no (%)* | | | |
| *A. MTX+SSZ+HCQ+GCs im* | 11 (26) | 32 (41) | 0.11 |
| *B. MTX+SSZ+HCQ+GCs oral* | 10 (24) | 29 (37) | 0.14 |
| *C. MTX+GCs oral* | 21 (50) | 17 (22) | 0.002 |

Abbreviations: ACPA, anti-citrullinated peptide antibodies; CI, confidence interval; DAS, Disease Activity Score; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; GCs, glucocorticoids; HCQ, hydroxychloroquine; im, intramuscular; IQR, interquartile range; MTX, methotrexate; RA, rheumatoid arthritis; RF, rheumatoid factor; SJC44, swollen joint count (44 joints); SSZ, sulfasalazine; TJC44, tender joint count (44 joints).

**Table 4: Predicting active disease (DAS≥2.4) at 3 months with (prognostic) variable(s), using univariate logistic regression (A) and a logistic regression model with backward selection (B).**

**A.**

| | OR (95% CI) | p value |
|---|---|---|
| Age (years) | 1.01 (0.98 – 1.03) | 0.72 |
| Sex (1=female) | 4.07 (1.61 – 10.27) | 0.003 |
| Symptom duration (days) | 1.00 (0.99 – 1.00) | 0.387 |
| RF (1=positive) | 0.59 (0.27 – 1.29) | 0.187 |
| ACPA (1=positive) | 0.66 (0.30 – 1.48) | 0.318 |
| Erosion typical for RA (1=present) | 0.41 (0.13 – 1.31) | 0.132 |
| Response to GCs at 2 weeks (ref. = good) | | |
| • *Moderate* | 4.09 (1.43 – 11.72) | 0.009 |
| • *None* | 10.29 (3.34 – 31.64) | <0.001 |
| Treatment *(ref. =MTX+GCs oral)* | | |
| • *MTX+SSZ+HCQ+GCs im* | 0.28 (0.11 – 0.71) | 0.007 |
| • *MTX+SSZ+HCQ+GCs oral* | 0.28 (0.11 – 0.73) | 0.009 |
| DAS | 3.50 (1.95 – 6.30) | <0.001 |
| SJC44 | 1.01 (0.95 – 1.08) | 0.704 |
| TJC44 | 1.13 (1.06 – 1.19) | <0.001 |
| ESR (mm/hr) | 1.01 (1.00 – 1.04) | 0.062 |
| General Health (0-100mm) | 1.02 (1.00 – 1.04) | 0.017 |

**B.**

| | OR (95% CI) | p value |
|---|---|---|
| Sex (1=female) | 5.98 (1.67 – 21.40) | 0.006 |
| Response to GCs at 2 weeks (ref. = good) | | |
| • *Moderate* | 1.67 (0.48 – 5.88) | 0.424 |
| • *None* | 14.00 (3.31 – 59.21) | <0.001 |
| Treatment *(ref. = MTX+GCs oral)* | | |
| • *MTX+SSZ+HCQ+GCs im* | 0.25 (0.07 – 0.90) | 0.03 |
| • *MTX+SSZ+HCQ+GCs oral* | 0.18 (0.05 – 0.69) | 0.01 |
| DAS | 5.54 (2.55 – 12.04) | <0.001 |

Abbreviations: ACPA, anti-citrullinated peptide antibodies; CI, confidence interval; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; GCs, glucocorticoids; HCQ, hydroxychloroquine; im, intramuscular; MTX, methotrexate; OR, odds ratio; RA, rheumatoid arthritis; RF, rheumatoid factor; SJC44, swollen joint count (44 joints); SSZ, sulfasalazine; TJC44, tender joint count (44 joints).

## DISCUSSION

We investigated if a GC response at 2 weeks, defined by EULAR response criteria, can predict active disease after 3 months of DMARD induction therapy. Patients who do not respond to GC bridging therapy at 2 weeks have an overall OR of having active disease at 3 months of 10.29 (95% CI 3.34 to 31.64;p<0.001) in comparison with responders. If we stratify for induction therapy arms ORs (95% CI) were 4.2 (0.75 to 23.18); 10.7 (0.98 to 115.7) and infinite for respectively treatment arms (A), (B) and (C). In treatment arm C, MTX with an oral GC tapering scheme, all GC none-responders have active disease after 3 months of DMARD treatment. Until now a clinical applicable predictor for treatment response of classical DMARDs in the very early stage was missing. However, we have shown that assessment of disease activity at 2 weeks, reflecting initial response to GCs, might be a predictor of active disease after 3 months of induction DMARD treatment.

Although our data do not necessarily indicate a direct causal association it is tempting to speculate about possible synergistic effects of GCs and DMARDs. GCs and DMARDs have mutual anti-inflammatory pathways. The anti-inflammatory actions of GCs are mediated via the GC receptor and include an transrepressive effect on the transcription factor nuclear factor kappa B (NF-κB).[19] Other studies have shown that SSZ and MTX both suppress activation of NF-κB by inhibiting degradation of IκBα in vitro.[20,21] Another mutual pathway might be the effect of GCs and DMARDs on the intracellular levels of cyclic AMP (cAMP). GCs and DMARDs elicit a rise in intracellular cAMP levels, resulting in inhibition of proinflammatory cytokine production.[22,23] Because of these mutual anti-inflammatory pathways it can be hypothesized that GC response reflects DMARD response, especially with MTX and/or SSZ usage.

Other non-modifiable baseline predictors associated with active disease after 3 months of DMARD induction therapy are gender and baseline DAS. The only modifiable baseline predictor is the choice of induction therapy. First, the relationship between gender and active disease is probably found because women experience more pain, resulting in higher DAS values and more functional impairment than men.[24,25] Second, the baseline disease activity is an important predictor of disease activity (states) during follow-up, which is reconfirmed in our study.[26] Finally, the choice of induction therapy, which is the only modifiable predictor at presentation, determines the clinical response.

The EULAR treatment guideline recommends a treat-to-target approach in which rheumatologists should strive for remission or low disease activity within 3 months, in patients with newly diagnosed RA with active disease.[2] Until the desired target is reached, treatment should be altered every 1-3 months.[2] Recommended induction therapy consists of MTX with or without GCs.[1] However, some points in the mentioned recommendation can be discussed.

First, the choice of induction therapy wherein DMARD monotherapy is preferred over a combination of DMARDs. Current guidelines are based upon a systemic review[27], which concluded that in DMARD-naïve patients the efficacy/toxicity ratio favours MTX monotherapy over combination therapy. However, in this review triple DMARD therapy versus MTX monotherapy in DMARD-naïve patients was not compared. Furthermore, trials favouring triple DMARD therapy (BeSt, FIN-RACo and COBRA trial) were excluded from this review.[4,28,29] In a previous publication we have already shown that in patients with early RA a combination of DMARDs is better than MTX monotherapy in achieving low disease activity after 3 months[5], which is supported by a recent systemic review by Graudal and Jürgens.[30]

Second, the time span for the optimal effect of DMARDs takes at least 6-12 weeks[3], and thus the right choice of induction DMARD treatment has an important role in obtaining recommended treatment goals. Furthermore, several studies have shown that only about 70% will respond sufficiently to the initial treatment.[4,5] A tailor-made treatment approach might be preferable, however, no clinical applicable predictors for early treatment response are available.

Therefore, in daily practice we advise starting with a combination of DMARDs. However, if MTX monotherapy is preferred, either by the rheumatologist or patient, we recommend combining MTX with a GC bridging scheme and determining the response to GCs after 2 weeks. Patients who do not respond to GCs after 2 weeks have a higher risk of not reaching the treatment goals and, therefore, a higher risk of a poorer outcome. It seems sensible to intensify the initiated DMARD treatment, if patients do not respond to GC after 2 weeks.

Our study had certain limitations. First, sample size calculations were not based upon our research question and therefore we had a small sample size, especially restricting the stratified analysis for induction therapy arms. Despite the small sample size we found significant ORs for active disease after 3 months of DMARD treatment of approximately 10 for non-responders relative to good responders.

Second, not all patients in the high-probability stratum had a DAS assessment at 2 weeks, which possibly introduces a selection bias. The DAS assessment at 2 weeks was part of a substudy, primarily evaluating differences in GC sensitivity. Inclusion in the tREACH and the mentioned substudy started concurrently, with all randomised patients automatically enrolled in the substudy. The DAS assessment at 2 weeks was terminated, because the substudy had reached its predefined sample size. Therefore, we think that a significant selection bias did not arise.

Third, the requirements for EULAR response criteria are a baseline DAS>2.2, as a result of which 12 patients (9%) were excluded from the analyses. Consequently, in daily practice we cannot use a GC response to predict DMARD response in patients with a low baseline DAS. In our study, however, we showed that none of the patients with a baseline DAS≤2.2 had active disease after 3 months of DMARD treatment. Therefore, if adequate DMARD treatment is initiated, we can assume that patients with a baseline DAS≤2.2 will respond to this treatment. Future research is necessary to validate our findings and to evaluate the clinical applicability of GC response as a prediction tool in daily practice.

In conclusion, determining GC response at 2 weeks is a useful tool for recognising those patients who will probably have active disease (DAS≥2.4) after 3 months of DMARD treatment.

## Supplement 1: Relationship between GC response at 2 weeks and active disease at 3 months using the DAS28, and patients with a baseline DAS28>3.3 (n=120)

NOTE: 12 patients had a baseline DAS28≤3.3. All these patients had a DAS28<3.2 after 3 months of DMARD treatment.

**Table 1: Baseline characteristics for patients with a DAS28 >3.3, also stratified for active disease (DAS28≥3.2) after 3 months of induction DMARD treatment.**

| | **Total population** | **Active disease** | | **p value*** |
|---|---|---|---|---|
| | **(n=120)** | YES (n=59) | NO (n=61) | |
| Age (years)*, median (IQR)* | 55 (45 – 64) | 55 (46 – 63) | 54 (44 – 66) | 0.62 |
| Sex, female*, no(%)* | 79 (66) | 45 (76) | 34 (56) | 0.02 |
| Symptom duration (days)*, median (IQR)* | 161 (96 – 201) | 137 (88 – 197) | 172 (133 – 214) | 0.07 |
| RF pos.*, no(%)* | 78 (65) | 37 (63) | 41 (67) | 0.61 |
| ACPA pos.*, no(%)* | 84 (70) | 41 (69) | 43 (70) | 0.90 |
| Morning stiffness >1hr.*, no(%)* | 93 (78) | 46 (78) | 47 (77) | 0.90 |
| Erosion*, no(%)* | 20 (17) | 8 (14) | 12 (20) | 0.37 |
| Fulfillment RA criteria, *no(%)* | | | | |
| • *1987* | 83 (69) | 42 (71) | 41 (67) | 0.64 |
| • *2010* | 114 (95) | 58 (98) | 56 (92) | 0.10 |
| DAS28*, mean (95% CI))* | 4.96 (4.78 – 5.14) | 5.30 (5.05 – 5.55) | 4.63 (4.39 – 4.87) | 0.0002 |
| TJC28*, median (IQR)* | 6 (2 – 10) | 4 (8 – 13) | 4 (2 – 9) | 0.001 |
| SJC28*, median (IQR)* | 6 (4 – 10) | 6 (4 – 10) | 6 (3 – 10) | 0.95 |
| ESR (mm/hr), *median (IQR)* | 22.5 (13 – 39) | 24 (16 – 44) | 20 (13 – 34) | 0.07 |
| General Health (0-100mm), *median (IQR)* | 53 (37.5 – 67.5) | 55 (49 – 71) | 52 (29 – 62) | 0.02 |
| Treatment, *no (%)* | | | | |
| *A. MTX+SSZ+HCQ+GCs im* | 42 (35) | 18 (31) | 24 (39) | 0.31 |
| *B. MTX+SSZ+HCQ+GCs oral* | 40 (33) | 17 (29) | 23 (38) | 0.30 |
| *C. MTX+GCs oral* | 38 (32) | 24 (41) | 14 (23) | 0.04 |

*p value= testing difference in baseline characteristics between patients with and without active disease after 3 months of induction DMARD treatment.

Abbreviations: ACPA, Anti-citrullinated peptide antibodies; CI, Confidence Interval; DAS28, Disease Activity Score with an 28 joint count; ESR, Erythrocyte Sedimentation Rate; GCs, glucocorticoids; HCQ, hydroxychloroquine; im, intramuscular; IQR, Interquartile range; MTX, methotrexate; RF, Rheumatoid Factor; SSZ, sulfasalazine; SJC28, Swollen Joint Count (28 joints); TJC28, Tender Joint Count (28 joints).

**Table 2: Overall relationship between active disease (DAS28≥3.2) after 3 months of induction DMARD treatment and response to GCs at 2 weeks (A) and also stratified for induction therapy (B).**

**A.**

| Response to GCs at 2 weeks | Active disease YES | NO |
|---|---|---|
| • Good, *no(%)* | 11 (23) | 36 (77) |
| • Moderate, *no(%)* | 26 (53) | 23 (47) |
| • None, *no(%)* | 22 (92) | 2 (8) |

**B.**

| Response to GCs at 2 weeks | Active disease YES | NO |
|---|---|---|
| MTX+SSZ+HCQ+GCs im, *no(%)* | | |
| • *Good* | 4 (25) | 12 (75) |
| • *Moderate* | 6 (35) | 11 (65) |
| • *None* | 8 (89) | 1 (11) |
| MTX+SSZ+HCQ+GCs oral, *no(%)* | | |
| • *Good* | 2 (11) | 16 (89) |
| • *Moderate* | 11 (65) | 6 (35) |
| • *None* | 4 (80) | 1 (20) |
| MTX+GCs oral, *no(%)* | | |
| • *Good* | 5 (38) | 8 (62) |
| • *Moderate* | 9 (60) | 6 (40) |
| • *None* | 10 (100) | 0 (0) |

**Table 3: Predicting active disease (DAS28≥3.2) at 3 months with (prognostic) variable(s), using univariate logistic regression (A) and a logistic regression model with backward selection (B).**

**A.**

| | OR (95% CI) | p value |
|---|---|---|
| Age (years) | 1.01 (0.98 – 1.03) | 0.68 |
| Sex (1=female) | 2.55 (1.17 – 5.59) | 0.02 |
| Symptom duration (days) | 1.00 (0.99 – 1.00) | 0.14 |
| RF (1=positive) | 0.82 (0.39 – 1.74) | 0.61 |
| ACPA (1=positive) | 0.95 (0.44 – 2.08) | 0.91 |
| Erosion typical for RA (1=present) | 0.64 (0.24 – 1.70) | 0.37 |
| Response to GCs at 2 weeks (ref. = good) | | |
| • *Moderate* | 3.70 (1.54 – 8.90) | 0.003 |
| • *None* | 36 (7.29 – 177.82) | <0.001 |
| Treatment *(ref. = MTX+GCs oral)* | | |
| • *MTX+SSZ+HCQ+GCs im* | 0.44 (0.18 – 1.07) | 0.07 |
| • *MTX+SSZ+HCQ+GCs oral* | 0.43 (0.17 – 1.07) | 0.07 |
| DAS28 | 2.10 (1.39 – 3.18) | <0.001 |
| SJC28 | 0.99 (0.92 – 1.06) | 0.77 |
| TJC28 | 1.12 (1.04 – 1.21) | 0.003 |
| ESR (mm/hr) | 1.02 (1.00 – 1.04) | 0.05 |
| General Health (0-100mm) | 1.02 (1.00 – 1.04) | 0.02 |

**B.**

| | OR (95% CI) | p value |
|---|---|---|
| Response to GCs at 2 weeks (ref. = good) | | |
| • *moderate* | 2.29 (0.87 – 6.00) | 0.09 |
| • *none* | 30.35 (6.00 – 153.45) | <0.001 |
| DAS28 | 1.96 (1.20 – 3.18) | 0.007 |

Abbreviations: ACPA, anti-citrullinated peptide antibodies; CI, confidence interval; DAS28, Disease Activity Score with an 28 joint count; ESR, erythrocyte sedimentation rate; GCs, glucocorticoids; HCQ, hydroxychloroquine; im, intramuscular; MTX, methotrexate; OR, odds ratio; RA, rheumatoid arthritis; RF, rheumatoid factor; SJC28, swollen joint count (28 joints); SSZ, sulfasalazine; TJC28, tender joint count (28 joints).

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CHAPTER 7

# Brief Report: To squeeze or not to squeeze, that is the question! Optimizing the disease activity score in 28 joints by adding the squeeze test of metatarsophalangeal joints in early rheumatoid arthritis.

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**Objective**
To optimize use of the Disease Activity Score in 28 joints (DAS28) in early rheumatoid arthritis (RA) by adding the 'squeeze test' of forefeet.

**Methods**
The squeeze test is used to examine bilateral compression pain (BCP) across the metatarsophalangeal (MTP) joints. For this study, data for patients participating in the treatment in the Rotterdam Early Arthritis Cohort study, an ongoing clinical trial that evaluates different induction therapies in patients with early RA, were randomly divided into 2 subsets. In subset 1 (149 patients and 819 disease activity assessments), the mathematical function of the DAS28-squeeze was constructed using a linear regression model with the DAS as the dependent variable and the DAS28 and squeeze test as the independent variables. A DAS28-BCP disease state was also constructed, in which DAS28 disease state categorizations were upgraded one state if the result of the squeeze test was positive. In subset 2 (153 patients and 754 assessments), concordance in disease states between the DAS28, DAS28-squeeze, and DAS28-BCP disease states was compared, using both the DAS and Boolean-defined remission criteria as reference.

**Results**
Agreement between the DAS and the DAS28-squeeze (82%) was significantly higher than agreement between the DAS and the DAS28 (76%). When we assessed the group of patients who had arthritis of the forefeet only (22 patients and 46 assessments), overall agreement between the DAS and the DAS28 was 40%, while agreement between the DAS and the DAS28-squeeze was 59% and that between the DAS and the DAS28-BCP disease state was 65%. Furthermore, the specificities of the DAS28-squeeze and the DAS28-BCP (80% and 81%, respectively) were higher than that of the DAS28 (76%), while the sensitivities of the DAS28, DAS28-squeeze, and DAS28-BCP to identify true remission according to the Boolean criteria were 88%, 87%, and 81%, respectively.

**Conclusion**
Adding the squeeze test of forefeet to the DAS28 has value for dependably classifying the disease state in patients with early RA.

**Key words**
- Forefoot; Squeeze test; Metatarsophalangeal joints; DAS28

## INTRODUCTION

In the last 2 decades, significant progress was made in understanding the underlying pathophysiologic mechanism of and treatment modalities for rheumatoid arthritis (RA). This ultimately led to the unassailable need for early detection of the disease, early initiation of intensive therapy, and 'tight control' followup driven by regular measurements of disease activity.[1]

Tight-control monitoring of disease activity in clinical practice is commonly performed using the Disease Activity Score in 28 joints (DAS28)[2], because it is easy to perform. The DAS28 comprises a 28-joint count excluding the feet. However, at the time of presentation, ~60% of patients with early RA had forefoot involvement; after 2 years, the prevalence decreased to 36% and then stabilized.[3] Moreover, patients with disease in remission according to the DAS28 may have relatively large numbers of 'residual joint counts,' especially swollen joints.[4] According to a recent report, ~40% of patients with disease in remission according to the DAS28 had forefoot involvement (pain and/or swelling in at least 1 metatarsophalangeal [MTP] joint. [5]

In daily practice, however, assessment of MTP joint synovitis is cumbersome[6]; therefore, an alternative simple test to include foot involvement might be of added value to assess disease activity at an early stage, whereupon treatment decisions could be made. The squeeze test of forefeet, which examines bilateral compression pain (BCP) across the MTP joints (Figure 1), might be such a test.

Therefore, our objective was to analyze whether DAS28 disease state assessments in patients with a diagnosis of RA according to the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria[7,8] could be improved by adding the 'squeeze test.'

## PATIENTS AND METHODS

### Patients

For this study, we used data from the ongoing treatment in the Rotterdam Early Arthritis Cohort (tREACH) study.[9] The tREACH study, a multicenter, stratified, single-blind trial evaluating different induction treatment strategies in early RA, is performed in 8 rheumatology centers in The Netherlands. Patients are examined every 3 months, and treatment decisions are based on the original DAS thresholds. [72,65] The medical ethics committee at each participating center approved the study protocol, and all patients gave written informed consent before inclusion. For the present analysis, we selected patients who had a randomisation date before December 1, 2010 and fulfilled the 2010 ACR/EULAR criteria for RA.[7,8]

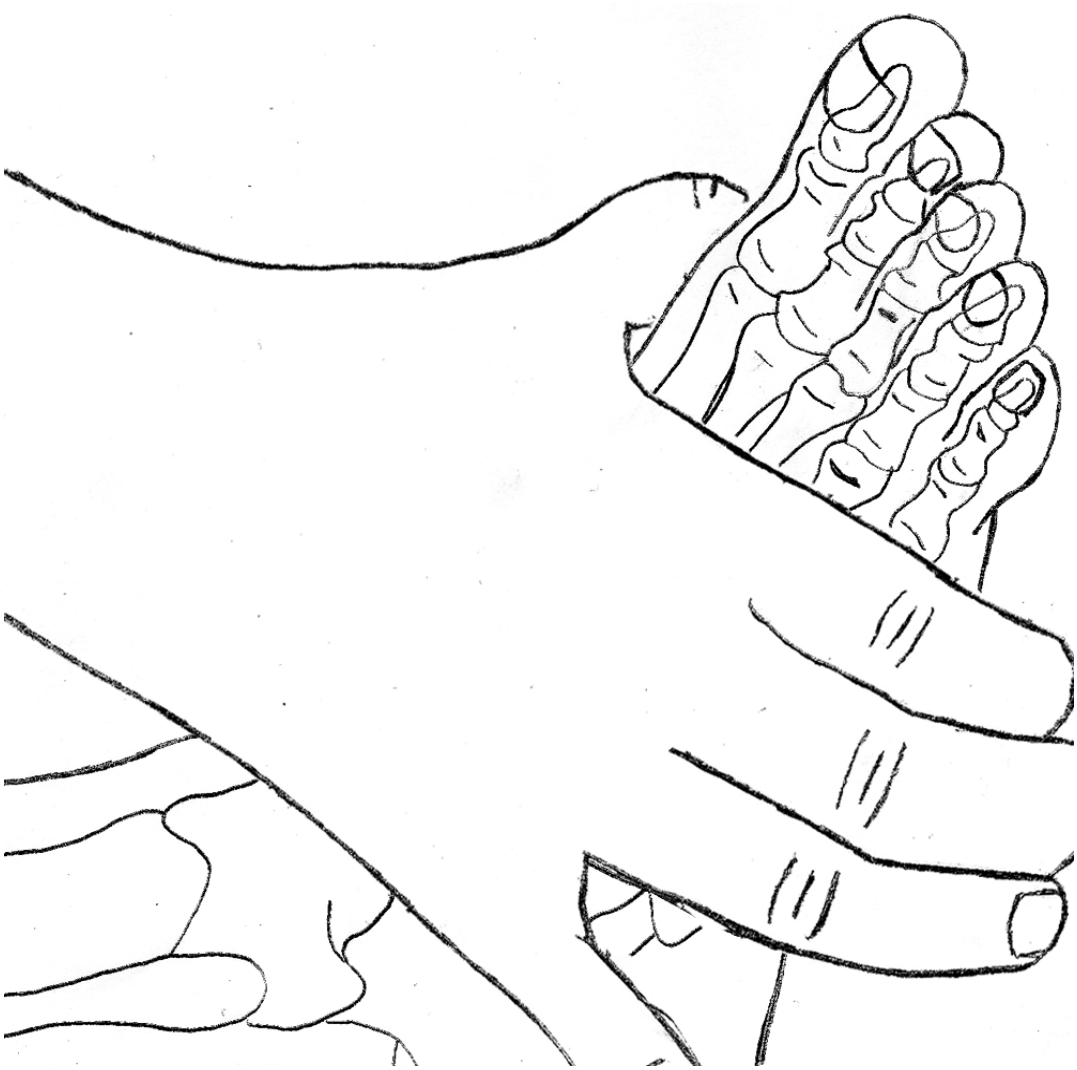


**Figure 1:** The squeeze test of forefeet. The squeeze test is performed by placing the thumb just below the first metatarsophalangeal (MTP) joint (to prevent direct compression of this joint) and placing the index finger over the fifth MTP joint. The metatarsal joints are then compressed bilaterally, using a force equal to a handshake.

## Methods

The clinical characteristics of each patient were recorded at baseline. At each 3-month visit, the following variables were assessed: a 44-joint count for swelling, a graded 53-joint count for tenderness (Ritchie Articular Index [RAI])[11,12], squeeze test of MTPs, general health, patient's global assessment of disease activity (PGA), erythrocyte sedimentation rate, and C-reactive protein (CRP). The squeeze test was performed after completion of the joint examination. The squeeze test of MTP joints (Figure 1) is performed by placing the thumb and index finger, respectively, just below the first MTP joint and over the fifth MTP joint. The thumb is placed just below the first MTP joint to prevent direct compression of this joint. Thereafter, the metatarsal joints are bilaterally compressed, using a force equal to a handshake. The DAS and DAS28 thresholds for remission and moderate-to-high disease activity were <1.6 and ≥2.4 and <2.6 and ≥3.2, respectively.

### Statistical analyses

For this study, patients were randomly divided into 2 subsets. The first subset (n=149 patients) was used to develop a new disease activity measure, the DAS28-squeeze. In the second subset (n=153 patients), the DAS28-squeeze was validated. Comparisons between the baseline characteristics of patients in each subset were performed using student's t tests, chi-square tests, or Wilcoxon's rank sum tests, when appropriate.

In subset 1 (development group), the mathematical function of the DAS28-squeeze was constructed with a linear regression model with the DAS as the dependent variable and the DAS28 and squeeze test as the independent variables. The constant was suppressed to preserve an uncomplicated model. To provide insight into the stability of the estimated model, we performed an additional bootstrap analysis[13] 100 times, and the average weighted coefficients were added to the model. This model was then validated in subset 2 (validation group) by predicting the DAS based on the new formula.

In addition, we constructed a simpler model, the DAS28-BCP disease state, in which the disease state of patients is determined by the DAS28, and patients with a positive squeeze test result on either side are upgraded to a higher disease state (i.e., from remission to low disease activity).

Scatter plots were used to visualize the performance of the DAS28, DAS28-squeeze, and DAS28-BCP disease states compared with the DAS, as reference for each disease state. The Stuart-Maxwell test was used to assess agreement between disease state categorizations.[14] We also tested concordance in remission rates between the recently described Boolean-defined remission criteria[109] and remission according to the DAS28, the DAS28-squeeze, and the DAS28-BCP disease states. The Boolean-defined remission criteria are as follows: at any time point, the patient must have a tender joint count (TJC) of ≤1, a swollen joint count (SJC) of ≤1, a CRP level of ≤1 mg/dl, and a PGA of ≤1 on a 0–10 scale.[15,16] Both a 28-joint count and a 44-joint count for tenderness and swelling were used for the Boolean remission criteria. The discriminative abilities of the DAS28, the DAS28-squeeze, and the DAS28-BCP disease states for identifying true remission (Boolean criteria) were expressed by sensitivity and specificity.

All statistical analyses were carried out using Stata version 11.1. P values less than 0.05 were considered significant.

## RESULTS

### Baseline characteristics

Table 1 shows the baseline characteristics of the 2 subsets of patients used to develop (n=149) and validate (n=153) the DAS28-squeeze and DAS28-BCP disease states. Patients in both subsets represented a common population of patients with early RA. No difference between the subsets was observed except for morning stiffness duration of >1 hour (p=0.03).

**Table 1. Baseline characteristics of the patients with rheumatoid arthritis in the subsets used to develop and validate the DAS28-squeeze***

| | Development group (n=149) | Validation group (n=153) |
|---|---|---|
| Age (years), *mean (95% CI)* | 55 (53 - 57) | 52 (50 - 55) |
| Sex, female | 99 (66) | 106 (69) |
| Symptom duration (days), *mean (95% CI)* | 159 (144 - 174) | 152 (139 - 166) |
| RF pos. | 84 (56) | 88 (58) |
| ACPA pos. | 88 (59) | 84 (55) |
| Erosions | 19 (13) | 28 (18) |
| Morning stiffness >1hour.† | 115 (77) | 133 (87) |
| No. of tender joints, *median (IQR)* | | |
| • *44 joints* | 11 (5 - 15) | 10 (5 - 16) |
| • *28 joints* | 6 (3 - 10) | 6 (2 - 10) |
| Ritchi Articular Index (RAI), *median (IQR)* | 8 (5 - 11) | 7 (4 - 10) |
| No. of swollen joints, *median (IQR)* | | |
| • *44 joints* | 8 (4 - 12) | 8 (4 - 12) |
| • *28 joints* | 6 (3 - 10) | 6 (3 - 10) |
| Forefoot involvement | 122 (82) | 118 (77) |
| • *Swelling* | 76 (51) | 76 (50) |
| • *pain* | 108 (72) | 106 (69) |
| Squeeze test | | |
| • *Positive 1-sided test result* | 31 (21) | 30 (20) |
| • *Positive 2-sided test result* | 64 (43) | 59 (39) |
| General Health (0–100mm), *median (IQR)* | 54 (34 - 68) | 50 (30 - 67) |
| PGA (0 – 10), *median (IQR)* | 6 (4 - 8) | 6 (4 - 8) |
| ESR (mm/hr), *median (IQR)* | 22 (12 - 39) | 21 (11 - 39) |
| CRP (mg/dl), *median (IQR)* | 7 (4 - 18) | 7 (4 - 20) |
| DAS, *mean (95% CI)* | 3.43 (3.28 - 3.59) | 3.37 (3.21 - 3.53) |
| DAS28, *mean (95% CI)* | 4.82 (4.62 - 5.02) | 4.88 (4.66 - 5.09) |

* Except where indicated otherwise, values are the number (%).

†p = 0.03 versus development group.

Abbreviayions: ACPA, anti–citrullinated protein antibody;CI, confidence interval; CRP, C-reactive protein; DAS, disease activity score; DAS28, Disease activity score using an 28 joint count; DAS28-squeeze, Disease Activity Score in 28 joints with the addition of the squeeze test of forefeet; ESR, erythrocyte sedimentation rate; IQR, interquartile range; PGA, Physician's global assessment and RF, Rheumatoid Factor.

### Development of DAS28-squeeze

In the development subgroup (149 patients and 819 assessments) the DAS28-squeeze was constructed using linear regression and had the following mathematical formula: DAS28-squeeze = 0.64 x DAS28 + 0.23 x squeeze test. The squeeze test was coded as follows: 0 = test negative on both forefeet, 1 = test positive on 1 side, 2 = test positive on both forefeet. We set DAS28-squeeze thresholds for remission and moderate-to-high disease activity at <1.6 and ≥2.4, respectively, in accordance with DAS (dependent variable) thresholds. The DAS28-squeeze model had an explained variance of 97.5%. We also created more complicated DAS28-squeeze models by using the quadratic term and natural logarithm of the squeeze test. However, these models had similar explained variances and were therefore not used.

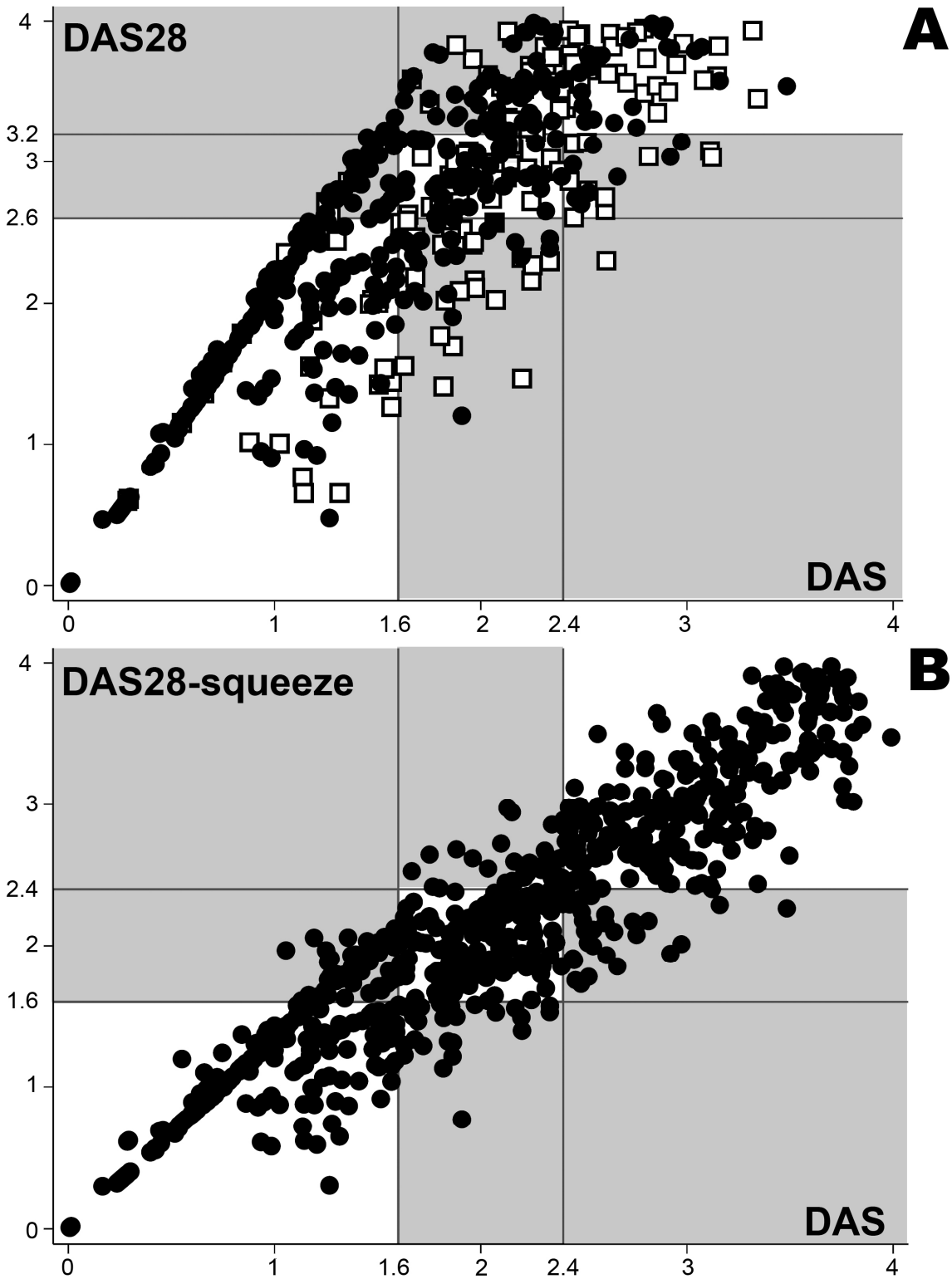
**Validation and agreement in disease state categorizations**

Overall data were available for 153 patients (754 assessments) in the validation subgroup. The correlations between the DAS and the DAS28 and between the DAS and the DAS28-squeeze were 93% and 94%, respectively. However, concordance of disease state categorizations between the DAS, DAS28, and DAS28-squeeze are more important, because treatment adjustments are based on these thresholds. Agreements in disease state classifications between the DAS and the DAS28 and between the DAS and the DAS28-squeeze are shown as scatter plots in Figures 2A and B. In both scatter plots, a strongly linear pattern was observed, especially for the state of remission measured by the DAS and the DAS28-squeeze. This linear pattern was attributable to the fact that the 44-joint SJC and the 28-joint SJC as well as the RAI and the 28-joint TJC, which are used for calculation of the DAS and DAS28- squeeze, respectively, were equal.

In the DAS28-BCP disease state model, all disease activity assessments with a positive squeeze test result at either forefoot (n=270 [36%]) were reclassified to a higher disease state. Among those assessments, 85% (n=230) showed forefoot involvement on physical examination (painful and/or swollen joints). In contrast, the squeeze test was negative in 156 (40%) of 386 assessments of patients with forefoot involvement. Figure 2C shows the proportional agreement and disagreement in disease state classifications between the DAS and the DAS28, DAS28-squeeze, or DAS28-BCP disease state. The DAS28, DAS28-squeeze, and DAS28-BCP disease states had a significant overall disagreement with the DAS regarding disease state classification. However, overall agreement between the DAS and DAS28-squeeze was 82% (95% confidence interval [95% CI] 79–85%), which was significantly higher compared with the overall agreement between the DAS and the DAS28 (76% [95% CI 73–79%]; $p<0.01$). The overall percent agreement between DAS and DAS28-BCP disease state was 75% (95% CI 71–78%).

To investigate the potential of the DAS28-squeeze and DAS28-BCP disease states, we selected patients who had forefoot arthritis without arthritis in any other joint on physical examination (22 patients and 46 assessments). The DAS28 and DAS28-squeeze but not the DAS28-BCP had a significant overall disagreement with the original DAS regarding disease state classification. However, overall agreement between the DAS and the DAS28 was 40% (95% CI 23–52%), which was significantly lower than the agreement between the DAS and the DAS28-squeeze (59% [95% CI 43–73%]; $p<0.05$) or between the DAS and the DAS28-BCP (65% [95% CI 50–79%]; $p<0.01$).

Subsequently, we compared true remission (Boolean criteria with a 44-joint count for swelling and tenderness) with remission according to the DAS28, the DAS28-squeeze, or the DAS28-BCP disease state. True remission was not defined in 196 assessments, because of missing data (no PGA and/or CRP). In 67 (13%) of 529 disease activity assessments, true remission was achieved. The DAS28, DAS28-squeeze, and DAS28-BCP disease states, respectively, met their own remission thresholds in 169 (31%), 150 (28%), and 140 (26%) disease activity assessments. The sensitivities of the DAS28, DAS28-squeeze, and DAS28-BCP to identify true remission were 88% (95% CI 78–95%), 87% (95% CI 76–94%), and 81% (95% CI 78–85%), respectively.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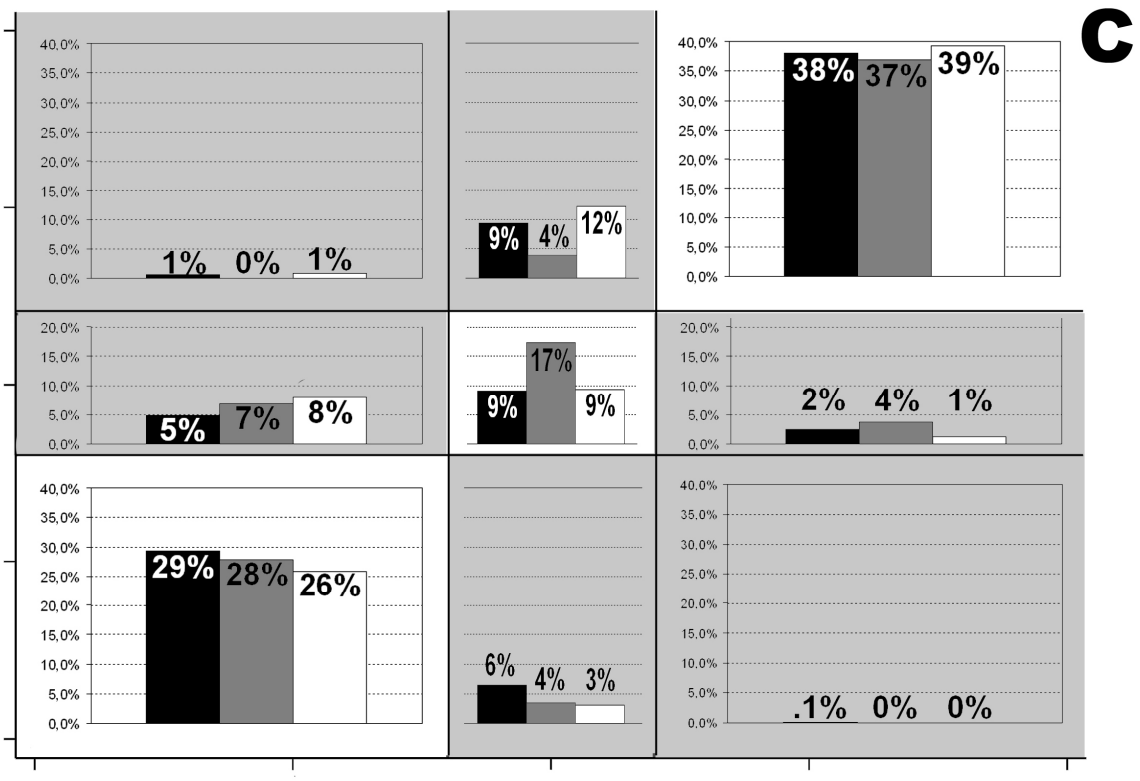


**Figure 2.** Agreement in disease state categorization between the Disease Activity Score (DAS) and the 28-joint DAS (DAS28)/DAS28-squeeze in rheumatoid arthritis, according to the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria. **A** and **B,** Scatter plots for the DAS versus the DAS28 (**A**) and for the DAS versus the DAS28-squeeze (**B**). The vertical and horizontal lines represent the thresholds for corresponding disease activity scores on the x-axis and y-axis, respectively. The square symbols in **A** represent patients with a positive squeeze test result for either foot. **C,** Schematic diagram showing agreement (white rectangles) and disagreement (shaded rectangles) between the DAS and the DAS28, DAS28-squeeze, or DAS28 bilateral compression pain (BCP) disease state. In the DAS28-BCP disease state model, all patients represented by the square symbols in **A** were reclassified into a higher disease state and moved above the horizontal threshold lines. The bar charts represent the distribution of DAS28 (solid bars), DAS28-squeeze (shaded bars), and DAS28-BCP (open bars) disease states over the 9 rectangles.

The specificities of the DAS28, DAS28-squeeze, and DAS28-BCP were 76% (95% CI 72–80%), 80% (95% CI 76–84%), and 81% (95% CI 78–85%), respectively. Similar results for sensitivity and specificity were observed using the Boolean remission criteria with a 28-joint count for swelling and tenderness (data not shown).

The DAS28-squeeze and DAS28-BCP disease states, respectively, correctly reclassified 18 (16%) and 24 (22%) of 110 DAS28 remission classifications that did not fulfill the Boolean remission criteria. However, the DAS28-squeeze and DAS28-BCP, respectively, failed to identify true remission in 1 (2%) and 5 (8%) of 59 assessments fulfilling Boolean criteria that were correctly identified by the DAS28.

## DISCUSSION

In this study, we showed that compared with DAS, the DAS28-squeeze improved disease state categorization in patients with RA according to 2010 criteria.[7,8] Moreover, the addition of the squeeze test elicited correct reclassification of DAS28 remission assessments that were nonremission assessments according to the Boolean criteria.[15,16]

The feet are frequently affected in both early and established RA, and foot impairment is an important cause of disability during the course of the disease.[103] Visser *et al*[17] demonstrated that forefoot involvement in patients with early arthritis is a strong prognostic indicator for the development of RA. Moreover, disease activity indices based on 28 joints underestimate the actual disease activity and expected joint damage in RA patients with predominantly forefoot involvement.[18] A clinically simple solution may be implementation of the squeeze test of forefeet into disease activity scores such as the DAS28-BCP disease state and upgrading DAS28 disease state categorizations one state if the results of the squeeze test are positive.

Our study had certain limitations. First, we used many assessments obtained in a relatively small number of patients. Dependency between assessments within patients will exist, but because disease activity indices were compared within each assessment, we believe that this within-patient dependency will not have much influence on the results. Furthermore, when we used only the second assessment and not the first because of the distribution of disease state categorizations, overall agreement between the DAS and the DAS28, DAS28-squeeze, or DAS28-BCP disease states increased, but similar differences in overall agreement remained (data not shown).

Second, we used the original DAS as the reference standard, because it is the only index that includes feet in calculation of disease activity. Furthermore, all treatment decisions within tREACH are based on the original DAS. However, because no head-to-head comparisons between different disease activity indices are available, it remains unclear whether either the DAS or the DAS28 underestimates or overestimates disease activity, which would lead to different patient outcomes.

Third, the individual joint examination of feet and the squeeze test are performed consecutively. Because both examinations are related, the results of the individual joint examination of feet may influence the squeeze test, and an information bias could be introduced. However, at the time of the examination, the research nurses who performed the tests did not know our research question.

Finally, although both models perform better than the DAS28, both models sometimes detect active disease in patients in whom the Boolean remission criteria are met. This may be attributable to the presence of residual synovitis in the forefeet that was not detected during MTP joint assessment but was possibly identified with the squeeze test. This hypothesis could be validated using imaging techniques.

In conclusion, the squeeze test of the forefeet might add value to the disease state categorizations of the DAS28. An important role may be reserved for the DAS28-BCP disease state, because it is a simple and clinically applicable tool.

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CHAPTER 8

# General discussion

Although the management of rheumatoid arthritis (RA) has underwent major paradigm changes, in the last two decades, a lot of unresolved questions remain and there is still room for improvement. The unresolved questions concerning the management of early RA and possible improvements are discussed in this chapter. We will address the following unresolved questions, which were mentioned in the general introduction:

- Applicability of current guidelines in patients with early RA
- Most appropriate initial treatment regimen:
    - Initial MTX monotherapy (iMM) versus initial triple DMARD therapy (iTDT)
    - GC bridging therapy: a single injection versus an oral tapering scheme
- Cost-effectiveness of various initial treatment regimens with a treat-to-target approach in early RA.
- How to monitor disease activity in early RA

Thereafter, methodological considerations, followed by the applicability in daily practice are discussed. Finally, recommendations for future research are made.

**Early detection of the disease**

The ACR/EULAR 2010 classification criteria for RA are more and more incorporated in daily practice of rheumatologists.[1] The 2010 EULAR recommendations for the management of RA, however, were formulated using data from studies in patients fulfilling 1987 criteria for RA.[2-3] Thus trials in the early phase of RA are needed for validation of current recommendations. In our tREACH trial, we used the Visser model to stratify patients into probability tertiles according to their likelihood of progressing to persistent arthritis.[4] The Visser algorithm and 2010 criteria for RA have similar discriminative abilities to identify patients at risk of persistent arthritis at 1 year.[5] Because of these similar discriminative abilities all upcoming recommendations for daily practice could also be applied for patients fulfilling 2010 classification criteria for RA.

Thanks to the introduction of the 2010 criteria of RA we are able to detect RA in an earlier phase of the disease. However, the time period in which the window of opportunity exist is very short, namely the first 12 weeks after symptom onset.[6] Several studies showed that initiation of DMARDs in this period improved clinical outcome and delayed or even prevented radiographic damage.[6-11] Therefore, identifying those patients who will develop a persistent arthritis within the first 12 weeks after symptom onset is crucial. However, in the tREACH only 20% of patients fulfilling the 2010 criteria for RA were assessed within the window of opportunity by a rheumatologist. Ultrasonography and Magnetic Resonance Imaging (MRI) detect joint inflammation better than clinical examination and can, therefore, enhance the diagnostic ability of the 2010 criteria for RA.[12-13] Moreover, ultrasound and MRI are useful tools for predicting progression to RA from undifferentiated arthritis.[12] Thus, implementation of mentioned imaging techniques in daily practice would probably result in detecting RA in an even earlier stage of the disease. Consequently, the proportion of patients with RA assessed by rheumatologists within the window of opportunity would increase.

However, I think that early referral is more important than improving the diagnostic ability of the 2010 criteria for RA to increase the proportion of RA patients, assessed within the window of opportunity by rheumatologists. Although referral may be obstructed by the long waiting lists of rheumatologists, the majority of delays are caused by general practioners (GPs).[14] Interpretation of complaints, i.e. symptoms are not serious or will go away, and gradual onset of symptoms are associated with a prolonged delay in seeking help. On the other hand acute onset of symptoms, functional disability and/or loss of productivity resulted in instantly seeking medical help.[15-16] When patients eventually visit their GP, the GP has the difficult task of distinguishing those patients who will develop RA, which has an annual incidence of approximately 50 per 100.000.[17] Prescription of and acute response to NSAIDs may further delay diagnosis. Furthermore, GPs have insufficient knowledge to effectively detect and manage arthritis. Early referral guidelines for GPs are needed to reduce referral delay. However, not much research has been done yet in this field, but this will probably increase in upcoming years.

**Early initiation of 'intensive' therapy**

Early initiation of 'intensive' therapy is another major paradigm change in nowadays management of RA, because it improves clinical efficacy and may even prevent radiographic damage.[8, 11, 18-19] However, still no consensus has been reached about what the most appropriate initial 'intensive' treatment regimen should be.

I recommend iTDT over iMM as 1st choice in newly diagnosed RA patients, because treatment goals are attained faster and maintained with 40% fewer biologicals. No differences were seen in dosage adjustments due to adverse events (AEs), after stratification for drug. One single intramuscular GCs injection as well as an oral GC tapering scheme would suffice as bridging therapy.

Furthermore, iTDT had lower costs per QALY compared with iMM. Interestingly, all initial treatment regimens of the tREACH are cost-effective, according to the definition of Dutch policy makers. Besides lower costs, patients treated with iTDT also had better worker productivity. In line with the clinical effectiveness, aforementioned results underline again why iTDT instead of iMM, is preferred as 1st choice in very early RA.

However, some patients and/or rheumatologists may have some aversion for iTDT, mainly because of the large amount of drugs that have to be taken. Medication adherence in RA is strongly influenced by patient's belief about the needfulness of the drugs.[20] These beliefs are moulded by rheumatologists through the information given about the disease and treatment approach.[20] Therefore, if iMM is still preferred, either by the rheumatologist or patient, I recommend combining MTX with a GC bridging scheme and determining the response to GCs after 2 weeks. As it happens determining GC response at 2 weeks is a useful tool for recognising those patients who will probably have active disease (DAS≥2.4) after 3 months of DMARD treatment. Subsequently, treatment should be intensified to triple DMARD therapy in GC non-responders.

However, future research is needed to evaluate the efficacy and efficiency of the above proposed approach.

Although iTDT is superior to iMM in our trial, one could still contest if iTDT is the most appropriate initial intensive treatment regimen. In our trial, for example, we did not compare initial MTX plus a biological with iTDT. Studies comparing initial DMARD combination therapy with MTX plus a biological are sparse. However, the TEAR[21] as well as the BeSt[22] trial compared aforementioned treatment regimens and showed no difference in clinical effectiveness between both regimens. The 2012 ACR recommendations[23] for the management of RA advocate iTDT or initial MTX plus a biological in newly diagnosed RA patients with active disease and ≥1 poor prognostic factor(s). Updated EULAR recommendations will probably not recommend biologicals as part of the initial treatment strategy, in the near future, because (1) biologicals are only restituted after failing on 2 conventional DMARDs in an optimal dosage for 3 months, (2) striking evidence of superior efficacy over iTDT is lacking and (3) treatment is far more expensive than iTDT.

Due to our treat-to-target design initial treatment could already be intensified to biologicals after three months, if the target was not reached. In the iMM group one could argue if triple DMARD therapy instead of biologicals should be the first step-up. Controversy about improved clinical efficacy of step-up therapy to biological over triple DMARD therapy after iMM failure still exists.[21, 24] The 2010 EULAR guideline recommends treatment intensification to a biological, after failing on iMM, in patients with following prognostic factors: (1) auto-antibodies positivity, (2) high disease activity, and/or (3) erosive disease. In our trial 29/36 (81%) of iMM failures, after three months, had two or more aforementioned factors. Therefore, we think intensification to biologicals after failing on iMM was a valid choice. Nevertheless there are still doubts about cost-effectiveness, especially in the long-term, which also supports the prefential for iTDT over iMM.

GC bridging therapy is used to treat active disease in the period between induction of DMARD therapy and onset of their therapeutic effect.[25] We find that intramuscular and oral GCs are equally effective as bridging therapy and can both be used, but one single dose of GCs intramuscular might be more feasible. However, the duration and dosage of our GC tapering scheme was short (10 weeks) and low (initial dosage 15mg) in comparison with, for example, the original COBRA regimen (respectively 28 weeks, initial dosage 60mg).[18] Because GCs have disease-modifying traits with long-lasting benefits even after withdrawal, a different oral GC tapering scheme might be superior.[25] For the 2010 EULAR recommendations Gorter *et al*[26] reviewed the literature, looking at the efficacy of GCs in RA. They concluded that future research is needed for optimizing GC bridging therapy with DMARDs, especially focusing on optimal dosage and tapering schemes, which is in line with our findings.[26]

Our results are based upon data from the first year of follow-up. During this first year, however, not all patients had attained and/or maintained the predefined treatment goals. Additionally, medication is tapered in patients with sustained

remission. Hence, the average burden of the disease is still fluctuating, which will probably reach a 'steady state' after a couple of years of follow-up. Several studies have demonstrated that early treatment response is associated with less active disease, functional impairment and indirectly less joint destruction and treatment changes needed to achieve the predefined treatment goals in the longterm.[27-29] Furthermore, there is also a relationship between early treatment response and retainment of work productivity.[30] However, in comparison with mentioned studies, which were performed in patients fulfilling 1987 criteria for RA, we included patients in an earlier phase of RA, representing a larger population. Therefore, the results of the long-term follow-up of the tREACH, including analyses of joint destruction and cost-effectiveness, should clarify if the benefits of iTDT remain in the longterm. Taking aforementioned considerations into account the longterm conclusions will, in our case, probably favour iTDT, because of faster attainment and better maintenance of predefined treatment goals and more frequent tapering of medication.

**A treat-to-target approach**

Although all disease activity indices (DAIs) have been developed in cohorts comprising patients with RA according to the 1987 criteria, DAIs already have been used in early RA to uphold recommended treatment goals. [3, 31-33] Therefore, in this thesis, we compared the characteristics of DAIs in RA according to the 2010 and 1987 classification criteria.[1, 3] The performance of the DAIs in patients fulfilling 2010 criteria for RA were comparable with those in RA according to 1987 criteria, although lower levels of disease activity were seen for patients who only fulfilled the 2010 criteria. Therefore, we think it is valid to use DAIs in a treat-to-target approach for patients who fulfill 2010 criteria for RA.

To achieve the predefined treatment goals patients should be monitored strictly with a DAI.[2, 34-35] There are various DAIs available for monitoring RA.[36-39] There is no DAI recommended by the 2010 EULAR guideline developers, apart from that it should include a swollen and tender joint count. [2, 34] But, if a particular DAI is chosen to assess disease activity in a patient with RA, the same DAI should be used during the entire follow-up of that patient, because usage of various DAIs in a single patient leads to inconsistent disease state categorizations. Consequently, these inconsistencies significantly influence therapeutic decisions and accompanying costs. As DAI usage is imperative to uphold current EULAR treatment recommendations, physicians should consider these therapeutic and economic consequences before choosing a particular DAI. However, the consequence of using various DAIs on functional impairment and joint damage over time is not known and has still to be investigated.

My DAI preference for daily practice is the DAS28, because (1) it is easy to use and (2) its ability to detect active disease is in between the other DAIs. The DAS28 is more conservative compared with the SDAI and CDAI and more liberal compared with the DAS in detecting active disease. Remission rates, however, are much higher with DAS28 usage compared with other DAIs. I advise that the decision to taper treatment

should not only depend on measuring sustained remission with DAS28, but also on the absence of forefeet arthritis and radiographic progression.

Feet are frequently affected in the early stages of the disease, while in DAS28 feet are excluded from the disease activity assessment.[40] Moreover, DAS28 underestimate the actual disease activity and expected joint damage in RA patients with predominantly forefoot involvement.[37, 41-42] Therefore, DAS28 should be optimised for usage in early RA patients. A clinically simple solution may be implementation of the squeeze test of forefeet – examining bilateral compression pain (BCP) across the MTP joints - into the DAS28. For daily practice the DAS28-BCP disease state, in which DAS28 disease state categorizations are upgraded one state if the results of the squeeze test is positive at either side, might be the solution. Because, adding the squeeze test of forefeet to the DAS28 has value for dependably classifying the disease state in patients with early RA. The DAS28-BCP disease state model, however, needs to be validated in another early RA cohort, before it can be implemented in daily practice.

Ultrasound may also be a useful tool for monitoring disease activity in early RA, because of better detection of joint inflammation as opposed to clinical examination.[12] However, a validated and accepted (universal) ultrasound scoring system is still missing.[43] Most important unresolved question herein is that of how many and which joints should be scanned for a reliable reflection of the actual disease activity.[43] A major disadvantage of ultrasound is that it is time-consuming. Therefore, I think ultrasound will not be used for monitoring disease activity in early RA in the near future. Nevertheless, an exception might be verifying sustained remission before commencing tapering of treatment. Especially, since patients with disease in remission according to a certain DAI, particularly those using an 28 joint count, may have relatively large numbers of 'residual joint counts', including swollen joints, causing unexpected radiographic progression over time.[44-45]

## METHODOLOGICAL CONSIDERATIONS

### Study design

The treatment in the Rotterdam Early Arthritis Cohort (tREACH) is a stratified single-blinded randomized clinical trial (RCT), which is nested in the REACH. The REACH is a prospective, inception cohort, initiated in the greater Rotterdam area in July 2004, to study (etio)pathogenic, diagnostic and prognostic factors in a very early stage of RA. Recruitment of patients was done by GPs and/or rheumatologists of eight hospitals. Inclusion criteria for the REACH study were arthritis ≥1 joint or, in the absence of joint swelling, artralgy in ≥2 joints with 2 or more of following criteria: (1) morning stiffness ≥1 hour, (2) joint pain in hands and/or feet, (3) difficulties wearing rings or shoes, (4) a family history of RA, (5) Symmetrical presentation of joint complaints, (6) pins and needles in the fingers and/or (7) unexplained fatigue <1 year. Due to this nested design of the tREACH within the REACH we were able to include patients within an earlier phase of the disease, because of less referral delay by GPs.

The strong advantages of a RCT are elimination of (1) confounding and selection bias by randomisation and (2) information bias by blinding. Confounding involves the possibility that an observed association is due, totally or in part, to the effects of differences between the study groups (other than the exposure under investigation). Although patients are randomised, sometimes confounding by randomisation occurs, especially in small groups, which is recognisable by baseline imbalances.[46-47] This happened in our trial, which was probably due to the variable block randomisation *stratified for centre*. Because patients are randomised per centre, relatively small groups are randomised, which increases the chance of confounding by randomisation. However, these baseline imbalances were in favour of iMM; after correction differences between both groups increased favouring iTDT.

Bias is a systemic error within the study. Systemic errors are caused by prejudice in selection of patients, measuring outcomes, or analysing data, which will lead to results that are flawed. There are two important types of bias that may effect a study, namely selection and information bias.[46-47] In our study selection bias is eliminated by randomisation. For our study, only research nurse were blinded for allocated treatment arm. This design was chosen, since we wanted to mimic daily practice as well as possible. Single blinding however could be a potential source of information bias, because not everyone is blinded and therefore measurements may be distorded. In our case possibly favouring iMM, because of the aversion for iTDT by the rheumatologist and/or patient. The same reasoning is also applicable for reporting (serious) adverse events, which was done by the attending rheumatologists. However, I think the tREACH has a good internal validity, because we tried to minimize the possible distorting effects of confounders and/or bias. [46-47] Therefore, our results are trustworthly and incorrupted.

The external validity on the other hand says something about the generalisability of the (main) findings to, for example, patients with newly diagnosed RA in daily practice of rheumatologists.[46-47] When the protocol was written, the 2010 criteria for RA still had to be developed. Therefore, we based our design on the Visser model, which predicts the likelihood of progressing to persistent arthritis.[4] Interestingly, the Visser algorithm and 2010 criteria for RA have similar discriminative abilities to identify patients at risk of persistent arthritis.[5] Moreover, similar results were found in both subgroups consisting of RA patients according to 2010 and 1987 criteria.[1, 3] Therefore, we think our results could be applied to all newly diagnosed RA patients fulfilling 1987 as well as 2010 classification criteria for RA. Especially, since we mimicked daily practice as well as possible in our RCT.

**Analyses**

Statistics are the mathematical science that deals with the organization, summarisation and interpretation of data acquired from the investigated population. Statistical analyses are especially useful for drawing conclusions, which enable us to answer the predefined research questions. This is also known as (null) hypothesis testing. The result of (null) hypothesis testing is never free of error. Two types of error are distinguished, namely type I and II error.[46-47]

Type I and II errors are intertwined with each other. If circumstances are unaltered, decreasing the probability of a type I error, will lead to an increase of a type II error. A type I error is the incorrect rejection of a correct/true (null) hypothesis. For example, sending an innocent person to jail is a type I error. The type I error rate is affected by the α level. In general the α level is set at 5%, which means that 1 out of 20 statistical analyses will reject a correct hypothesis by chance.[40-41]

On contrary, with a type II error an incorrect/false (null) hypothesis is accepted by mistake. Setting a criminal free is an example of a type II error. A type II error is not really an error, but there is not enough evidence to reject the hypothesis. The probability of a type II error is called β. The probability of correctly rejecting a false null hypothesis equals 1- β and is called power. The power is most often set at 80%. Power analyses are used to calculate the minimum sample size required to detect a predefined difference in effect size.[40-41] In the tREACH, for example, sample-size calculation was based upon area the under the curve (AUC) of the HAQ, using data from the BeSt study[22], where mean AUC HAQ of combination therapy and monotherapy respectively were 7.7 (SD 5.5) and 10.5 (SD 7.4). A target sample size of 270 patients per probability stratum was needed to detect mentioned difference with a power of 80% and two-sided α=0.05. This size is sufficient to detect a difference of 6.1 AUC DAS and 20% difference in radiographic progression.

Due to the economic recession and exponentially increasing health care cost, especially in rheumatology due to higher prescription rates of expensive biologicals, restitution of biologicals was altered by the government. Biologicals are not restituted by health insurance companies directly to individuals anymore, but hospitals are responsible for the provision of biologicals to patients.[48] Therefore, efficient use of expensive drugs is needed to be able to continue optimal rheumatic care in the future.[49] That's why we published the results of our interim analyses (chapter 2).

An interim analyses investigates wether there is a difference in the treatment groups before completion of the trial.[50] Interim analyses are most often used to diminish unnecessarily risk of possible harmful effects or detect an enormonous beneficial effect of a certain treatment, whereby it's unethetical to continue the trial.[50] However, the disadvantage of interim analyses is the fact that repeated testing of the null hypothesis increases the likelihood of a type I error by giving more opportunities to reject the hypothesis. However, we only performed one interim and final analysis and therefore we think that the chance of a type I error was negligible.

Although the trial was designed and powered to compare the clinical efficicacy of iTDT with iMM, new research question emerged during the trial. These new hypothesis were tested in different post-hoc analyses. Post-hoc analyses encloses investigating and drawing conclusions from the data for hypothesis, which are not defined in the protocol.[51] Major disadvantage of post-hoc analyses is misuse of this tool, leading to a fishing expedition for significant results. In this thesis, chapter 5, 6 and 7 are post-hoc analyses from the tREACH trial. However, in all these studies the research questions were defined before the analyses were performed. Furthermore, the investigated outcomes were not related to each other. Therefore, I am convinced that we did not misuse the post-hoc analyses method. Still, the problem of underpowering exists, because the trial was not designed to answer these research questions.

**Specific limitations of research questions**

In preceding paragraphs I discussed the common methodological considerations associated with the design and (post-hoc and/or interim) analyses of a RCT. For specific limitations of research questions I would like to refer to corresponding chapters.

## CLINICAL IMPLICATIONS

- Initial triple DMARD therapy is recommended over initial MTX monotherapy, as first choice in patients with newly diagnosed RA
- However, if MTX monotherapy is preferred, we recommend combining MTX with a GC bridging scheme and determining the response to GCs after 2 weeks. Subsequently, treatment should be intensified to triple DMARD therapy in GC non-responders.
- A single intramuscular GC injection as well as an oral tapering scheme can be used as bridging therapy
- If a particular disease activity index (DAI) is chosen to assess disease activity in a patient with RA, the same DAI should be used during the entire follow-up of that patient.

## FUTURE RESEARCH SUGGESTIONS

Although several unresolved questions for daily practice are resolved in this thesis, management of early RA will still evolve in next couple of years. Future research is necessary to optimize the management of early RA. I will point-by-point touch upon most important research objectives:

- A 'tailor made' versus a population based treatment approach.
    - For example comparing a treatment approach which makes use of our GC response model versus treating all patients with iTDT.
    - Or depending the intensity of the initial treatment regimen on the presence of prognostic markers (i.e. erosive disease, anti-citrullinated peptide antibodies or rheumatoid factor positivity) versus treating all patients with iTDT.
- Comparing the clinical efficacy of a single GC injection intramuscular with a oral GC tapering with a higher initial dosage and/or longer duration than used in the tREACH.
- Tapering DMARDs and biologicals in sustained remission. Most important questions are:
    - When to commence tapering?
    - How to taper DMARDs or biologicals: gradually versus immediate stop?
    - What is the optimal interval between taperings?
- Comparing a treat-to-target approach that aims for remission with an approach that aims for low disease activity. Hereby, also taking cost-effectiveness into account.
- Comparing the difference in clinical efficacy, radiographic progression and cost-effectiveness between treat-to-target approaches, which use different DAIs for monitoring the disease.
    - Noteworthy is the fact that the DAS28-BCP disease state model may also be validated in such a trial.

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CHAPTER 9

# Summary

Major paradigm changes in the management of rheumatoid arthritis (RA) have occurred in the last two decades, due to evolvement of clinical trial methodology, emergement of new therapeutic options – in particular biologicals – and reevaluating treatment strategies. These major paradigm changes are:

- Early detection of the disease;
- Early initiation of 'intensive' therapy;
- A treat-to-target approach

Although the management of RA has underwent these major paradigm changes, a lot of unresolved questions remain and there is still room for improvement. Therefore the focus of this thesis is on the management of early RA. In this chapter the findings of the conducted studies are summarized.

For all upcoming studies, data of a currently ongoing clinical trial, namely the treatment in the Rotterdam Early Arthritis Cohort (tREACH) were used. The tREACH trial is a single-blinded randomized clinical trial in patients ≥18 years with recent-onset arthritis (symptom duration < 1 year). Main goal of the tREACH is to evaluate different initial treatment strategies in early RA. Patients, who had a high probability (> 70%) of progressing to persistent arthritis, based on the prediction model of Visser, were included. Noteworthy is the fact that the Visser algorithm and 2010 criteria for RA have similar discriminative abilities to identify patients at risk for persistent arthritis at 1 year. Patients were randomised into one of following initial treatment regimens:

A. Triple Disease Modifying Anti-Rheumatic Drug (DMARD) therapy (methotrexate (MTX) + sulfasalazine + hydroxychloroquine) with a single glucocorticoid (GC) injection intramuscularly
B. Triple DMARD therapy with an oral GC tapering scheme
C. MTX with oral GCs similar to B.

A treat-to-target approach was used, with patients being examined every 3 months, aiming for low disease activity, defined as DAS<2.4.

Early detection of the disease is one of the major paradigm changes in the management of RA, which ultimately led to the development of the 2010 classification criteria for RA. These criteria for RA are more and more incorporated in daily practice of rheumatologists. All guidelines for the management of RA, however, are based upon data from studies in patients fulfilling 1987 criteria for RA. Thus trials in the early phase of RA are needed for validation of current guidelines. All upcoming studies are conducted in early RA patients and can, therefore, be used to validate current guidelines.

Early initiation of 'intensive' therapy is another major paradigm change in nowadays management of RA, because it improves clinical efficacy and may even prevent radiographic damage. However, there is still debate on the most appropriate initial treatment regimen in patients with newly diagnosed RA. Most important discussion herein is that of initial MTX monotherapy (iMM) versus a combination of DMARDs. Hence, in ***chapter 2***, we compared the clinical efficacy of (1) initial triple DMARD therapy (iTDT) versus iMM, independent of GCs, and (2) of different GC bridging

therapies: oral tapering versus a single injection, using the 3 months data of the tREACH trial. iTDT reduced disease activity more rapidly after 3 months than iMM. Consequently, 50% fewer biological were prescribed in the iTDT group. Although the proportion of patients with medication adjustments due to adverse events (AEs) differed significantly between treatment arms, no differences were seen after stratification for the drug. One single intramuscular GC injection or an oral GC tapering scheme can be used as bridging therapy, because they are equally effective. No difference in serious adverse events were seen between treatment arms.

Several studies have demonstrated that the choice of the initial treatment regimen influences the initial clinical response, which indirectly influence the amount of joint destruction and treatment intensifications needed to maintain current treatment goals in the longterm. The longterm follow-up of the tREACH must clarify if this also applies for patients with early RA. Therefore, in ***chapter 3***, the 1-year clinical efficacy of the different initial treatment strategies are studied. iTDT had a better clinical efficacy and efficiency than iMM in early RA. The burden of disease activity and functional impairment over time was less in the iTDT group compared with iMM. Furthermore, treatment goals were attained faster and maintained with less frequent treatment intensifications, which led to the prescription of ~40% fewer biologicals, after 3 months up to 1 year, in the iTDT group. Moreover, more patients with iMM failed on their first biological, reducing therapeutic options rather swiftly. Radiographic progression did not differ between groups. After stratification for drug no differences in dosage adjustments due to AEs were seen. Moreover, treatment could be tapered more often in the iTDT group, without increasing flare ratios. On contrary no differences were seen in both GC bridging therapies. The longterm data of the tREACH confirmed once more that iTDT is preferred over iMM, especially because of its efficiency due to attaining and maintaining treatment goals faster with less expensive drugs.

The policy for covering prescribed drugs by health insurance companies and governments is more and more influenced by cost-effectiveness, because of exponentially increasing health care costs. Therefore, for health economic reasons efficient use of expensive drugs, especially biologicals, is needed to be able to continue optimal rheumatic care in the future. Therefore, we investigated, in ***chapter 4***, which initial treatment regimen within the tREACH trial had the best cost-effectiveness ratio. iTDT had lower costs per Quality Adjusted Life-Years (QALY) compared with iMM. Total costs are the sum of the direct and indirect costs. Direct costs are the costs of treatment and medical consumption, whereas indirect costs are costs due to loss of productivity (i.e. sick leave and unemployment). Direct as well as indirect costs were significantly higher in the iMM group compared with the iTDT group. The difference in direct costs was due to ~40% more biological usage over time. Less unemployment, long-term sickness and reduction in contract hours on the other hand caused the difference in indirect costs. Interestingly, all initial treatment regimens within the tREACH trial are cost-effective, according to the definition of Dutch policy makers. Besides lower costs

iTDT had better worker productivity. This underlines again why iTDT instead of iMM is preferred as first choice in very early RA.

A treat-to-target approach is advocated in order to obtain better functional and radiological outcomes in RA. To achieve the predefined treatment target patients should be monitored strictly with a disease activity index (DAI) and treatment should be adjusted until the target is reached. There are various DAIs available for monitoring RA. Interestingly, although all DAIs have been developed in cohorts comprising patients with RA according to the 1987 criteria, DAIs already have been used in early RA, although validation is lacking in this early population. Therefore, in ***chapter 5***, we (1) described the performance of DAIs in RA according to 1987 and 2010 criteria and (2) investigated how inconsistencies between DAIs influenced therapeutic decisions and accompanying costs. DAIs performed similar in RA according to 2010 and 1987 criteria. Knowing that DAIs are essential in guiding treatment decisions, choosing a particular DAI could be cumbersome, because usage of various DAIs in a single patient leads to inconsistent disease state categorizations. Consequently, these inconsistencies significantly influence therapeutic decisions and accompanying costs. Therefore, for the selection of a DAI the therapeutic and economic consequences should be considered.

Management of RA is still evolving, particularly in the areas of efficiency. Ideally a 'tailor made' treatment approach is used to circumvent problems as over-treatment and accompanying (serious) adverse events. Since the time span for the optimal effect of DMARDs takes at least 6-12 weeks, the right choice of the initial DMARD therapy plays an important role in obtaining recommended treatment goals. About 60% will respond sufficiently to the initial treatment. Therefore, it would be helpful to be able to predict treatment response to the initial DMARD therapy as early as possible, ultimately leading to a 'tailor made' treatment approach. In ***chapter 6*** we link the early effect of GCs to initial DMARD response. We investigated whether the GC response at 2 weeks, according to the EULAR response criteria, can predict active disease, defined as DAS≥2.4, after 3 months of initial DMARD treatment. Patients who do not respond to GC bridging therapy at 2 weeks have a 10-fold increased risk of having active disease after 3 months of treatment compared with GC responders. Therefore, determining GC response at 2 weeks could be a useful tool for daily practice, resulting in a more 'tailor made' treatment approach. An approach could be combining MTX monotherapy with a GC bridging scheme and determining the response to GCs after 2 weeks. Subsequently, treatment should be intensified, to triple DMARD therapy, if patients do not respond to GCs. However, future research is needed to evaluate the efficacy and efficiency of above proposed approach.

The unassailable need for early detection of the disease, eventually resulted in the development of the 2010 classification criteria for RA. The feet are frequently affected in the early stages of the disease. However, in daily practice rheumatologists often use DAIs for monitoring RA, which exclude the feet, because of their user-friendliness. The most often used DAI is the DAS28. Therefore, in ***chapter 7***, we tried to optimize DAS28 usage in early RA by adding the 'squeeze test' of forefeet. The squeeze

test examines bilateral compression pain (BCP) across the metatarsophalangeal (MTP) joints, which is a sensitive measure for the existence of arthritis in the forefoot. First, the mathematical function of the DAS28-squeeze was constructed using a linear regression model with the DAS as the dependent variable and the DAS28 and squeeze test as the independent variables. A DAS28-BCP disease state was also constructed, in which DAS28 disease state categorizations were upgraded one state if the result of the squeeze test was positive at either side. Thereafter, we investigated if adding the squeeze test to the DAS28 improved disease state categorization, using both DAS and Boolean remission criteria as reference. The squeeze test of forefeet adds value to the disease state categorizations of the DAS28. An important role may be reserved for the DAS28-BCP disease state, because it is a simple and clinically applicable tool.

Finally, in ***chapter 8***, I addressed the unresolved questions mentioned in the general introduction by making use of our main findings. Thereafter, methodological considerations, followed by the applicability in dialy practice are discussed. Finally, recommendations for future research are made.

CHAPTER 10

# Nederlandse samenvatting

In de laatste 20 jaar hebben de vooruitgang in onderzoeksmethodologie, opkomst van nieuwe therapeutische opties – met name biologicals – en het verbeteren van behandelstrategiën geleid tot grote paradigmaveranderingen in de behandeling van reumatoïde artritis (RA). Deze grote paradigmaveranderingen zijn:

- Vroege herkenning van de ziekte
- Vroege 'intensieve' behandeling van de ziekte
- Doelgerichte behandeling van de ziekte

Ondanks dat de behandeling van RA dramatisch is veranderd, zijn er nog altijd veel onopgeloste vragen en is er genoeg ruimte voor verbetering. De nadruk van dit proefschrift ligt dan ook op de behandeling van vroege RA. In dit hoofdstuk worden de bevindingen van de uitgevoerde onderzoeken samengevat.

Voor de komende onderzoeken is data van een nog lopend onderzoek, genaamd treatment in the Rotterdam Early Arthritis Cohort (tREACH), gebruikt. Het tREACH onderzoek is een enkelblind, gerandomiseerd onderzoek, die in meerdere ziekenhuizen word uitgevoerd. In dit onderzoek worden alle patiënten >18 jaar met een recent ontstane gewrichtsontsteking (klachtenduur <1 jaar) zo snel mogelijk gezien en behandeld. Het belangrijkste doel van de tREACH is het vergelijken van de effectiviteit van verschillende geinitieërde behandelstrategiën in vroege RA. Patiënten met een >70% kans op het ontwikkelen van persisterende artritis, op basis van het voorspelmodel van Visser, werden geïncludeerd. Noemenswaardig is het feit dat het Visser model en de 2010 classificatie criteria voor RA evengoed patiënten herkennen met een verhoogd risico op een chronische gewrichtsonsteking na 1 jaar. Patiënten werden gerandomiseerd naar één van de volgende initiële behandelstrategiën:

A. Combinatietherapie, bestaande uit methotrexaat (MTX), sulfasalazine en hydroxychloroquine, en 1x een glucocorticoïd (GC) injectie intramusculair.
B. Combinatietherapie met een orale GC afbouwschema.
C. MTX met een gelijksoortige GC afbouwschema als B.

Het doel van de behandeling is het bereiken van 'lage' ziekteactiviteit, wat gedefinieerd is als DAS<2.4 (Disease Activity Score). Patiënten worden elke 3 maanden beoordeelt, en zolang het behandeldoel niet is bereikt, wordt er krachtiger behandeld.

Vroege herkenning van de ziekte is één van de paradigmaveranderingen in de behandeling van RA, wat uiteindelijk tot de ontwikkeling van de 2010 classificatie critieria voor RA heeft geleid. Deze criteria worden steeds meer in de dagelijkse praktijk gebruikt. De huidige richtlijnen zijn echter gebaseerd op gegevens van onderzoeken bij patiënten die aan de 1987 classificatie criteria voor RA voldeden. Aldus zijn er onderzoeken in de vroege fase van RA nodig om de huidige richtlijnen te valideren. Alle onderzoeken in dit proefschrift werden uitgevoerd in patiënten met vroege RA en met deze gegevens kunnen de huidige richtlijnen worden gevalideerd.

Vroege 'intensieve' behandeling is een andere belangrijke paradigma-verandering in de behandeling van RA. Dit vanwege een betere klinische effectiviteit, die mogelijk zelfs radiologische schade voorkomt. Er is echter nog steeds geen consensus bereikt over wat de beste initiële behandelstrategie is. Dit is één van de

belangrijkste onopgeloste vragen in de behandeling van RA. De belangrijkste discussie hierin is die van het starten met MTX monotherapie versus een combinatie van Disease Modifying Anti-Rheumatic Drugs (DMARDs). Vandaar dat we, in ***hoofdstuk 2***, de effectiviteit van (1) initiële combinatietherapie (iCT) vergelijken met initiële MTX monotherapie (iMM), onafhankelijk van GC, en (2) verschillende overbruggingstherapieën met GC - een orale afbouwschema versus een eenmalige injectie - hebben bestudeerd. Hierbij hebben we gebruik gemaakt van de 3 maands data van het tREACH onderzoek. iCT brengt een snellere daling in ziekte-activiteit teweeg in vergelijking met iMM. Hierdoor worden 40% minder biologicals, na 3 maanden, voorgeschreven in de iCT groepen. Hoewel het percentage patiënten met medicatiedosis aanpassingen als gevolg van bijwerkingen significant verschilden tussen de behandelgroepen, werden deze verschillen teniet gedaan na stratificatie voor medicijngebruik. Daarom raden wij iCT, in plaats van iMM aan als eerste keus bij nieuw gediagnosticeerde RA patiënten. Zowel een eenmalige GC injectie als een orale GC afbouwschema kan als overbruggingstherapie worden gebruikt, aangezien beide even effectief zijn. Er werden geen verschillen gevonden in ernstige bijwerkingen tussen de behandelarmen

Diverse studies hebben aangetoond dat de keuze van de initiële behandelstrategie de initiële klinische respons en indirect de ernst van de gewrichtsschade en het aantal medicatie aanpassingen, welke nodig zijn om de voorafgestelde behandeldoelen te handhaven, op de lange termijn beïnvloedt. De lange termijn resultaten van het tREACH onderzoek moeten verduidelijken of bovenstaande ook geldt voor patiënten met vroege RA. Om deze reden werd, in ***hoofdstuk 3***, de 1-jaars effectiviteit van de verschillende initiële behandelstrategieën vergeleken. Patiënten met iCT hadden over de gehele periode minder last van de ziekte-activiteit en functionele beperkingen, welke gepaard gaan met de ziekte, in vergelijking met patiënten met iMM. Na 3 maanden werden circa 40% minder biologicals, wat zeer dure geneesmiddelen zijn, voorgeschreven in de iCT groep in vergelijking met de iMM groep. Dit verschil veranderde niet meer over de tijd. Tevens faalde meer patiënten in de iMM groep op hun 1e biological, waardoor minder therapeutische opties overblijven. Er werden geen verschillen gevonden tussen de verschillende initiële behandelstrategieën in röntgenologische schade na 12 maanden behandeling. Hoewel het percentage patiënten met medicatiedosis aanpassingen, als gevolg van bijwerkingen, significant verschilden tussen de behandelgroepen, werden deze verschillen teniet gedaan na stratificatie voor medicijngebruik. Tevens konden medicijnen vaker worden afgebouwd in de iCT groep, zonder een procentuele toename van het aantal opvlammingen in ziekte-activiteit. Er werden daarentegen geen verschillen gezien in beide GC overbruggingstherapiën. De lange termijn resultaten van de tREACH bevestigen nogmaals dat iCT de voorkeur geniet boven iMM, omwille van zijn klinische effectiviteit en efficiëntie, wat blijkt uit het sneller bereiken en handhaven van de voorafgestelde behandeldoelen met minder dure geneesmiddelen.

Doordat de kosten in de gezondheidszorg exponentieel groeien, gaat kosten-effectiviteit steeds meer een belangrijkere rol spelen bij beleidsmakers - de zorgverzekeraars en overheid - die de vergoeding voor medicijnen bepalen. Om deze reden is het efficiënt gebruik van dure geneesmiddelen, met name biologicals, erg belangrijk, zodat de excellente reumatologisch zorg ook voor de toekomst gewaarborgd is. Daarom onderzochten we, in ***hoofdstuk 4***, welke van de drie behandelarmen in de tREACH studie de beste kosten-effectiviteits ratio had. Beide iCT hebben lagere kosten per per Quality Adjusted Life-Years (QALYs) in vergelijking met iMM. De totale kosten worden bepaald door de som van de directe en indirecte kosten. Directe kosten zijn de kosten van behandeling en medische dienstverlening, terwijl indirecte kosten kosten zijn als gevolg van verlies in productiviteit (bv. ziekteverzuim en werkloosheid). Zowel de directe als indirecte kosten waren hoger in de iMM groep in vergelijking met de iCT groepen. Het verschil in directe kosten werd veroorzaakt door het verschil in gebruik van biologicals (ca. 40% van 3 maanden tot 1 jaar). Een afname in werkloosheid, minder patiënten met langdurig ziekteverzuim en geringer afname in contracturen waren de oorzaken voor het verschil in indirecte kosten. Noemenswaardig is het feit dat alle behandelarmen binnen de tREACH kosteneffectief zijn volgens de Nederlandse definitie; opgesteld door het college voor zorgverzekeringen. Naast de lagere kosten hadden patiënten met iCT ook een beter arbeidsrendement. Dit onderstreept eens te meer waarom iCT de voorkeur geniet boven iMM.

Doelgerichte behandeling in RA heeft er toe geleid dat er minder radiologische schade optreed met verbetering van de functionele capaciteit. Om de voorafgestelde behandeldoelen te bereiken worden patiënten nauwlettend in de gaten gehouden met een meetinstrument voor ziekte-activiteit. Er wordt steeds krachtiger behandeld, totdat het doel is bereikt. Verschillende meetinstrumenten voor ziekte-activteit zijn ontwikkeld. Interessant is het feit dat alle ziekte-activiteit meetinstrumenten (ZAM) ontwikkeld zijn in patiëntenpopulaties die aan de 1987 classificatie criteria voor RA voldeden. Toch worden deze ZAM gebruikt bij patiënten met vroege RA, ondanks dat ze niet gevalideerd zijn. Derhalve bestuderen wij, in ***hoofdstuk 5***, (1) hoe ZAM in patienten met RA volgens de 1987 en 2010 classificatie criteria presteren en (2) wat de therapeutische en economische gevolgen zijn van inconsistenties tussen ZAM. Het gedrag van ZAM, in patiënten met RA volgens de 1987 en 2010 classificatie criteria, is vergelijkbaar. Het gebruik van verschillende ZAM in één patiënt leidt tot inconsistente ziekte-activiteit categorisering, wat een significante weerslag heeft op de therapeutische beslissingen en de bijbehorende kosten. Wetende dat ZAM essentieel zijn in de behandeling van RA, zal bovenstaande de keuze voor een bepaalde ZAM zeker niet vergemakkelijken. Bij het kiezen van een ZAM dient men dus ook rekening te houden met de therapeutische en economische gevolgen.

De behandeling van RA is nog in ontwikkeling, met name op het gebied van het efficiënt gebruik van DMARDs en biologicals is nog veel vooruitgang te boeken. Idealiter wordt behandeling op maat gegeven om problemen als overbehandeling met de bijbehorende (ernstige) bijwerkingen te omzeilen. Aangezien het minimaal 6-12

weken duurt voordat DMARDs hun optimale werking hebben, speelt de keuze van de initiële behandelstrategie een belangrijke rol in het behalen van de huidige behandeldoelen. Ongeveer 60% van de patiënten reageert afdoende op hun initiële behandeling. Als we de respons op de initiële behandeling in een zeer vroeg stadium kunnen voorspellen, wordt behandeling op maat meer en meer een feit. In ***hoofdstuk 6*** koppelen we de vroege behandeleffecten van GC aan de initiële DMARD respons. We hebben onderzocht of het behandeleffect van GC na 2 weken, actieve ziekte - gedefinieerd als een DAS≥2.4 - na 3 maanden DMARD behandeling kan voorspellen. Patiënten die niet reageren op overbruggingstherapie met GC, na 2 weken, hebben een 10-voudig verhoogd risico op actieve ziekte in vergelijking met patiënten die wel op GC reageren. Derhalve is het bepalen van het behandeleffect van GC na 2 weken een bruikbaar instrument voor de dagelijkse praktijk, aangezien het tot een meer op maat gesneden benadering van de behandeling van RA leidt. In de dagelijkse praktijk kan bijvoorbeeld in nieuw gediagnosticeerde RA patiënten worden gestart met iMM in combinatie met een GC overbruggingstherapie. Na 2 weken wordt het GC behandel-effect bepaald. Indien onvoldoende respons op GC, wordt er krachtiger behandeld met bijvoorbeeld een combinatie van DMARDs. Echter, de effectiviteit en efficiëntie van de hierboven voorgestelde behandelaanpak moet nog worden onderzocht.

De onbetwistbare noodzaak voor vroege detectie van de ziekte heeft uiteindelijk geleid tot de ontwikkeling van de 2010 classificatie criteria voor RA. Gewrichts-ontstekingen aan de voeten komen vaak voor, met name in de vroege fase van de ziekte. Daarentegen worden in de dagelijkse praktijk vaak ZAM gebruikt die geen rekening houden met de betrokkenheid van de voetgewrichten, dit vanwege hun gebruiksgemak. De meest gebruikte ZAM is de DAS28. Derhalve hebben we, in ***hoofdstuk 7***, geprobeerd om de accuratesse van de DAS28 in vroege RA te verbeteren door het toevoegen van de voorvoet knijptest. Deze knijptest onderzoekt de aanwezigheid van tangentiële drukpijn (TDP) over de metatarsofalangeale (MTP) gewrichten, wat een gevoelige maat is voor het bestaan van artritis aan de voorvoet. Allereerst hebben we een regressiemodel gemaakt, waarin de DAS werd verklaard door de DAS28 en de knijptest. Tevens hebben we een DAS28-TDP model ontwikkeld, waarin de ziekte-activiteit categorisering van de DAS28 wordt opgewaardeerd in aanwezigheid van TDP in één of beide voorvoeten. Vervolgens hebben we onderzocht of het toevoegen van de knijptest de ziekte-activiteit categorisering van de DAS28 verbeterd, waarbij de DAS en de Boolean remissie criteria als referentie werden gebruikt. De knijptest heeft een additieve waarde voor de DAS28 in vroege RA, omdat toevoeging van deze test tot een betrouwbaarder ziekte-activiteit categorisering leidt. Hierbij is wellicht een belangrijke rol weggelegd voor het DAS28-TDP model bij het opvolgen van de ziekte in de dagelijkse praktijk, vanwege zijn eenvoud en gebruiksgemak.

Tenslotte worden in ***hoofdstuk 8*** de onopgeloste vragen uit de algemene inleiding bediscussieerd aan de hand van de bevindingen uit onze onderzoeken. Vervolgens worden de methodologische beperkingen en klinische implicaties besproken. En tot slot worden er aanbevelingen voor toekomstig onderzoek gedaan.

# ADDENDUM

PhD portfolio

Publications

About the Author

Acknowledgements

Role of funding source

Dankwoord

## PhD portfolio

| | |
|---|---|
| **Name:** | Pascal Hendrik Pieter de Jong |
| **ErasmusMC Department:** | Rheumatology |
| **Research school:** | NIHES |
| **PhD period:** | July 2008 – December 2011 |
| **Promotor:** | Prof.dr. J.M.W. Hazes |
| **Copromotor:** | Dr. A.E.A.M. Weel |

## GENERAL ACADEMIC AND RESEARCH SKILLS

2008

- Good clinical practice, ErasmusMC, Rotterdam, the Netherlands
- Morello webclient (webpage design), ErasmusMC, Rotterdam, the Netherlands

2009

- Cursus MRI voor reumatologen, Mercury Hotel, Dordrecht, the Netherlands
- MRI Masterclass, Kurhaus, Scheveningen, the Netherlands

2010

- Course: 'Teach the Teacher', ErasmusMC, Rotterdam, the Netherlands
- Scientific English Writing, ErasmusMC, Rotterdam, the Netherlands

## IN-DEPTH COURSES

2011 Master of science, specialisation Clinical epidemiology
NIHIS, ErasmusMC, Rotterdam, the Netherlands
*- period: 2009 – 2011*
*- ECTS: 70*

**Program components**

- **Erasmus Summer programme**

| | |
|---|---|
| Principles of Research Medicine | 0.7 |
| Clinical Decision Analysis | 0.7 |
| Methods of Clinical Research | 0.7 |
| Clinical Trials | 0.7 |
| Topics in Meta-analysis | 0.7 |
| Pharmaco-epidemiology | 0.7 |
| Health Economics | 0.7 |
| Case-control Studies | 0.7 |
| Primary and Secondary Prevention Research | 0.7 |
| History of Epidemiologic Ideas | 0.7 |
| Social Epidemiology | 0.7 |
| Markers and Prognostic Research | 0.7 |
| The Practice of Epidemiologic Analysis | 0.7 |

- **Core curriculum**

| | |
|---|---|
| Study Design | 4.3 |
| Classical Methods for Data-analysis | 5.7 |
| Clinical Epidemiology | 5.7 |
| Methodologic Topics in Epidemiologic Research | 1.4 |
| Modern Statistical Methods | 4.3 |

- **Advanced short courses**

| | |
|---|---|
| Missing values in Clinical Research | 0.7 |
| Courses for the Quantitative Researcher | 1.4 |
| Repeated Measurements in Clinical Studies | 1.9 |
| Advanced Topics in Clinical Trials | 1.9 |

- **Skills Courses**

| | |
|---|---|
| English Language | 1.4 |
| Working with SPSS for Windows | 0.15 |
| A first glance at SPSS for Windows | 0.15 |

- **Research**

| | |
|---|---|
| Development of Research Proposal | 2.5 |
| Oral Research Presentation | 1.4 |
| Research Period | 30.3 |

## (INTER)NATIONAL CONFERENCES

2013

- de Jong PH, Hazes JM, Han HK, Huisman M, van Zeben D, van der Lubbe PA, Gerards AH, van Schaeybroeck B, de Sonnaville PB, Krugten MV, Luime JJ, Weel AE. *Initial triple DMARD therapy is more efficient than methotrexate monotherapy in recent onset rheumatoid arthritis; 1-year data of a randomized clinical trial (tREACH)*. ACR, Oktober 2013, San Diego. *(oral presentation)*
- de Jong PH, Weel AE, Luime JJ, Barendregt PJ, van Zeben D, van der Lubbe PA, Gerards AH, de Jager MH, de Sonnaville PB, Grillet BA, Hazes JM. *Better cost-effectiveness and worker productivity in triple DMARD therapy versus methotrexate monotherapy in early rheumatoid arthritis; Cost-utility analysis of the tREACH trial.* ACR, Oktober 2013, San Diego. *(oral presentation)*
- de Jong PH, Hazes JM, Han HK, Huisman M, van Zeben D, van der Lubbe PA, Gerards AH, van Schaeybroeck B, de Sonnaville PB, Krugten MV, Luime JJ, Weel AE. *Initial triple DMARD therapy is more efficient than methotrexate monotherapy in recent onset rheumatoid arthritis; 1-year data of a randomized clinical trial (tREACH)*. NVR najaarsdagen, September 2013, Papendal. *(oral presentation)*
- de Jong PH, Hazes JM, Han HK, Huisman M, van Zeben D, van der Lubbe PA, Gerards AH, van Schaeybroeck B, de Sonnaville PB, Krugten MV, Luime JJ, Weel AE. *Randomized comparison of triple DMARD therapy with methotrexate monotherapy in early rheumatoid arthritis, unbiased for glucocorticoids (the tREACH trial).* EULAR, May 2013, Madrid. *(oral presentation)*
- de Rotte MC, de Jong PH, Quax RA, den Boer E, Pluijm SM, de Jonge R, Hazes JM. *Glucocorticoids and methotrexate have a synergistic working on decrease of rheumatoid arthritis disease activity.* EULAR, May 2013, Madrid. *(poster presentation)*

2012

- de Jong PH, Quax RA, Huisman M, Gerards AH, Feelders RA, de Sonnaville PB, Luime JJ, Weel AE, Hazes JM. *Early glucocorticosteroid response predicts the effect of DMARDs after 3 months of therapy.* EULAR, May 2012, Berlijn. *(poster presentation)*
- de Jong PH, Hazes JM, Barendregt PJ, Huisman M, van Zeben D, van der Lubbe PA, Gerards AH, de Jager MH, de Sonnaville PB,Grillet BA, Luime JJ, Weel AE. *Induction therapy with a combination of DMARDs is superior to methotrexate monotherapy, unbiased for corticosteroids. First results of the tREACH trial; induction strategies in early arthritis.* EULAR, May 2012, Berlijn. *(poster presentation)*

2011

- de Jong PH, Hazes JM, Barendregt PJ, Huisman M, van Zeben D, van der Lubbe PA, Gerards AH, de Jager MH, de Sonnaville PB,Grillet BA, Luime JJ, Weel AE. *Combination of DMARDs prohibit the need of early initiation of biologicals, independent of glucocorticoids. tREACH a RCT to investigate different induction therapies in early RA.* ACR, November 2011, Chicago. *(poster presentation)*
- de Jong PH, de Man YA, Luime JJ, Weel AE, Hazes JM. *DAS28 with squeeze might help in identifying true remission.* EULAR, May 2011, Londen. *(poster presentation)*

2010

- de Jong PH, Hazes JM, Luime JJ, Weel AE**.** *Measures of disease activity provide various clinical decisions in individual patients.* ACR, November 2010, Atalanta. *(poster presentation)*
- de Jong PH, Hazes JM, Luime JJ, Weel AE. *Het gebruik van gemodificeerde ziekte-activiteit indices kan klinische beslissingen bij individuele patiënten beïnvloeden.* NVR najaarsdagen, September 2010, Papendal. *(oral presentation)*

## TEACHING ACITIVITIES

| | |
|---|---|
| 2009 – 2011 | Teaching course 'Klinisch redeneren' to first and third year medical students at the Erasmus university |
| 2009 | Lecture: 'Nieuwe inzichten in de diagnostiek en behandeling van Reumatoïde Arthritis, het tREACH onderzoek' to general practioners. Het Arsenaal, Vlissingen, the Netherlands |

## OTHER

| | |
|---|---|
| 2009 – 2011 | Organising annual tREACH conference |
| 2008 – 2011 | Management of research nurses / tREACH |

## PUBLICATIONS

- **de Jong PH,** Hazes JM, van Zeben D, van der Lubbe PA, de Jager MH, de Sonnaville PB, Luime JJ, Weel AE. *Treatment decisions and related costs differ significantly depending on the choice of a disease activity index in RA, according to 1987 and 2010 classification criteria*. Rheumatology (Oxford). 2012;51(7):1269-77.

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- **de Jong PH,** Weel AE, de Man YA, Huisman AM, Gerards AH, van Krugten MV, Luime JJ, Hazes JM. *Brief Report: To squeeze or not to squeeze, that is the question! Optimizing the disease activity score in 28 joints by adding the squeeze test of metatarsophalangeal joints in early rheumatoid arthritis.* Arthritis Rheum. 2012;64(10):3095-101.

- **de Jong PH,** Hazes JM, Barendregt PJ, Huisman AM, van Zeben D, van der Lubbe PA, Gerards AH, de Jager MH, de Sonnaville PB, Grillet BA, Luime JJ, Weel AE. *Induction therapy with a combination of DMARDs is better than methotrexate monotherapy: first results of the tREACH trial*. Ann Rheum Dis. 2013;72(1):72-8

- **de Jong PH,** Quax RA, Huisman AM, Gerards AH, Feelders RA, de Sonnaville PB, Luime JJ, Weel AE, Hazes JM. *Response to glucocorticoids at 2 weeks predicts the effectiveness of DMARD induction therapy at 3 months: post hoc analyses from the tREACH study.* Ann Rheum Dis. 2013;72:1659-1663.

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- de Rotte MC, den Boer E, **de Jong PH**, Pluijm SM, Bulatović Ćalasan M, Weel AE, Huisman AM, Gerards AH, van Schaeybroeck B, Wulffraat NM, Lindemans J, Hazes JM, de Jonge R. *Methotrexate polyglutamates in erythrocytes are associated with lower disease activity in rheumatoid arthritis patients.* Ann Rheum Dis. (revision)

- Quax RA, **de Jong PH**, Koper JW, van der Wal R, Hop WC, den Dulk AC, Weel AE, Huisman AM, van Zeben D, de Jong FH, Hazes JM, Lamberts SW, Feelders RA. *Recent-onset and longstanding active rheumatoid arthritis are associated with relatively low salivary cortisol levels and decreased dexamethasone-mediated cortisol suppression.* (Submitted)

- **de Jong PH**, Hazes JM, Han HK, Huisman AM, van Zeben D, van der Lubbe PA, Gerards AH, van Schaeybroeck B, de Sonnaville PB, Krugten MV, Luime JJ, Weel AE. *Initial triple DMARD therapy is more efficient than methotrexate monotherapy in recent onset rheumatoid arthritis; 1-year data of a randomized clinical trial (tREACH)*. (Submitted)

- **de Jong PH**, Hazes JM, Luime JJ, Barendregt PJ, van Zeben D, van der Lubbe PA, Gerards AH, de Jager MH, de Sonnaville PB, Grillet BA, Rutten-van Mölken MP, Weel AE. *Best cost-effectiveness and worker productivity with initial triple DMARD therapy compared with methotrexate monotherapy in early rheumatoid arthritis; Cost-utility analysis of the tREACH trial.* (Submitted)

- de Rotte MC, **de Jong PH**, den Boer E, Pluijm SM, Ozcan B, Weel AE, Lindemans J, Hazes JM, de Jonge R. *Methotrexate use and erythrocyte-methotrexate polyglutamate levels are associated with glycosylated hemoglobin in rheumatoid arthritis patients*. (Submitted)

## ABOUT THE AUTHOR

Pascal Hendrik Pieter de Jong was born on July 13th 1980 in Rotterdam, the Netherlands. After graduating athenaeum in 1998 at the Gemini College in Ridderkerk, he started with his medical studies at the University Centre in Antwerpen, Belgium and graduated his propaedeutic examination in 1999. In that same year he was admitted at the Erasmus University Rotterdam for his medical studies. In 2003 he obtained his doctoral medical degree. Two years later, in 2005 after his internships, he received his medical degree cum laude from the Erasmus University Rotterdam. Subsequently, he started his residency in Pediatrics and later on in Internal Medicine. In July 2008 he started the work described in this thesis under the supervision of Prof.dr. J.M.W. Hazes and Dr. A.E.A.M. Weel. In this period he also participate in the Master of Science program Clinical Epidemiology by the NIHES (Netherlands Institute of Health Sciences), from which he graduated in 2011. From January 2012 onwards, he started his residency in Internal Medicine at Erasmus MC (head: Prof.dr. J.L.C.M. van Saase), whereupon in 2015 he will start with his fellowship rheumatology (head: Prof.dr. J.M.W. Hazes).

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## ROLE OF THE FUNDING SOURCE

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