# Individualised biological treatment in rheumatoid arthritis

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# Individualised biological treatment in rheumatoid arthritis

Geïndividualiseerde biological behandeling bij reumatoïde artritis
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op dinsdag 27 januari 2015 des middags te 4.15 uur

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Noortje van Herwaarden
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# one

# GENERAL INTRODUCTION

## RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic autoimmune disease of unknown aetiology. The prevalence is between 0.5% and 1% of the adult population. It affects women about three times more often than men. The onset of the disease is mostly between the fourth and sixth decade of life.[1, 2] RA is characterised by inflammation of synovial joints, most often of the small joints of hands and feet. This leads to pain, stiffness, swelling and subsequent limited function. The inflammation can cause damage to cartilage and bone.[3] Also, systemic manifestations can occur, including for example, skin vasculitis and pulmonary nodules or interstitial fibrosis.[2] The main goal of treatment is to reduce pain and swelling, prevent joint destruction and maintain physical, social and emotional functioning.

## PHARMACOLOGICAL TREATMENT OF RHEUMATOID ARTHRITIS

The pharmacological treatment options for RA have grown steadily the past decades. In the past a limited number of drugs was available including Non-Steroidal Anti Inflammatory Drugs (NSAIDs), conventional synthetic Disease Modifying Anti Rheumatic Drugs (csDMARDs) and glucocorticoids. Whereas NSAIDs only relieve symptoms like pain and stiffness, csDMARDs (like among others methotrexate, sulfasalazine, leflunomide and hydroxychloroquine) and glucocorticoids also influence the natural course of RA.[4]

Due to a better understanding of the pathogenesis of the disease, development of a new group of biological DMARDs (bDMARDs) was possible. These biologic agents target different cells (B- and T-cells) and cytokines (tumor necrosis factor (TNF), interleukin 6 (IL-6)) involved in the inflammatory cascade. Anti-Tumor Necrosis Factor (TNF) agents are a subgroup of these biologic agents. The most widely used anti-TNF agents in rheumatoid arthritis are adalimumab, a human anti-TNF monoclonal antibody against human TNF-α, and etanercept, a human TNF receptor fusion protein. Other anti-TNF agents include certolizumab pegol, infliximab and golimumab. They all have proven to be effective in improving, clinical, functional and radiographic outcomes in patients with RA.[5-9] Other bDMARDs that have demonstrated their effectiveness in RA treatment include rituximab, a chimeric monoclonal antibody against CD20 positive B-cells[10], tocilizumab, a humanised anti-Interleukin-6 (IL-6) receptor antibody against human IL-6-receptor[11] and abatacept, a soluble recombinant fusion protein inhibiting T-cell activation.[12]

With these different treatment options, the current goal in treating RA is to achieve and sustain low disease activity or even remission. To reach that goal, treatment is initiated early in the disease and patients are treated with a combination of different drugs to reach low disease activity as soon as possible.[13, 14] Additionally, a tight control strategy or "treat-to-target", which consists of regular measurement of disease activity and making treatment adjustments to reach a predefined target

(usually low disease activity or remission), has been shown to improve clinical, functional and radiographic outcomes compared with routine outpatient care.[15, 16]

## INDIVIDUALISED TREATMENT

Biological DMARDs have a few drawbacks. One is a modest, in part dose dependant, increased risk of adverse effects, mostly of (serious) infections and skin cancer.[17-20] Another important drawback is the high costs of the bDMARDs, compared to the csDMARDs.[21] Therefore optimal dosing of these drugs is warranted by use of these drugs in the right patients, using the lowest effective dose/longest effective interval and stopping the drug when possible, to achieve optimal effect and minimise adverse effects and costs. The different bDMARDs available for RA have their own pharmacological characteristics and subsequently need different strategies to reach the lowest effective dose. This thesis will therefore discuss several dosing strategies for rituximab, tocilizumab and anti-TNF agents.

### Rituximab

Rituximab is given in RA patients intravenously using two induction infusions two weeks apart. Treatment thereafter is discretionary. Optimal dosing/scheduling of rituximab is therefore different compared to the other bDMARDs, as it is not registered in a fixed treatment schedule. Although the registered dose of rituximab is 2 x 1000 mg, results from the randomised pivotal trials support that 2x 500 mg is equivalent for all major outcomes.[22]

This thesis focuses however not on the dose, but on the retreatment schedule of rituximab. Retreatment is advised after at least 16 weeks.[23] Duration of response to rituximab differs between patients, with most patients needing retreatment within 6 to 12 months.[24-26] This large inter-individual variability in duration of response makes it difficult to optimally time retreatment. Different treatment strategies are being used in clinical practice, including 1) on demand retreatment, with retreatment in case of increase in disease activity, 2) treat-to-target, with retreatment when a predefined target is met, and 3) fixed retreatment, with retreatment for example every 6 months.[22] However, the optimal rituximab treatment strategy for the individual patient has yet to be determined.

### Tocilizumab

The registered dose of tocilizumab is 8mg/kg intravenously every 4 weeks in Europe.[23] Only a few small studies on tocilizumab dose reduction or discontinuation are available at this point. With respect to discontinuation, a tocilizumab discontinuation study showed 35.1% and 13.4% of patients still in low disease activity 24 and 52 weeks after tocilizumab discontinuation, respectively.[27] Another small study with patients who discontinued tocilizumab showed 45.7% of patients still in low disease activity after 52 weeks.[28] In the ACT-RAY study, 86% of patients experienced flare in

disease activity after tocilizumab withdrawal, but responded well when tocilizumab was reinstated.[29] A study following patients after discontinuing tocilizumab because of the ending of clinical trials showed 44% of patients continued to be in remission during the 12 months after tocilizumab withdrawal.[30]

Dose reduction of tocilizumab was studied in only two small studies. One showed no difference in disease activity after tocilizumab dose reduction (from 8mg/kg to 6mg/kg and/or 4 mg/kg) compared to disease activity before dose reduction in 22 patients.[31] The other study lengthened the interval between tocilizumab infusions from every 4 weeks to 6 weeks and then 8 weeks in patients in stable remission and found 35.7% of patients with persistent remission at 7 months follow up.[32]

### Anti-TNF agents

Although use of rituximab and tocilizumab is increasing in RA, the most widely used bDMARDS in RA are anti-TNF agents. The two most used anti-TNF agents are adalimumab, registered as 40 mg subcutaneously every week, and etanercept registered as 50 mg subcutaneously every week or 25 mg twice a week.[23] The last decade, the interest in dose reduction and discontinuation of anti-TNF agents in the context of low disease activity is increasing. Previous research suggests that dose reduction or discontinuation of anti-TNF agents without deterioration of disease activity is possible in a relevant proportion of patients, although success rates are highly variable among studies.[33-52] Study population, outcomes and follow up duration among these studies also vary widely.

Although the data on dose reduction and discontinuation of anti-TNF agents is increasing some important questions on feasibility and applicability remain unanswered. Previous controlled studies mostly used fixed dose reduction or discontinuation without the possibility to escalate or restart again in case of flare.[44, 45] A disease activity guided strategy (monitoring the disease during dose reduction and increasing the dose in case of disease worsening) gives the possibility to titrate to the lowest effective dose for each individual patient. However, it has not been demonstrated that this disease activity guided dose reduction strategy results in equally good care as continuing treatment unaltered.

Dose reduction and discontinuation of bDMARDs appears to be cost effective, however this has not been demonstrated in a controlled setting so far.[33, 53-56] Although titrating patients to the lowest dose may save medication costs, it may also lead to increased number of patient contacts and consequent costs.

## PREDICTION

To further optimize an individual dose reduction strategy, predictors for successful dose reduction or discontinuation are helpful. Flares of disease activity that occur in a considerable proportion of the patients when reducing anti-TNF agent dose can

possibly lead to worsening of function and quality of life and also more radiographic joint damage.[57] Serum drug levels and antidrug antibodies are, amongst others, proposed as possible predictors for successful anti-TNF agent down titration.[58-60] The rationale behind this possible predictive value is that 1) a patient with no/low serum drug levels and/or anti-drug antibodies might be able to successfully stop the TNF inhibitor as effect is not to be expected and 2) a patient with high serum levels should probably be able to reduce the dose as preservation of the same clinical effect is to be expected with a lower dose. However, a dose reduction and discontinuation study in RA patients using infliximab showed no predictive value of serum trough levels and antidrug antibodies for successful dose reduction or discontinuation.[61] For the other bDMARDs these hypotheses have not been tested in practice.

## AIM AND OUTLINE OF THIS THESIS

This thesis explores the possibilities to individualise the dose and dosing-interval of different bDMARDs for patients with RA.

The optimal treatment strategy for rituximab is still unclear. In **chapter 2** we investigated whether the duration of response after the first infusion could be used in timing of future rituximab treatment.

There is limited data available on dose reduction of bDMARDs other than anti-TNF agents. In **chapter 3** the feasibility of disease activity guided dose reduction of tocilizumab in patients with RA and low disease activity is described.

The number of studies on dose reduction and discontinuation of anti-TNF agents is increasing. **Chapter 4** of this thesis is a systematic review on the available evidence of randomised controlled trials and controlled clinical trials on down titration and discontinuation of anti-TNF agents compared to usual care (no dose reduction/ discontinuation) in patients with rheumatoid arthritis and low disease activity.

Although the evidence on dose reduction and discontinuation of anti-TNF agents is increasing a number of questions on feasibility, applicability and cost-effectiveness in daily clinical practice remain. We therefore conducted a randomised clinical non-inferiority trial (Dose REduction Strategies of Subcutaneous TNF inhibitors, DRESS study) on disease activity guided dose reduction of adalimumab and etanercept compared to usual care. In **chapter 5** the design of this study and the choices that were made in the design process are described. **Chapter 6** presents the results of the study, including clinical, functional and radiographic outcomes as well as cost effectiveness.

In a proportion of patients dose reduction of anti-TNF agents leads to an increase in disease activity. Ideally, prior to start of a dose reduction strategy the chance of success is determined using predictive characteristics of that individual patient. Among possible predictors mentioned in previous research are serum drug levels and antidrug antibodies. In **chapter 7** the results of the predictive value of serum

drug levels and antibodies of adalimumab and etanercept before start of a dose reduction strategy in the DRESS study in predicting successful dose reduction or discontinuation are described.

Chapter 8 gives a summary of all our results. Gained insights are discussed, and clinical recommendations and perspectives for future research are suggested.

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# two

## CAN RESPONSE DURATION AFTER THE FIRST RITUXIMAB TREATMENT BE USED IN TIMING OF RITUXIMAB RETREATMENT?

van Herwaarden N, van der Maas A, Jansen TL, Dutmer EA, Hartkamp A, van Riel PL, Kievit W, van den Bemt BJ, den Broeder AA.

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The optimal strategy concerning the moment of Rituximab (RTX) retreatment in patients with rheumatoid arthritis (RA) is yet to be determined.[1] Four different approaches can be conceived. The most prevalent approach is on demand retreatment when the disease activity increases, based on judgement of the physician, after initial response. This, however, inevitably results in temporary deterioration of disease activity and inferior disease control and is possibly associated with worse outcome.[2,3] A second strategy includes a fixed retreatment schedule. However, because response duration varies considerably between patients, the choice of the optimal interval on a group level is difficult. These two strategies have been compared head-to-head, and no differences in disease activity and joint damage progression were found after one year follow up.[4] A third strategy is a treatment-to-target strategy, which is a more formalised adaptation of the first strategy. Emery et al. compared a treatment-to-target strategy with a treatment-as-needed strategy, revealing more patients with major clinical response in the treatment-to-target strategy group. [5] An interesting fourth alternative strategy could be to retreat a patient when there is loss of response (LoR), and thereafter using a fixed interval based on the first response duration. However, this is only feasible when the intra-individual variation in response duration is low, in contrast to the large inter-individual variation.

In this retrospective study, RA patients treated with at least three RTX courses, according to the on demand retreatment strategy, were included. Data were collected from patient charts by two research physicians. The date of LoR was operationalised in two different ways:1/ the start date of the (first infusion of the) next cycle. 2/ The date of clinical LoR, which was based on patient chart review by the research physicians. This last (sensitivity) analysis was added, because the date of retreatment could be biased by other factors, like patient preferences or (non) availability of outpatient-care infusion capacity.

Seventy RA patients were included, with table 1 showing the baseline characteristics. The dosage of the first RTX treatment cycle was 2 x 1000 mg in 69 patients, in 1 patient the dosage was unknown. The dosage of the second RTX cycle was 2 x 1000 mg in 57 patients, 2 x 500 mg in 6 patients and 1 x 1000 mg in 7 patients. Concomitant DMARD treatment changes were infrequent and comparable between first and second interval. Forty patients were treated with systemic corticosteroids at baseline; changes in systemic steroid treatment were also comparable between first and second interval. Mean duration in days until retreatment was 301 (SD 95) for the first and 341 (SD 123) for the second RTX infusion interval. When interval was measured between infusion until LoR it was 252 (SD 93) for the first and 307 (SD 126) days for the second interval. Thus, the mean difference between the first and second interval was 40 days ((SD 119), p=0.003) when measured as time between actual infusions, and 55 days ((SD 127), p=0.0003) when operationalised as clinical LoR. The correlation between the first and second RTX interval was only low to moderate with

**Table 1.** Baseline characteristics

| | n = 70 |
|---|---|
| Age, years (SD) | 58 (10.2) |
| Woman, n (%) | 57 (81) |
| Disease duration, years median [p25-p75] | 13 [6-18] |
| Rheumatoid factor positive, n (%) | 61 (87) |
| Anti-CCP positive, n (%) | 53/65 (76) |
| DAS28 at first RTX (SD) | 5.1 (0.99) |
| Previous DMARDs, n median [p25-p75] | 5 [3-6] |
| Previous biologicals n, median [p25-p75] | 2 [2-3] |
| Concomitant DMARD, n (%) | 32 (46) |
| Concomitant MTX, n (%) | 21 (30) |
| Concomitant corticosteroid, n (%) | 40 (57) |
| Corticosteroid dose, mg (SD) | 10 (4.0) |
| Concomitant statin, n (%) | 7 (10) |

anti-CCP= anti-cyclic citrullinated peptide; DAS28 = 28 joints disease activity score; RTX = rituximab; DMARD = disease-modifying antirheumatic drug; MTX = methotrexate

r=0.43 (p=0.0002), when using the clinical LoR r=0.36 (p=0.002). Figure 1 presents the Bland and Altman analyses between the first and second infusion interval, with limits of agreement of -190 and +272 days.

We hypothesised that the duration of response after the first RTX cycle might be used for individual timing of retreatment, thus reducing both over- and undertreatment. However, perhaps surprisingly, a lack of correlation between the duration of response after the first and second RTX course was found, and therefore the first interval is not useful as basis for a retreatment strategy. An interesting finding in this study was the significantly longer second RTX interval (11 vs 10 months). This phenomenon has not been described in literature before. The larger second interval could not be explained by other RTX dose regimens, as lower dosages were given in the second RTX course. Also, DMARD co medication and corticosteroids were not intensified in the second interval. Although this finding of a longer second interval has to be confirmed, a consequence for daily clinical practice could be that a fixed dose regimen would result in ever increasing overtreatment in a patient with multiple RTX courses.

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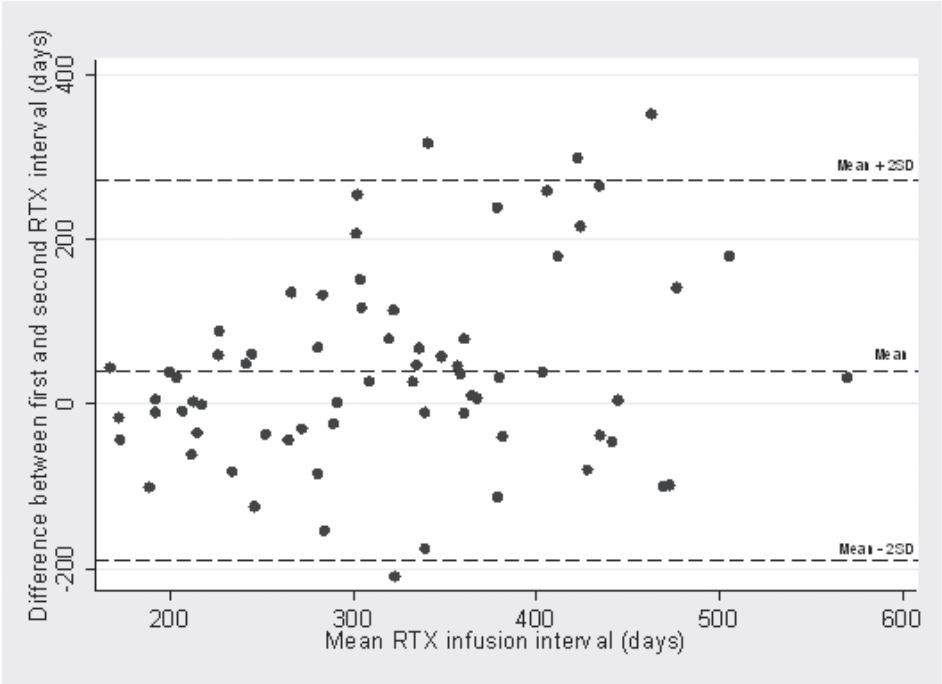


**Figure 1.** Difference between first and second RTX intervals vs. mean duration of the interval.

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# three

## DOSE REDUCTION OF TOCILIZUMAB IN RHEUMATOID ARTHRITIS PATIENTS WITH LOW DISEASE ACTIVITY

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## ABSTRACT

### Objectives

Tocilizumab is effective in the treatment of rheumatoid arthritis (RA). A proportion of patients achieve low disease activity using a lower than registered starting dose. We investigated the feasibility of dose reduction to 4 mg/kg in patients who reached low disease activity at the registered dose of 8 mg/kg.

### Methods

In this retrospective study data were collected of 22 patients successfully treated with tocilizumab 8mg/kg for about 6 months and tapered to 4 mg/kg because of low disease activity. In case of loss of disease control, the dose could be increased again to 8 mg/kg. Percentage of patients with successful dose reduction and difference in DAS28 was described.

### Results

Mean DAS28 at time of dose reduction was 2.3 (SD 0.9). After 3 and 6 months follow up, 77% (95% CI 54-91) and 55% (95% CI 32-76) of patients had successfully reduced the dose without losing disease control, respectively. DAS28 at 3 and 6 months was somewhat higher than baseline, 2.7 (SD 1.2) and 2.5 (SD 1.0) respectively. All patients who experienced worsening of disease activity after dose reduction regained low disease activity after dose escalation.

### Conclusions

Dose reduction of tocilizumab seems feasible in a substantial proportion of patients. Dose escalation after flare was effective in all patients.

## INTRODUCTION

Tocilizumab is an effective treatment in rheumatoid arthritis (RA) patients after failure of disease modifying anti-rheumatic drugs (DMARD) and/or anti-TNF treatment. (1-4) Tocilizumab can be given either as monotherapy (5,6) or in combination with methotrexate or other DMARDs.(1-4)

The optimal dosing of tocilizumab with regard to efficacy and safety is somewhat under debate. Registration in Europe indicates a starting dose of 8 mg/kg, compared to 4 mg/kg with escalation to 8 mg/kg based on clinical response in the United States.(7,8) Although previous research has demonstrated superior efficacy of the higher dose with regard to the clinical outcomes,(9) the majority of patients responds as well to 4 mg/kg.(1-4) Furthermore, radiographic change is similar between both starting doses.(1). Risk of adverse events was analysed in a meta-analysis, (10) revealing no statistical difference with regard to adverse events (AEs), serious adverse events (SAEs) and infections between patients treated with 8mg/kg and 4 mg/kg. However, a significantly greater risk of serious infections was found in the 8 mg/kg group, but after exclusion of one study this difference disappeared. On the other hand, a lower dose of tocilizumab is possibly associated with higher immunogenicity.(1,4) In conclusion, 8 mg/kg is safe and more effective, but a large proportion of patients would be adequately treated with 4 mg/kg as well. A personalised strategy – starting with 8 mg/kg, and tapering in case of low disease activity – could possibly lead to a more cost-effective dosing of tocilizumab.

The number of studies on dose reduction and discontinuation of other biologics – mostly TNF inhibitors - when disease activity is low is increasing. These studies show that a substantial proportion of patients are able to maintain low disease activity after dose reduction.(11-14) Although such studies have not been done on tocilizumab to our knowledge, a stopping study showed that 35% and 13% of RA patients maintained a DAS28<3.2 24 and 52 weeks, respectively, after discontinuation of tocilizumab monotherapy.(15)

Recently, an international consensus statement on IL-6 blocking agents was published,(16) advising to start tocilizumab treatment with 8 mg/kg. Dose reduction to 4 mg/kg is advocated in case of adverse events. Also, a number of future research question is proposed in this consensus statement, with one of these being whether tocilizumab can be withdrawn or dose reduced in patients who have attained low disease activity. Therefore, in this proof of principle study, we examine the proportion of RA patients with successful dose reduction of tocilizumab to 4 mg/kg after achieving low disease activity at a 8 mg/kg dose. Secondary aims are to assess time to flare and the incidence of secondary ineffectiveness after dose escalation.

## MATERIALS AND METHODS

### Design

According to the treatment protocol of the Sint Maartenskliniek Nijmegen, RA patients start with tocilizumab 8 mg/kg every 4 weeks. After about 6 months, dose is reduced to 4 mg/kg if patients have low disease activity (DAS28<3.2 and/or judgement of rheumatologist). In case of loss of disease control after dose-reduction (DAS28>3.2 and/or judgement of rheumatologist), the dose is increased again to 8 mg/kg. In this retrospective observational study, baseline patient-, disease- and treatment characteristics were collected as well as data on disease activity before and 3 and 6 months after dose reduction and when applicable 3 and 6 months after dose escalation.

### Patients

Patients with RA (according to the 2010 ACR RA and/or 1987 ACR RA criteria and/or clinical diagnosis of the treating rheumatologist) treated according to the above mentioned protocol between September 2010 and April 2013 were included. Patients who reduced the dose to 4 mg/kg for the reason of AEs only were excluded; patients with a combination of low disease activity and AEs were included. Written informed consent was obtained for retrospective data collection.

### Statistical analyses

Descriptive statistics were provided with mean (+/- standard deviation (SD)) and median (interquartile ranges) depending on distribution. The proportion and 95% confidence interval (CI) of patients with successful dose reduction after 3 and 6 months was given. A Kaplan-Meier survival curve was used to plot proportion of patients after dose reduction still at a 4 mg/kg tocilizumab dose during 6 months follow up. Baseline characteristics were compared between patients with successful dose reduction and patients who failed dose reduction at 6 months using Fisher's exact test, Student's t-test or Mann-Whitney U-test when appropriate.

## RESULTS

### Patients

Dose was reduced to 4 mg/kg in 22 patients because of low disease activity (figure 1). In 14 patients tocilizumab dose reduction was not attempted, mainly due to non-adherence to the local protocol. Table 1 shows the characteristics of the 22 patients at baseline (tocilizumab start 8 mg/kg). There was no statistically significant difference in the baseline characteristics between patients with successful dose reduction and patients who failed dose reduction at 6 months follow up.

The mean duration of a 8 mg/kg dose before dose reduction to 4 mg/kg was 11 months (SD 6.2). In 5 patients tocilizumab dose was lowered to 4 mg/kg earlier

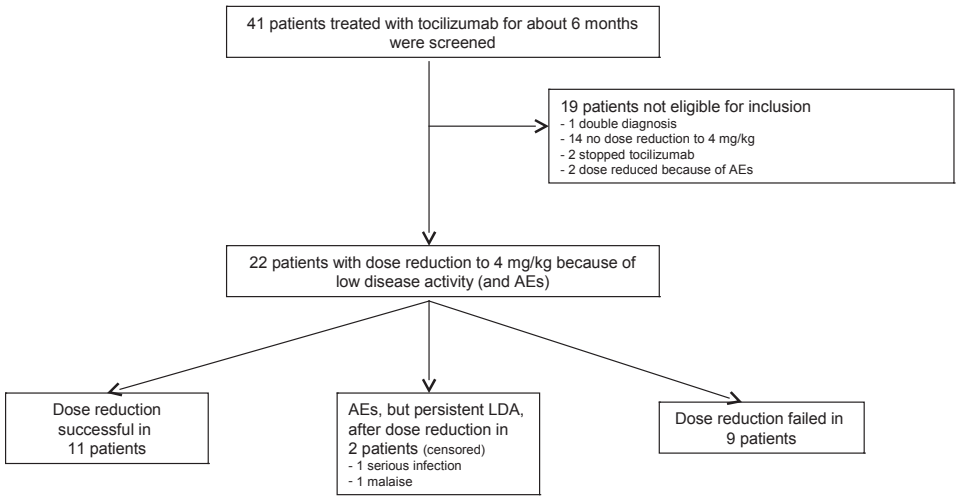


**Figure 1.** Flow diagram of rheumatoid arthritis patients treated according to the dose reduction protocol.
AEs, adverse events; LDA, low disease activity

**Table 1.** Baseline characteristics (start tocilizumab 8mg/kg)

| | All | Successful dose reduction* | Failed dose reduction | p value |
|---|---|---|---|---|
| | n = 22 | n = 13 | n = 9 | |
| Age, years (SD) | 61 (12) | 62 (12) | 59 (13) | 0.50 |
| Woman, n (%) | 20 (91) | 11 (85) | 9 (100) | 0.49 |
| Disease duration, years median [p25-p75] | 10 [5-17] | 10 [8-17] | 10 [5-13] | 0.48 |
| Rheumatoid factor positive, n (%) | 14 (64) | 9 (69) | 5 (56) | 0.66 |
| Anti-CCP positive, n (%) | 14/19 (74) | 9/11 (82) | 5/8 (63) | 0.60 |
| Erosive disease, n (%) | 13 (59) | 9 (69) | 4 (44) | 0.38 |
| DAS28 before start Tocilizumab (SD) | 4.9 (0.9) | 5.0 (0.8) | 4.9 (1.2) | 0.85 |
| Previous DMARDs, n median [p25-p75] | 3 [2-5] | 3 [2-4] | 5 [3-6] | 0.15 |
| Previous biologicals, n median [p25-p75] | 3 [2-5] | 2 [1-4] | 4 [2-5] | 0.24 |
| Concomitant DMARD, n (%) | 11 (50) | 6 (46) | 5 (56) | 1.00 |
| Concomitant MTX, n (%) | 6 (27) | 2 (15) | 4 (44) | 0.18 |
| Concomitant glucocorticoid, n (%) | 14 (64) | 6 (46) | 8 (89) | 0.07 |

*including censored patients
anti-CCP, anti-cyclic citrullinated peptide; DAS28, 28 joints disease activity score; DMARD, disease-modifying antirheumatic drug; MTX, methotrexate

than the local protocol prescribed (< 6 months after tocilizumab start), because of AEs as well as low disease activity. No infusion reactions occurred during the study.

### Proportion on 4 mg/kg Tocilizumab

Three months after dose reduction to 4 mg/kg, 17 out of 22 patients, 77 % (CI 54-91) used 4 mg/kg tocilizumab. After 6 months this was 11 out of 20 patients, 55% (CI 32-76%) (figure 2). Two patients were censored before 6 months follow up. They stopped tocilizumab after dose reduction because of AEs. Seven out of 9 flares after dose reduction (78%), occurred within the first 16 weeks.

### Disease activity score

Figure 3 shows the DAS28 at different time-points. Mean DAS28 at time of dose reduction to 4 mg/kg tocilizumab was 2.3 (SD 0.9). Three months after dose reduction, DAS28 was 2.7 (SD 1.2) and after 6 months 2.5 (SD 1.0) in patients still using 4 mg/kg. Nine patients experienced a worsening of disease activity in the 6 six months after dose reduction to 4 mg/kg. In 7 patients tocilizumab was escalated to 8 mg/kg, in 2 patients dose was escalated to 6mg/kg (because of AEs on 8mg/kg). After tocilizumab dose escalation, 8 patients regained low disease activity based on

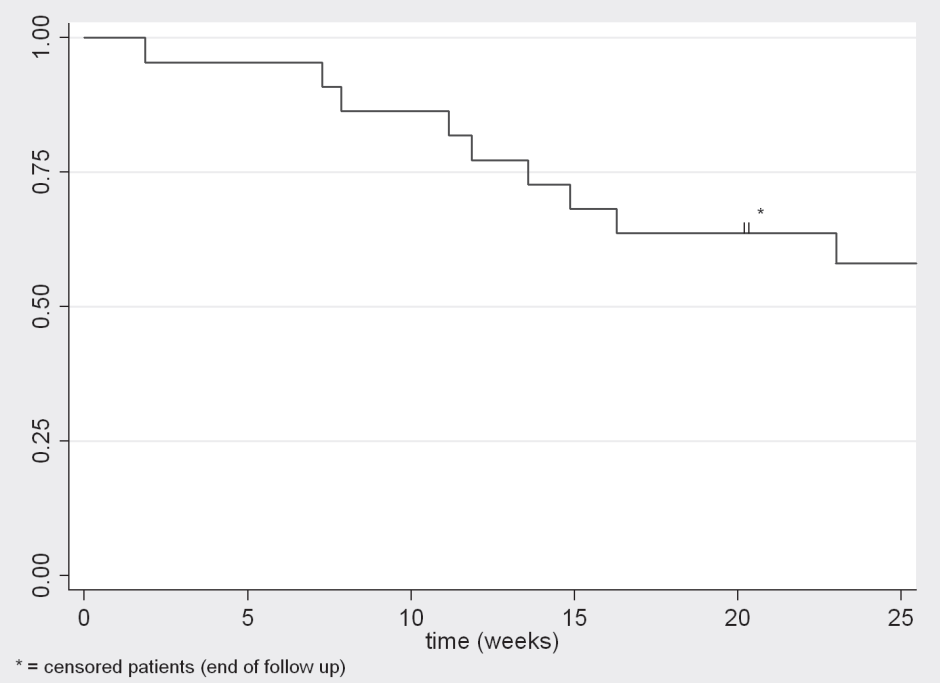


**Figure 2.** Kaplan-Meier curve of tocilizumab 4 mg/kg

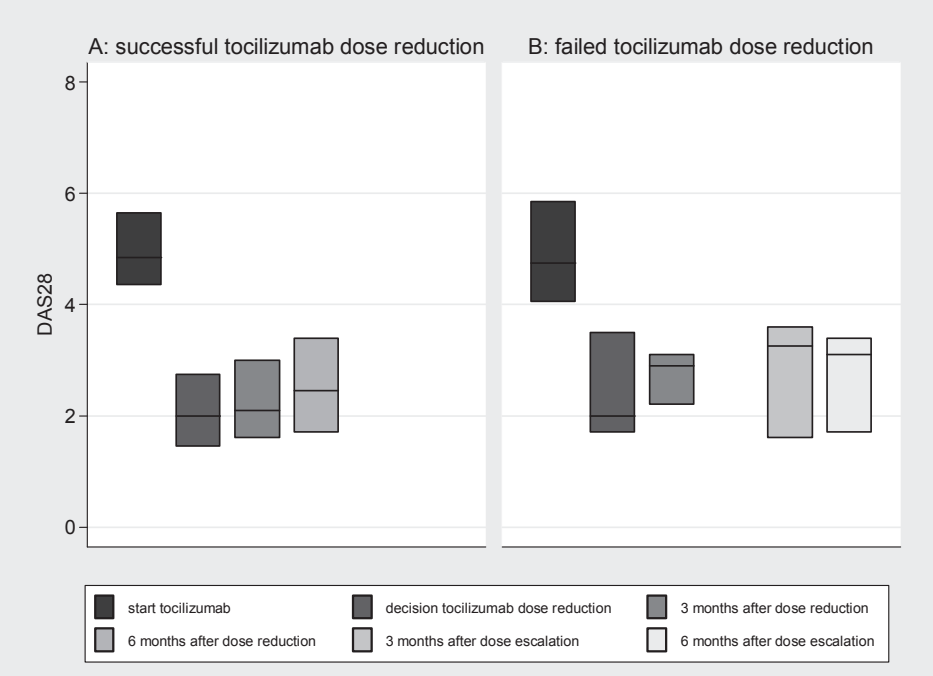


**Figure 3.** Box-plots showing DAS28 at different time-points in patients with successful dose reduction at 6 months follow up (A) and patients who fail in 6 months after dose reduction (B).

clinical judgement, although in one patient time to regain low disease activity was more than 6 months. One patient stopped tocilizumab, because of persistent AEs, but with low disease activity. Mean DAS28 3 months after escalation to 6 or 8 mg/kg was 2.8 (SD 1.0), after 6 months 2.8 (SD1.1).

## Co-medication

DMARD change after dose reduction occurred in 4 patients (1 stopped, 2 dose reduction, 1 dose escalation). All four of these patients still used 4 mg/kg tocilizumab after 6 months. Oral glucocorticoids were escalated in 2 patients after tocilizumab dose reduction; both patients also needed tocilizumab escalation. In 4 patients oral glucocorticoids were reduced or stopped after tocilizumab dose reduction, 3 of these patients needed tocilizumab escalation. Seven patients received either an intra-articular or intramuscular injection, in 4 of these patients tocilizumab was escalated.

## DISCUSSION

In this study we demonstrated the feasibility and safety of dose reduction to 4 mg/kg tocilizumab in RA patients using 8 mg/kg for about six months with low disease activity. Three and six months after dose reduction a substantial proportion of patients still had low disease activity while using 4 mg/kg tocilizumab. Also, flares occurred predominantly in the first four months, and responded well to tocilizumab escalation in all patients.

Although this is a small retrospective study, without a control group, we feel the results are promising as these are the first data presented on this topic. The proportion of patients doing well at a 4 mg/kg dose of over 50% that we found fits nicely within the expected range based on previous trials. The range of ACR50 response on 8 mg/kg tocilizumab in those trials is 29 – 53% and for 4 mg/kg tocilizumab 17-37%; although after different follow up. (1-4) Comparing these ranges shows a relative difference between 4 mg/kg and 8 mg/kg tocilizumab of about 40%, congruent with the more than 50% of patients maintaining response to 4 mg/kg in this study. We did not find predictors for successful those reduction after 6 months, this was not surprising because of the small number of patients in this study.

The mean DAS28 three and six months after dose reduction was somewhat higher than before dose reduction. This increase might be caused by an increase in disease activity caused by dose reduction in some patients. Another contributing factor could be a regression to the mean phenomenon, which has been described previously in RA patients.(17) However, due to the lack of a control group these effects cannot be distinguished.

Change in co-medication after tocilizumab dose reduction could have influenced the results. However, change in DMARD was infrequent and mostly consisted of dose reduction. Change in glucocorticoids was more frequent, but occurred mostly temporarily in patients with worsening of disease activity after dose reduction who also needed tocilizumab escalation. Therefore, overestimation of the success rate of dose reduction due to increase of co-medication is unlikely.

An interesting finding in this study was the time to flare after dose reduction to 4 mg/kg. The large majority of flares occurred during the first 16 weeks after dose reduction; hereafter flaring was infrequent. This finding has also been described in another dose reduction study in infliximab.(11) For clinical practice, this means that it is quickly obvious whether successful dose reduction is feasible or not.

In conclusion, we found that dose reduction of tocilizumab from 8 to 4 mg/kg in responding RA patients is feasible in the majority of patients. Important questions that remain and should be targeted in larger studies with longer follow-up are for example safety, cost-effectiveness and possible risk of progressive radiographic joint damage due to dose reduction. Furthermore, identification of predictors for

successful dose reduction could lead to even more optimal personalised treatment of RA patients using tocilizumab by preventing unnecessary flares.

## ACKNOWLEDGEMENTS

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# four

# DOWN-TITRATION AND DISCONTINUATION STRATEGIES OF TUMOR NECROSIS FACTOR-BLOCKING AGENTS FOR RHEUMATOID ARTHRITIS IN PATIENTS WITH LOW DISEASE ACTIVITY

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*Adapted from the full publication in Cochrane Database Syst Rev. 2014;29(9).*

## ABSTRACT

### Background

Anti-tumor necrosis factor (TNF) agents are effective in treating patients with rheumatoid arthritis (RA), but they are associated with (dose-dependent) adverse effects and high costs. To prevent overtreatment, several trials have assessed the effectiveness of down-titration compared with continuation of the standard dose.

### Objectives

To evaluate the benefits and harms of down-titration (dose reduction, discontinuation or disease activity guided dose tapering) of anti-TNF agents (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab) on disease activity, functioning, costs, safety and radiographic damage compared with usual care in patients with RA and low disease activity.

### Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), Issue 8, 2013; Ovid MEDLINE (1946 to 8 September 2013); EMBASE (1947 to 8 September 2013); Science Citation Index (Web of Science); and conference proceedings of the American College of Rheumatology (2005 to 2012) and European League against Rheumatism (2005 to 2013). We contacted authors of the seven included studies to ask for additional information on their study; five responded.

### Selection criteria

Randomised controlled trials (RCTs) and controlled clinical trials (CCTs) comparing down-titration (dose reduction, discontinuation, disease activity-guided dose tapering) of anti-TNF agents (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab) to usual care/no down-titration in patients with RA and a low disease activity state.

### Data collection and analysis

Two review authors independently selected studies, assessed risk of bias and extracted data.

### Main results

Six RCTs and one CCT (total 1203 participants), reporting anti-TNF down-titration, were included. Three studies (559 participants) reported anti-TNF dose reduction compared with anti-TNF continuation. Five studies (732 participants) reported anti-TNF discontinuation compared with anti-TNF continuation (two studies assessed both anti-TNF discontinuation and dose reduction), and one study assessed disease activity-guided anti-TNF dose tapering (137 participants). These studies include only adalimumab and etanercept; controlled data on other anti-TNF agents are absent.

Two studies were available in full text; one was assessed as having low risk of bias and the other high risk. Five studies were available only as one or more abstracts. Because data provided in these abstracts were limited, risk of bias was unclear. Clinical heterogeneity between the trials was high.

Dose reduction of anti-TNF (etanercept data only) showed no statistically significant or clinical relevant difference in disease activity score in 28 joints (DAS28) (mean difference (MD) 0.10, 95% confidence interval (CI) -0.11 to 0.31) (scale 0.9 to 8; higher score indicates worse disease activity). The proportion of participants who maintained low disease activity was slightly lower among participants given reduced doses of the anti-TNF agent (risk ratio (RR) 0.87, 95% CI 0.78 to 0.98, absolute risk difference (ARD) 9%). Radiographic outcome was slightly worse, but this was not clinically meaningful, compared with continuation of anti-TNF (MD 0.11, 95% CI 0.08 to 0.14) (scale 0 to 448; higher score indicates greater joint damage). Function was not statistically different between anti-TNF dose reduction and continuation (MD 0.10, 95% CI 0.00 to 0.20) (scale 0 to 3; higher score indicates worse functioning). Reinstalment of anti-TNF after failure of dose reduction showed a 5% risk of persistent flare. Data on numbers of serious adverse events (SAEs) (RR 0.58, 95% CI 0.23 to 1.45, ARD -2%) and withdrawals due to adverse events (AEs) (RR 0.57, 95% CI 0.17 to 1,92, ARD -1%) were inconclusive. Most outcomes were based on moderate quality evidence.

Participants who discontinued anti-TNF (adalimumab and etanercept data) had higher mean DAS28 (DAS28-erythrocyte sedimentation rate (ESR): MD 1.10, 95% CI 0.86 to 1.34) and DAS28-C-reactive protein (CRP): MD 0.57 95% CI -0.09 to 1.23) and were less likely to maintain a low disease activity state (RR 0.43, 95% CI 0.27 to 0.68, ARD 40%). Also, radiographic and functional outcomes are worse after anti-TNF discontinuation (MD 0.66, 95% CI 0.63 to 0.69, and MD 0.30, 95% CI 0.19 to 0.41, respectively). Data on numbers of SAEs (RR 1.26, 95% CI 0.61 to 2.63, ARD 2%) and withdrawals due to AEs (RR 0.72, 95% CI 0.23 to 2.24, ARD - 1%) were inconclusive. Most outcomes were based on moderate quality evidence.

The one study comparing disease activity-guided anti-TNF dose tapering (adalimumab and etanercept data) reported no statistically significant differences in functional outcomes (MD 0.20, 95% CI -0.02 to 0.42). Significantly higher mean disease activity was found among participants with tapered anti-TNF at study end (MD 0.50, 95% CI 0.11 to 0.89). No full text of this trial was available for this review. No other major outcomes were reported. All outcomes were based on low quality evidence.

## Authors' conclusions

We can conclude, mostly based on moderate quality evidence, that non-disease activity guided dose reduction of etanercept 50 mg weekly to 25 mg weekly, after at least three to 12 months of low disease activity, seems as effective as continuing

the standard dose with respect to disease activity and functional outcomes, although dose reduction significantly induces minimal and not clinically meaningful differences in radiological progression. Discontinuation (also without disease activity-guided adaptation) of adalimumab and etanercept is inferior to continuation of treatment with respect to disease activity and radiological outcomes and function. Disease activity-guided dose tapering of adalimumab and etanercept seems slightly inferior to continuation of treatment with respect to disease activity, with no difference in function. However the only study investigating this comparison included lower than projected numbers of participants.

Caveats of this review are that available data are limited. Also, the heterogeneity between studies and the suboptimal design choices (including absence of disease activity-guided dose reduction and discontinuation and use of superiority designs) limit definitive conclusions. None of the included studies assessed long-term safety and costs, although these factors are specific reasons why clinicians consider lowering the dose or stopping the administration of anti-TNF agents.

Future research should include other anti-TNF agents; assessment of disease activity, function and radiographic outcomes after longer follow-up; and assessment of long-term safety, cost-effectiveness and predictors for successful down-titration. Also use of a validated flare criterion, non-inferiority designs and disease activity-guided instead of fixed-dose tapering or stopping would allow researchers to better interpret study findings and generalise the information to clinical practice.

## PLAIN LANGUAGE SUMMARY

### Lowering the dose of or stopping anti-TNF drugs in people with rheumatoid arthritis who are doing well

We conducted a review of studies in which the dose of anti-TNF drugs (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab) was lowered or treatment was stopped in people with rheumatoid arthritis (RA) who use anti-TNFs and are doing well. Upon systematically searching for all relevant studies up to September 2013, we found seven studies involving 1203 participants. Study duration ranged from 24 weeks to 18 months.

### What is rheumatoid arthritis? What is stopping or lowering the dose of anti-TNF drugs?

When you have rheumatoid arthritis (RA), your immune system, which normally fights infection, attacks the lining of your joints. This makes your joints swollen, stiff and painful. The small joints of your hands and feet are usually affected first. No cure for RA is known at present, so treatments aim to relieve pain and stiffness, improve ability to move and prevent damage to the joints.

Anti-TNF agents are biological drugs for RA. They reduce complaints of RA by reducing inflammation in the joints, and they reduce radiographic joint damage. Reducing or stopping anti-TNF treatment when disease activity is low might reduce dose-dependent side effects and costs.

### Key results

Data were available for only two anti-TNF agents.

*Disease activity*

- People who lowered the dose of etanercept showed no increase in disease activity compared with people who continued etanercept (moderate-quality evidence).
- People who stopped adalimumab had a 0.6 units increase in disease activity on a scale of 0.9 to 8 compared with people who continued adalimumab (low-quality evidence).
- People who stopped taking etanercept had a 1.1 unit increase in disease activity on a scale of 0.9 to 8 compared with people who continued taking etanercept (moderate-quality evidence).
- People who tried gradual dose reduction of adalimumab or etanercept had a 0.5 unit increase in disease activity on a scale of 0.9 to 8 compared with people who continued adalimumab or etanercept (low-quality evidence).

*RA remission*

- 91 fewer people per 1000 remained in RA remission after the etanercept dose was lowered compared with continuation of 50 mg per week (absolute difference 9%; low-quality evidence).

– 413 fewer people per 1000 remained in RA remission after adalimumab or etanercept was stopped compared with continuation of adalimumab or etanercept (absolute difference 40%; very low-quality evidence).
– No studies were identified that explored how gradual dose reduction of anti-TNF affects RA remission.

*X-ray progression*

– People lowering the etanercept dose showed less than 1 unit more joint damage on x-rays on a scale of 0 to 448 than people who continued etanercept (virtually no change) (moderate-quality evidence).
– People who stopped etanercept showed less than 1 unit more joint damage on x-rays on a scale of 0 to 448 than people who continued etanercept (virtually no change) (moderate-quality evidence).
– No studies were identified that explored how gradual anti-TNF dose reduction would affect joint damage on x-ray.

*Function*

– People lowering the etanercept dose had no worsening of function compared with people who continued etanercept (moderate-quality evidence).
– People who stopped etanercept had a 0.3 increase on a scale of 0 to 3 compared with people who continued etanercept (moderate-quality evidence).
– People who tried gradual dose reduction of adalimumab or etanercept had no worsening of function compared with people who continued adalimumab or etanercept (low-quality evidence).

*Side effects*

– People lowering the dose of etanercept had fewer side effects compared with people who continued etanercept, but this could have happened by chance (moderate-quality evidence).
– People lowering the dose of etanercept had to stop the study because of side effects less often than people who continued etanercept, but this could have happened by chance (moderate-quality evidence).
– People who stopped etanercept had more side effects than those who continued etanercept, but this could have happened by chance (moderate-quality evidence).
– People who stopped etanercept had to stop the study because of side effects less often than people who continued etanercept, but this could have happened by chance (moderate-quality evidence).
– No studies were identified that looked at side effects experienced by people who tried gradual dose reduction of anti-TNF.

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## SUMMARY OF FINDINGS FOR THE MAIN COMPARISON

**Dose reduction in tumor necrosis factor-blocking agents compared with usual care (anti-TNF continuation) in patients with rheumatoid arthritis with low disease activity**

**Patient or population:** patients with rheumatoid arthritis with low disease activity using a standard dose of anti-TNF agents
**Settings:** clinical research centres
**Intervention:** dose reduction of anti-TNF agent
**Comparison:** usual care (anti-TNF continuation)

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | Number of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Anti-TNF continuation | Anti-TNF dose reduction | | | | |
| **Mean disease activity score**<br>Measured by DAS28 (scale from 0.9-8; higher score shows worse disease activity)<br>(follow-up 52 weeks) | Mean DAS28 in the control group was 2.4 | Mean DAS28 in the intervention group was 0.1 higher (0.11 lower-0.31 higher) | | 404<br>(1) | ⊕⊕⊕○<br>**moderate**[a] | Absolute risk difference: 1% more (95% CI from 1% fewer to 4% more)<br>Relative percentage change: 5% worsening (95% CI from 5% improvement to 15% worsening) |
| **Proportion of participants with persistent low disease activity**<br>Measured by DAS28<br>(follow-up 24-52 weeks) | 697 per 1000 | 606 per 1000<br>(543-683) | RR 0.87 (0.78-0.98) | 557<br>(3) | ⊕⊕○○<br>**low**[b] | Absolute risk difference: 9% fewer (95% CI from 17% fewer to 1% fewer)<br>Relative percentage change: 13% worsening (95% CI from 22% worsening to 2% worsening)<br>NNTH = 12 (95% CI from 6 to 471) |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Proportion of participants with persistent loss of response, refractory to reinstalment of tapered anti-TNF**<br>(follow-up 24 weeks) | See comment | 5/52 | Not estimable | 52<br>(1) | ⊕○○○<br>**very low**[c] | No comparison estimable because outcome not measured in control group |
| **Radiographic progression**<br>Measured by modified Sharp-van der Heijde score (scale from 0-448; higher score shows more radiographic joint damage)<br>(follow-up 52 weeks) | Mean radiographic progression in the control group was -0.06 | Mean radiographic progression in the intervention group was 0.11 higher (0.08-0.14 higher) | | 368<br>(1) | ⊕⊕⊕○<br>**moderate**[a] | Absolute risk difference: 0.02% more (95% CI from 0.02% more to 0.03% more)<br>Relative percentage change: 0.3% worsening (95% CI from 0.2% worsening to 0.3% worsening) |
| **Function**<br>Measured by HAQ (scale from 0-3; higher score is worse functioning)<br>(follow-up 52 weeks) | Mean function in the control group was 0.5 | Mean function in the intervention group was 0.1 higher (0-0.2 higher) | | 404<br>(1) | ⊕⊕⊕○<br>**moderate**[a] | Absolute risk difference: 3% more (95% CI from 0% to 7% more)<br>Relative percentage change: 20% worsening (95% CI from 0% to 40% worsening) |
| **Number of serious adverse events**<br>(follow-up 52 weeks) | 59 per 1000 | 34 per 1000<br>(14-86) | RR 0.58 (0.23-1.45) | 404<br>(1) | ⊕⊕⊕○<br>**moderate**[a] | Absolute risk difference: 2% fewer (95% CI from 7% fewer to 2% more)<br>Relative percentage change: 42% worsening (95% CI from 77% worsening to 45% improvement)<br>NNTB = not applicable (not statistically significant) |

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| | | | | | | |
|---|---|---|---|---|---|---|
| **Withdrawals due to adverse events** (follow-up 52 weeks) | 35 per 1000 | 20 per 1000 (6-67) | RR 0.57 (0.17-1.92) | 404 (1) | ⊕⊕⊕◯ **moderate**[a] | Absolute risk difference: 1% fewer (95% CI from 5% fewer to 2% more) Relative percentage change: 43% worsening (95% CI from 83% worsening to 92% improvement) NNTB = not applicable (not statistically significant) |

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** Confidence interval; **NNTB:** Number needed to treat for an additional beneficial outcome; **NNTH:** Number needed to treat for an additional harmful outcome; **RR:** Risk ratio.

GRADE Working Group grades of evidence.
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[a] One study (Smolen 2013 (PRESERVE)), which was sponsored by a pharmaceutical company.
[b] A large proportion of participants was included in studies with unclear risk of bias (allocation concealment and blinding not described (Botsios 2007; van Vollenhoven 2012), and only 1 of 3 studies (Smolen 2013 (PRESERVE)) reported power analyses (most studies published only as abstracts).
[c] One study (Botsios 2007) with unclear risk of bias (allocation concealment and blinding not described), no power analyses and no description of the study population (indirectness) (study published only as an abstract).



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## BACKGROUND

### Description of the condition

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterised by symmetrical joint inflammation often leading to joint damage. Tumor necrosis factor-blocking (anti-TNF) agents have proved effective as therapies for RA (Blumenauer 2002; Blumenauer 2003; Navarro-Sarabia 2005; Ruiz Garcia 2014; Singh 2009; Singh 2010). They improve clinical symptoms and functioning, inhibit joint destruction and have become an important part treatment prescribed for RA.

### Description of the intervention

Treatment of patients with RA has been evolving from traditional step-up regimens to more aggressive step-down strategies. Pivotal to these changes are the early start of treatment (hit early), the use of combination therapy including steroids with rapid escalation to biologics (hit hard) and, most important, frequent assessment of disease activity and treatment modification based on assessment. Strategies incorporating these concepts lead to the swift achievement of low disease activity or remission in most patients, which prevents joint damage and improves function and quality of life. An important disadvantage of the hit-hard approach compared with the traditional step-up approach, however, is that the former method does not allow for individual titration of the minimal effective treatment. Indeed, the traditional step-up approach largely prevents overtreatment, but high(er) disease activity at the beginning of the disease has to be accepted. To prevent overtreatment when high-dose or multi-drug strategies are used, treatment must be tapered down when low disease activity is reached up to the point that disease activity increases again or medication can be stopped. In this way, the minimal effective dose is found and overtreatment is prevented. Optimal dosing of biologics is especially important because of the risk of dose-dependent adverse effects and the risk of low cost-effectiveness due to high cost (den Broeder 2010).

The intervention that is the subject of this review is therefore dose reduction of anti-TNF agents (by adaptation of dose or dosing interval) or discontinuation or both in patients with RA and low disease activity status.

### How the intervention might work

Successful dose reduction or discontinuation of anti-TNF agents can be expected for several reasons. First, amongst patients who seem to respond to treatment with anti-TNF agents are patients who show spontaneous improvement (regression to the mean) (den Broeder 2010; van Vollenhoven 2004); this phenomenon applies to 10% to 30% of all patients, as was shown by proportions of placebo group response (Doherty 2009; St Claire 2004). Second, often concomitant medication is given that might induce a response. Both mechanisms are supported by the fact that a

proportion of patients who seem to do well while taking the drug have (neutralising) antibodies (< 5% to 43%) (Bartelds 2007; Klareskog 2011; Wolbink 2006).

Uncontrolled research has shown that down-titration of anti-TNF agents can be successful in a relevant proportion of patients. Most data are available for infliximab, adalimumab and etanercept, and most are derived from discontinuation studies.

### Why it is important to do this review

Although the adverse effects of anti-TNF agents reported in clinical trials were generally mild in severity, these drugs are associated with unintended effects including increased risk of infection and perhaps a dose-dependent increased risk of malignancy and rare severe adverse events (Bongartz 2006). The introduction of anti-TNF agents-and other biological drugs-has also led to an increase in cost because they are much more expensive than traditional disease-modifying antirheumatic drugs (DMARDs) (van Vollenhoven 2009).

At this time it is appropriate to conduct a systematic review of RCTs of anti-TNF down-titration as well as discontinuation studies, because several RCTs on this topic are emerging.

## OBJECTIVES

To evaluate the benefits and harms of down-titration (dose reduction, discontinuation or disease activity guided dose tapering) of anti-TNF agents (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab) on disease activity, functioning, costs, safety and radiographic damage compared with usual care in patients with RA and low disease activity.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

All randomised controlled trials (RCTs) and controlled clinical trials (CCTs) comparing down-titration of tumor necrosis factorblocking (anti-TNF) agents versus usual care/ no down-titration were considered for inclusion. The minimal required follow-up was six months. Both superiority and non-inferiority trials were included.

#### Types of participants

Patients with RA (1987 (Arnett 1988) and/or 2010 (Aletaha 2010 RA criteria) American College of Rheumatology (ACR) criteria) using anti-TNF agents in a standard (or lower) dosing regimen (adalimumab 40 mg every other week, etanercept 50 mg every week or 25 mg twice a week, infliximab 3 mg/kg every eight weeks, golimumab 50 mg every month, certolizumab pegol 200 mg every other week) for longer than six months and with a low disease activity state (clinical judgement of rheumatologist or

disease activity score in 28 joints (DAS28) < 3.2/DAS < 2.4/Clinical Disease Activity Index (CDAI) < 10/Simplified Disease Activity Index (SDAI) < 11 or DAS28 < 2.6/DAS < 1.6/CDAI < 2.8/SDAI < 3.3 (Aletaha 2005; Fransen 2005) or 2011 ACR/European League Against Rheumatism (EULAR) remission (Felson 2011)).

### Types of interventions

Protocollised down-titration or discontinuation of the antiTNF agent for optimal dose finding (not for other reasons, including reduction of side effects, availability, planned surgery, pregnancy). Non-protocollised change in medication (DMARDs, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids) was allowed. Comparison was usual care/no down-titration/continuation of anti-TNF.

### Types of outcome measures

*Major outcomes*

- Mean disease activity score; DAS28/DAS/CDAI/SDAI at six, 12, 18 and 24 months (Aletaha 2005; Prevoo 1995; Smolen 2003; van der Heijde 1990).
- Proportion of participants with persistent low disease activity (as specified above) after six, 12, 18 and 24 months.
- Proportion of participants with persistent loss of response, refractory to reinstalment of the tapered anti-TNF.
- Radiographic progression, as measured by Larsen (Larsen 1973), Sharp (Sharp 1971) or modified Sharp-van der Heijde score (mSvdH score) (van der Heijde 2000).
- Function (as measured by Health Assessment Questionnaire (HAQ)/Arthritis Impact Measurement Scale (AIMS).
- Number of serious adverse events
- Withdrawals due to adverse events

*Minor outcomes*

- Proportion of participants with a flare (or loss of response) (defined as any composite disease activity index-based flare criteria) during follow-up time.
- Quality of life as measured by Short Form (SF)-12/36,
- Costs (direct and indirect).
- Decremental cost-effectiveness ratio (difference in (direct and indirect) costs divided by difference in quality of life expressed as utility).
- Time to flare.
- Change in other medication (including DMARDs, NSAIDs, corticosteroids).

## Search methods for identification of studies

### Electronic searches

We searched the following electronic databases: the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and Web of Science. This search was not limited by language, year of publication or type of publication. The search period for all databases extended from inception to September 2013.

### Searching other resources

We searched proceedings of conferences from 2005 to 2012 of the ACR and from 2005 to 2013 of the EULAR for abstracts of RCTs and CCTs. We searched reference lists of identified clinical trials and performed citation tracking of the included trials in the ISI Web of Knowledge citation index. We searched trial registries for completed trials and for our ongoing trials table. We contacted experts (first authors of included studies) to ask about additional trials.

## Data collection and analysis

### Selection of studies

Studies were selected on the basis of the inclusion criteria outlined in "Criteria for considering studies for this review". Two review authors (NvH, BJFvdB) independently screened titles and abstracts for inclusion. Full articles were obtained if necessary. Differences were resolved by discussion and consensus and by consultation with a third review author (AAdB) if needed. In case the same study population was described in more than one publication, all publications were used, but for the analysis, all were grouped with the most informative publication as the primary reference and with other publications as secondary references. We kept a record of reasons for exclusion of studies.

### Data extraction and management

Two review authors (NvH, BJFvdB) independently abstracted data from each study using a data extraction form. Differences were resolved by discussion and consensus, and by consultation with a third review author (AAdB) if needed. The data extraction form was pilot-tested on a selection of trials. If necessary, we contacted the authors of a study to ask for missing data. The following data were extracted.

- General study information: first author, author affiliation, publication source and publication year.
- Study characteristics: design, setting, participant selection, method of randomisation, allocation procedure, blinding, inclusion/exclusion criteria and study duration.
- Population characteristics: age, sex, diagnostic criteria, disease duration, DMARD co-medication, previous DMARD use, previous anti-TNF use, rheumatoid factor status, anti-cyclic citrullinated peptide (CCP) status, disease activity state, total

number of participants recruited, total number of participants randomly assigned, total number of participants followed and numbers in each group.
- Intervention characteristics: anti-TNF agent, type of intervention (dose reduction/ interval widening/discontinuation), treatment comparators.
- Outcome measures as noted above.
- Analysis: statistical technique used, intention-to-treat analyses and/or per-protocol analyses used.
- Results with number, mean and standard deviation.





### Assessment of risk of bias in included studies

Risk of bias in the included studies was assessed by two review authors (NvH, BJFVdB) in accordance with the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Domains that were assessed include the following.
- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective reporting.
- Other sources of bias (baseline imbalance in possible prognostic variables: DMARD co-medication, duration of anti-TNF use and disease duration).

Each of these domains was judged as having low risk, high risk or unclear risk of bias.

### Measures of treatment effect

Results of these studies were analysed using RevMan 5.1. Continuous data were expressed as mean differences (MD) or standardised mean differences (SMDs). Dichotomous data were expressed as risk ratio (RRs). Rates were expressed as rate ratio (RRs). Data were summarised in meta-analyses if they were sufficiently homogeneous, both clinically and statistically.

### Unit of analysis issues

Participants were the unit of analysis.

### Dealing with missing data

Missing clinical data in trials were accepted when they represented less than 20% of findings. We planned to perform a sensitivity analysis if more than 20% of the data were missing, to explore the impact of including or excluding these studies. Attempts were made to obtain missing information on parameter variability by contacting the authors of the particular trial. In the event that study authors were not able or were not willing to provide this information, it was estimated from ranges if provided or was estimated from comparable trials.

### Assessment of heterogeneity

We evaluated heterogeneity first clinically by considering comparability across trials on the following variables: type of intervention (dose reduction/discontinuation/disease activity-guided dose tapering), type of anti-TNF agent, duration of anti-TNF use, baseline disease activity (low disease activity vs remission), disease duration, DMARD co-medication and presence of anti-TNF rescue strategy. We examined forest plots and tested for heterogeneity using the $Chi^2$ test with a P value < 0.10 indicating significant heterogeneity. We used the $I^2$ statistic (Higgins 2003) to describe the percentage of variability in effect estimates that is due to heterogeneity rather than to chance. A value greater than 50% may indicate substantial heterogeneity (Higgins 2011). If significant heterogeneity was detected, we did not pool data but performed subgroup analyses in an attempt to explain the heterogeneity.

### Assessment of reporting biases

Publication bias implies that studies that report favourable results are more likely to be published than those describing negative or inconclusive (non-significant) results, leading to a bias in the overall published literature. To minimise the effect of selective reporting of results, we searched trial registries for ongoing and unpublished studies. We found no unpublished studies that finished data collection at time of this review. We found a number of ongoing studies that are potentially interesting for a future update of this review. We planned to use a funnel plot to assess potential publication bias. Because of the small number of studies, however, the funnel plot was not informative.

We assessed reporting bias at the outcome level by comparing outcomes intended to be analysed using published protocols of the studies along with published results of the study.

### Data synthesis

When possible, we analysed data using an intention-to-treat model and, for non-inferiority studies, by also using a per-protocol model. We did this because intention-to-treat analyses can lead to false conclusions of non-inferiority in non-inferiority trials. We analysed outcomes of included studies using a random-effects model.

### Subgroup analysis and investigation of heterogeneity

We planned to do subgroup analyses, if sufficient data were available, for the following candidate effect modifiers: type of intervention (dose reduction/discontinuation/disease activity-guided dose tapering), type of anti-TNF agent, duration of anti-TNF use, baseline disease activity (low disease activity vs remission), disease duration, DMARD co-medication and presence of anti-TNF rescue strategy.

### Sensitivity analysis

We planned to perform the following sensitivity analyses when possible.

- Effect of risk of bias of included studies.
- Effect of imputation of missing data or statistical transformations.

### 'Summary of findings' table

We completed three separate 'Summary of findings' tables included in RevMan 5.2 to improve the readability of the review. Three subgroups of down-titration were examined for the seven outcomes in the separate table: (1) dose reduction, (2) discontinuation and (3) disease activity-guided dose tapering. The study population consisted of participants with RA with low disease activity using a standard dose of anti-TNF. Intervention provided was down-titration (dose reduction, discontinuation or disease activity-guided dose tapering). The intervention was compared with usual care (continuation or no formalised dose reduction of anti-TNF). In addition to the absolute and relative magnitude of effect, the number needed to treat for an additional beneficial outcome (NNTB) and the number needed to treat for an additional harmful outcome (NNTH) were calculated by comparing the intervention group with the control group. We used GRADE (Grades of Recommendation, Assessment, Development and Evaluation) software to conduct an overall grading of the quality of evidence. The GRADE approach specifies four levels of quality (high, moderate, low and very low). The highest quality rating is given for randomised trial evidence. Randomised trial evidence can be downgraded to moderate, low or very low depending on the presence of five factors.

- Limitations in the design and implementation of available studies suggesting high likelihood of bias.
- Indirectness of evidence.
- Unexplained heterogeneity or inconsistency of results.
- Imprecision of results.
- High probability of publication bias.

## RESULTS

### Description of studies

Results of the search are presented in Figure 1 and are described in detail in the next sections of this review.

### Results of the search

The database search in May 2013 (Web of Science) and September 2013 (MEDLINE, EMBASE and CENTRAL) retrieved 1456 search results and after deduplication 1167 search results. Reference checking, making contact with experts and performing additional handsearching of EULAR 2013 abstracts resulted in an additional 12

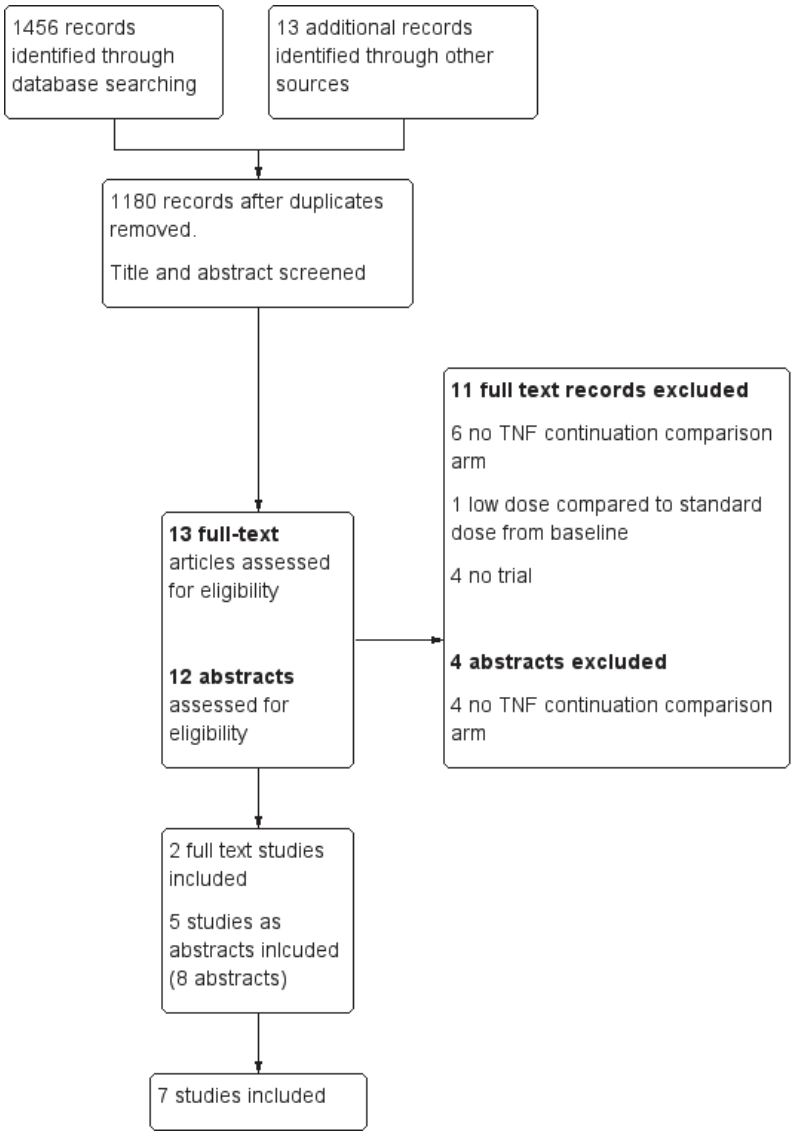


**Figure 1.** Flow chart study selection.

records. We assessed 13 full-text records and 13 abstracts for eligibility. Because several relevant abstracts were presented at conferences very recently, no full text was available for eight eligible abstracts (Botsios 2007; Chatzidionysiou 2012; Emery 2011 (OPTIMA); Fautrel 2012 (STRASS); Fautrel 2013; Kavanaugh 2012; Smolen 2012 (OPTIMA); van Vollenhoven 2012). Two studies included multiple abstracts, which presented different outcomes. Emery 2011 (OPTIMA), Kavanaugh 2012 and Smolen

2012 (OPTIMA) all reported data for the OPTIMA trial. For the purpose of this review, Emery 2011 (OPTIMA) is considered the primary publication. Both Fautrel 2012 (STRASS) and Fautrel 2013 reported data for the STRASS trial. For the purpose of this review, Fautrel 2012 (STRASS) is considered the primary publication. Authors of the included abstracts were contacted for additional information; four of the five authors replied. We learned that these studies are or will be submitted for publication. It is not clear whether the study by Botsios 2007 will be published as full text. Of the full-text records, two were eligible for inclusion: Harigai 2012 (BRIGHT) and Smolen 2013 (PRESERVE). Thus a total of seven studies (Characteristics of included studies) were included in this systematic review.

The total number of participants in the studies included in this review was 1203. Most participants (732) were included in studies comparing anti-TNF discontinuation versus anti-TNF continuation. Studies comparing anti-TNF dose reduction versus continuation included 559 participants. Only one study (137 participants) compared disease activity-guided anti-TNF dose tapering versus continuation. Six studies used a superiority design; one study used a non-inferiority design.

## Included studies

### Anti-TNF dose reduction versus anti-TNF continuation studies

#### Design

Three studies compared anti-TNF fixed-dose reduction versus anti-TNF continuation (Botsios 2007; Smolen 2013 (PRESERVE); van Vollenhoven 2012). All included studies were randomised controlled superiority studies comparing fixed anti-TNF dose reduction versus continuation. Smolen 2013 (PRESERVE) and van Vollenhoven 2012 were blinded placebo-controlled studies that reported three arms (both discontinuation and dose reduction of etanercept compared with etanercept continuation in a 1:1:1 randomisation ratio). The study by Botsios 2007 was reported as an open clinical controlled study; a randomisation ratio was not reported for this study.

The duration of included studies ranged from 24 weeks in Botsios 2007 to 48 weeks in van Vollenhoven 2012 and 52 weeks in Smolen 2013 (PRESERVE). The study by Smolen 2013 (PRESERVE) had a total follow-up of 88 weeks; however 52 weeks of follow-up were provided after randomisation for dose reduction or continuation of etanercept.

#### Sample size

The sample size varied from 73 participants (with 50 participants in this comparison) in the study by van Vollenhoven 2012 to 604 participants (with 404 participants in this comparison) in Smolen 2013 (PRESERVE).

#### Setting

The study by Botsios 2007 was reported as a single-centre study in Italy. Smolen 2013 (PRESERVE) reported that the study was conducted in 80 centres in Europe,

Latin America, Asia and Australia. The abstract reporting the study conducted by van Vollenhoven 2012 provided no information on study setting.

### Participants

The abstract reporting the study by Botsios 2007 did not provide information on participant characteristics. Most participants were female in the studies by van Vollenhoven 2012 and Smolen 2013 (PRESERVE). Mean age was approximately 47 years in the study by Smolen 2013 (PRESERVE) and 57 years in the study by van Vollenhoven 2012. Average disease duration ranged from six to 14 years. Duration of anti-TNF agents had to be > 3 months (Botsios 2007) or ≥ 11 months (van Vollenhoven 2012). Smolen 2013 (PRESERVE) started the anti-TNF agent at study start 36 weeks before randomisation for dose reduction or discontinuation.

In all included studies, participants had to have low disease activity (Smolen 2013 (PRESERVE); van Vollenhoven 2012) or remission (Botsios 2007). Duration of low disease activity had to be ≥ 3 months (Botsios 2007) or ≥ 11 months (van Vollenhoven 2012). Participants in the study by Smolen 2013 (PRESERVE) had to have a mean DAS28 ≤ 3.2 at 12 weeks before randomisation and a DAS28 ≤ 3.2 at the moment of randomisation. All included studies used a DAS28-based criterion to define low disease activity or remission.

### Interventions

Botsios 2007 reported etanercept dose reduction by comparing etanercept 25 mg twice a week versus etanercept 25 mg once a week. Smolen 2013 (PRESERVE) and van Vollenhoven 2012 reported etanercept dose reduction (25 mg/wk) compared with etanercept continuation (50 mg/wk). Participants were required to use methotrexate (MTX) co-medication (dose ranged from 7.5 to 25 mg/wk) in all included studies. In Botsios 2007, MTX and other treatments (not specified further) were continued at the same dosages. Smolen 2013 (PRESERVE) allowed up to three intraarticular corticosteroid injections during the study. However, no attempt was made to recapture low disease activity by reintroducing etanercept in participants whose condition had deteriorated after etanercept withdrawal.

### Outcomes

All studies reported a primary outcome measure. Most studies reported proportion of participants with low disease activity or remission as the primary outcome. All of those studies used DAS28-based criteria but different definitions. Botsios 2007 used DAS28 < 1.6 and Smolen 2013 (PRESERVE) used DAS28 < 3.2. The primary outcome in the study by van Vollenhoven 2012 was proportion of non-failures for etanercept 50 mg/wk versus placebo (failure defined as DAS28 ≥ 3.2 and an increase in DAS28 ≥ 0.6, or disease progression as determined by investigator or participant). Secondary outcomes reported in the included studies were very different. None of the included studies provided data on proportions of participants with a flare, costs or change in comedication.

### Anti-TNF discontinuation versus anti-TNF continuation studies

#### Design

Five of the included studies reported anti-TNF discontinuation compared with anti-TNF continuation (Chatzidionysiou 2012; Emery 2011 (OPTIMA); Harigai 2012 (BRIGHT); Smolen 2013 (PRESERVE); van Vollenhoven 2012). All included studies except Harigai 2012 (BRIGHT) were randomised controlled superiority studies comparing anti-TNF discontinuation versus continuation. Harigai 2012 (BRIGHT) was reported as a retrospective study; however the design indicated that it was a non-randomised controlled clinical trial. Emery 2011 (OPTIMA), Smolen 2013 (PRESERVE) and van Vollenhoven 2012 were blinded placebo-controlled studies. The other studies (Chatzidionysiou 2012; Harigai 2012 (BRIGHT)) were open-label studies. Chatzidionysiou 2012 was reported to be a pilot study. Smolen 2013 (PRESERVE) and van Vollenhoven 2012 reported three arms (both discontinuation and dose reduction of etanercept compared with etanercept continuation).

Smolen 2013 (PRESERVE) and van Vollenhoven 2012 reported a 1:1:1 randomisation ratio. Chatzidionysiou 2012 reported a 1: 1 randomisation ratio. The study by Emery 2011 (OPTIMA) did not report a randomisation ratio. Both Smolen 2013 (PRESERVE) and Emery 2011 (OPTIMA) reported a period (36 weeks and 26 weeks) in which etanercept and adalimumab, respectively, were started, before randomisation was provided for anti-TNF continuation, discontinuation or dose reduction.

The duration of the included studies was 28 weeks for Chatzidionysiou 2012, 48 weeks for van Vollenhoven 2012 and 52 weeks for the other studies. Emery 2011 (OPTIMA) and Smolen 2013 (PRESERVE) reported a total follow-up of 78 weeks and 88 weeks, respectively; however both described 52-week follow-up after randomisation for discontinuation or continuation of the anti-TNF agent.

#### Sample size

The sample size varied from 33 participants in the study by Chatzidionysiou 2012 to 604 participants (with 402 participants in this comparison) in Smolen 2013 (PRESERVE).

#### Setting

Two studies (Smolen 2013 (PRESERVE); Harigai 2012 (BRIGHT)) were reported as multi-centre studies. Smolen 2013 (PRESERVE) reported that the study was conducted in 80 centres in Europe, Latin America, Asia and Australia. Harigai 2012 (BRIGHT) reported that the study was conducted in 29 facilities in Japan. Abstracts reporting the study by Chatzidionysiou 2012, Emery 2011 (OPTIMA) and van Vollenhoven 2012 provided no information on study settings.

#### Participants

Three studies (Emery 2011 (OPTIMA); Smolen 2013 (PRESERVE); van Vollenhoven 2012) reported a minimum age of 18 years for inclusion. Only Smolen 2013 (PRESERVE)

reported an upper age limit (70 years) for inclusion. The mean age of participants was late 50s/early 60s in most studies, except Smolen 2013 (PRESERVE), in which the mean age of participants was about 47 years. Among the included studies, most participants were female. Mean disease duration ranged from six to 14 years, except in Emery 2011 (OPTIMA), in which the mean disease duration was only 3.9 months. Duration of the anti-TNF agent had to be > 3 months (Chatzidionysiou 2012) and ≥ 11 months (van Vollenhoven 2012). Both Emery 2011 (OPTIMA) and Smolen 2013 (PRESERVE) started the anti-TNF agent at study start, 26 and 36 weeks respectively before randomisation for dose reduction or discontinuation. The study by Harigai 2012 (BRIGHT) included participants who were previously treated with adalimumab in another trial; no minimum treatment duration was described. The mean treatment duration of adalimumab at baseline in this study was 46 months.

In all included studies, participants had to have low disease activity (Emery 2011 (OPTIMA); Harigai 2012 (BRIGHT); Smolen 2013 (PRESERVE); van Vollenhoven 2012) or remission (Chatzidionysiou 2012). The duration of low disease activity had to be four weeks (Emery 2011 (OPTIMA)), ≥ 3 months (Chatzidionysiou 2012) or ≥ 11 months (van Vollenhoven 2012). Participants in the study by Smolen 2013 (PRESERVE) had to have a mean DAS28 ≤ 3.2 at 12 weeks before randomisation and a DAS28 ≤ 3.2 at the moment of randomisation. Harigai 2012 (BRIGHT) included participants who were previously treated with adalimumab in another trial and had a DAS28-CRP < 2.7 at the latest adalimumab injection. All included studies used a DAS28-based criterion to define low disease activity or remission.

### Intervention and co-medication

Smolen 2013 (PRESERVE) and van Vollenhoven 2012 reported etanercept discontinuation compared with etanercept continuation. The studies by Chatzidionysiou 2012, Emery 2011 (OPTIMA) and Harigai 2012 (BRIGHT) reported adalimumab discontinuation compared with adalimumab continuation.

Participants were required to use MTX co-medication (dose ranged from 7.5 to 25 mg/wk) in most included studies. Only Harigai 2012 (BRIGHT) also included participants using adalimumab monotherapy. Participants included in Emery 2011 (OPTIMA) were MTX naive at the start of the study (26 weeks before randomisation for discontinuation or continuation of adalimumab). Change in (DMARD) co-medication was allowed in Harigai 2012 (BRIGHT). The study by Smolen 2013 (PRESERVE) allowed up to three intra-articular corticosteroid injections during the study. However, during this study, no attempt was made to recapture low disease activity by reintroducing etanercept in participants whose condition had deteriorated after etanercept withdrawal.

### Outcomes

All studies except the one reported in the abstract by Emery 2011 (OPTIMA) reported a primary outcome measure. These studies reported proportion of participants

with low disease activity or remission as the primary outcome. All studies used DAS28-based criteria, but different definitions were employed. Chatzidionysiou 2012 used DAS28 < 2.6 and Smolen 2013 (PRESERVE) used DAS28 < 3.2 at 28 and 52 weeks follow-up respectively. The primary outcome in the study by Harigai 2012 (BRIGHT) was the percentage of participants who maintained discontinuation of adalimumab for 52 weeks without reaching a DAS28-CRP above 2.7. The primary outcome in the study by van Vollenhoven 2012 was proportion of non-failures for etanercept 50 mg/wk versus placebo (failure defined as DAS28 ≥ 3.2 and an increase in DAS28 ≥ 0.6 or disease progression as determined by investigator and/or participant). Outcomes reported by Emery 2011 (OPTIMA) included proportion of participants with ACR20/50/70, proportion of participants with DAS28 < 3.2, proportion of participants with DAS28 < 2.6, proportion of participants with SDAI ≤ 3.3, proportion of participants with CDAI ≤ 2.8, proportion of participants with change in mSvdH score ≤ 0.5, mean change in mSvdH score, mean HAQ, and adverse events. Secondary outcomes reported in the included studies included many different domains, including participant-reported outcomes (function, quality of life), radiographic outcomes, number of flares, relapsefree survival and safety outcomes. None of the included studies provided data on costs.





### Disease activity-guided dose tapering until stop versus anti-TNF continuation studies

#### Design

One study compared disease activity-guided anti-TNF dose tapering with anti-TNF continuation (Fautrel 2012 (STRASS)). This study was a randomised controlled trial that was reported to be a non-inferiority study. The duration of this study was reported to be 18 months. The projected sample size for this study was 250 participants; however only 137 participants were included.

#### Participants

The mean age of participants included in the study by Fautrel 2012 (STRASS) was 55 years. Most participants were female. Disease duration at baseline was about 10 years. The duration of anti-TNF agents had to be > 1 year. Participants had to have remission for longer than six months, expressed as DAS28 < 2.6.

#### Interventions

Fautrel 2012 (STRASS) reported disease activity-guided dose tapering. Dose tapering in this study was done by increasing the interval between two subcutaneous injections by 50% every three months up to a complete stop in the fourth step; if DAS28 remission was not maintained, dose tapering was suspended or was reversed to the previous interval based on DAS28 level. This intervention was compared with unchanged continuation of adalimumab or etanercept.

### Outcomes

The primary outcome in the study by Fautrel 2012 (STRASS) was disease activity based on repeated DAS28 measures (every three months over 18 months) under the hypothesis of non-inferiority (difference < 0.3 DAS28 points between groups) of the dose tapering group. Secondary outcomes reported were function and radiographic progression.

### Excluded studies

Eleven full-text studies were excluded from this review. Six studies reported anti-TNF down-titration without an anti-TNF continuation control arm. The BeSt study (Klarenbeek 2011; van den Broek 2011; van der Kooij 2009) reported dose reduction of infliximab but included no control group that continued infliximab. Quinn 2005 and Bejarano 2010 also reported data after infliximab discontinuation without an infliximab continuation group. Adalimumab discontinuation was reported in the study by Detert 2013 (HIT-HARD). This study did not include an adalimumab continuation group. Tada 2012 (PRECEPT) reported low-dose versus standard-dose etanercept from study start. The study by Kobelt 2011 provided data from a Markov model. Aletaha 2010, Ichikawa 2007 and Keystone 2003 were overview articles. Four abstracts were excluded from this review. They reported anti-TNF dose reduction (Awan 2011), discontinuation (Smolen 2012; Villeneuve 2012) or both (Emery 2013) without an anti-TNF continuation comparison arm.

## Risk of bias in included studies

See Characteristics of included studies for risk of bias tables with information on all aspects of risk of bias. Figure 2 and Figure 3 provide graphic summaries of the risk of bias in included studies. Five of the seven included studies were published as abstracts only. Therefore most of the items scored remained unclear.

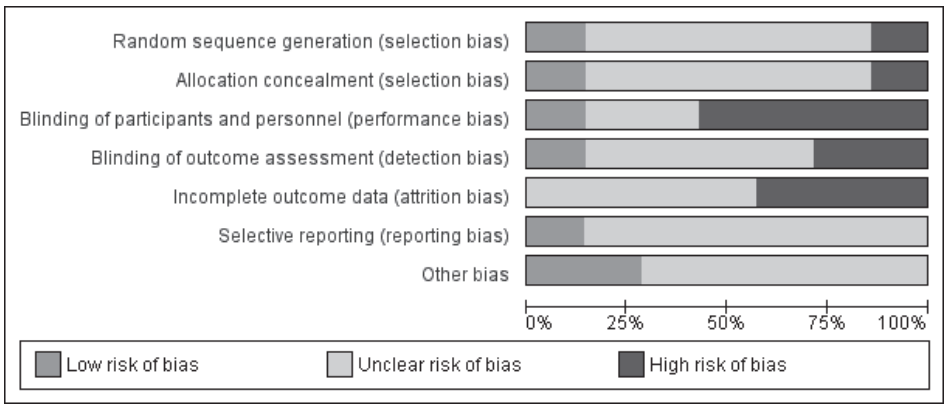


**Figure 2.** Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

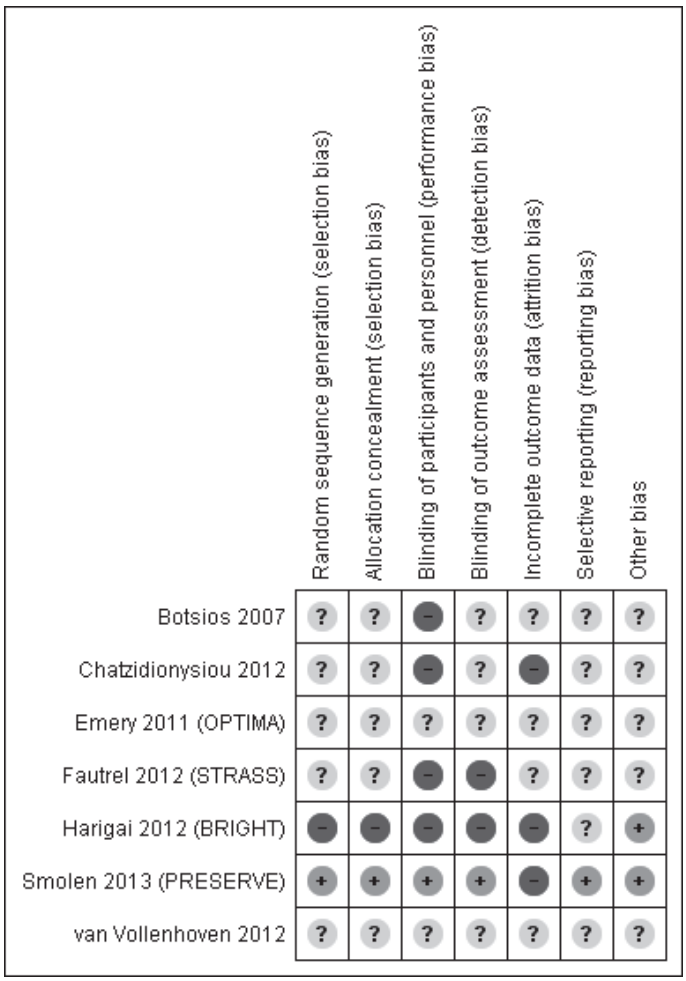


**Figure 3.** Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

## Allocation

One study described an adequate allocation concealment procedure using an ICOPhone interactive voice response system (Smolen 2013 (PRESERVE)). Participants in the study by Harigai 2012 (BRIGHT) were allocated at the discretion of the attending physicians. Methods of randomisation and allocation concealment were not described in the abstracts by Botsios 2007, Chatzidionysiou 2012, Emery 2011 (OPTIMA), Fautrel 2012 (STRASS) and van Vollenhoven 2012.

### Blinding

Three studies were reported to be placebo controlled (Emery 2011 (OPTIMA); Smolen 2013 (PRESERVE); van Vollenhoven 2012). The study by Smolen 2013 (PRESERVE) reported that participants, investigators, data-analysts and study staff were all masked to treatment allocation. The etanercept packages for each participant were identical. The abstracts by Emery 2011 (OPTIMA) and van Vollenhoven 2012 did not provide further details on blinding of physicians and outcome assessors. The other four trials (Botsios 2007; Chatzidionysiou 2012; Fautrel 2012 (STRASS); Harigai 2012 (BRIGHT)) were not placebo controlled. Blinding of outcome assessors was not described in these abstracts. The abstract by Fautrel 2012 (STRASS) reported blinding of X-ray readers only. Independent X-ray readers were blinded to participant characteristics and treatment arms.

### Incomplete outcome data

We used three criteria for judging this item. intention-to-treat analyses, imputation of missing data and attrition rate. Only one study performed an intention-to-treat analysis Smolen 2013 (PRESERVE). This study reported a modified non-responder imputation analysis in which participants who discontinued early because of poor efficacy were imputed as non-responders for all time points; all other participants were analysed by the last-observation-carried-forward method. All other postbaseline analyses were based on the last-observation-carried-forward method (except radiographic endpoints). Chatzidionysiou 2012 used nonresponder imputation for participants with no available DAS28 at the time of the primary outcome (this included most participants who had a flare in the adalimumab discontinuation group). Harigai 2012 (BRIGHT) regarded the DAS28-CRP of participants with missing data for tender joints, swollen joints, CRP or general health visual analogue scale as ≥ 2.7. In some analyses, missing data were replaced with zero for calculation of the theoretical minimum DAS28-CRP. The other abstracts did not describe the procedure for handling missing data (Botsios 2007; Emery 2011 (OPTIMA); Fautrel 2012 (STRASS); van Vollenhoven 2012). The study by Smolen 2013 (PRESERVE) reported fewer participants who completed the study in the group given placebo than in the etanercept 50 mg and 25 mg groups (141 vs 181 and 175 participants). Harigai 2012 (BRIGHT) reported six of 22 and four of 24 with missing data for the primary outcome. Chatzidionysiou 2012 reported that one participant was excluded from each treatment arm. The other abstracts (Botsios 2007; Emery 2011 (OPTIMA); Fautrel 2012 (STRASS); van Vollenhoven 2012) did not describe completion rate.

### Selective reporting

Most studies except Botsios 2007 and Harigai 2012 (BRIGHT) had an available study protocol. Smolen 2013 (PRESERVE) reported prespecified outcomes. The other studies (Chatzidionysiou 2012; Emery 2011 (OPTIMA); Fautrel 2012 (STRASS); van

Vollenhoven 2012) were published as abstracts only and therefore did not report all prespecified outcomes.

#### Other potential sources of bias

Harigai 2012 (BRIGHT) reported a large difference in DMARD co-medication at baseline; however this difference was not statistically significant. In the studies by Chatzidionysiou 2012, Emery 2011 (OPTIMA), Fautrel 2012 (STRASS) and van Vollenhoven 2012, the difference in baseline (prognostic) data was not described.





## Effects of interventions

### Anti-TNF dose reduction versus anti-TNF continuation

#### Major outcomes

See Summary of findings for the main comparison (pages 43-45).

- Mean disease activity: Of the three studies included for this comparison (559 participants), only one study (Smolen 2013 (PRESERVE)) provided data on mean disease activity, with 404 participants. Mean disease activity in participants with reduced etanercept was not statistically significantly different from that in participants who continued etanercept treatment (MD 0.10, 95% CI -0.11 to 0.31 after 52 weeks).
- Persistent low disease activity: All three included studies (Botsios 2007; Smolen 2013 (PRESERVE); van Vollenhoven 2012) provided data on persistent low disease activity, with 557 participants. Although the definition of low disease activity or remission was different across these studies, it was possible to pool the data, and results showed that participants with reduced etanercept were somewhat less likely to maintain low disease activity when compared with participants who continued etanercept (RR 0.87, 95% CI 0.78 to 0.98) (Figure 4).
- Proportion of participants with persistent loss of response, refractory to reinstalment of tapered anti-TNF: Of the three included studies included for this comparison (559 participants), only one study (Botsios 2007) provided data on this outcome, with 105 participants. Proportion of persistent flare after etanercept escalation was five of 52 participants (10%).
- Radiographic progression: Of the three studies included for this comparison (559 participants), one study provided data on radiographic progression (Smolen 2013 (PRESERVE)), with 368 participants. Participants with reduced etanercept dose showed slightly more radiographic damage mSvdH score compared with participants who continued etanercept treatment after 52 weeks (MD 0.11, 95% CI 0.08 to 0.14).
- Function: Of the three studies included for this comparison (559 participants), one study (Smolen 2013 (PRESERVE)) provided data on this outcome, with 404 participants. The mean HAQ-Disability Index (DI) at 52 weeks' follow-up was not statistically significantly different between the etanercept dose reduction group and the etanercept continuation group (MD 0.10, 95% CI 0.00 to 0.20).

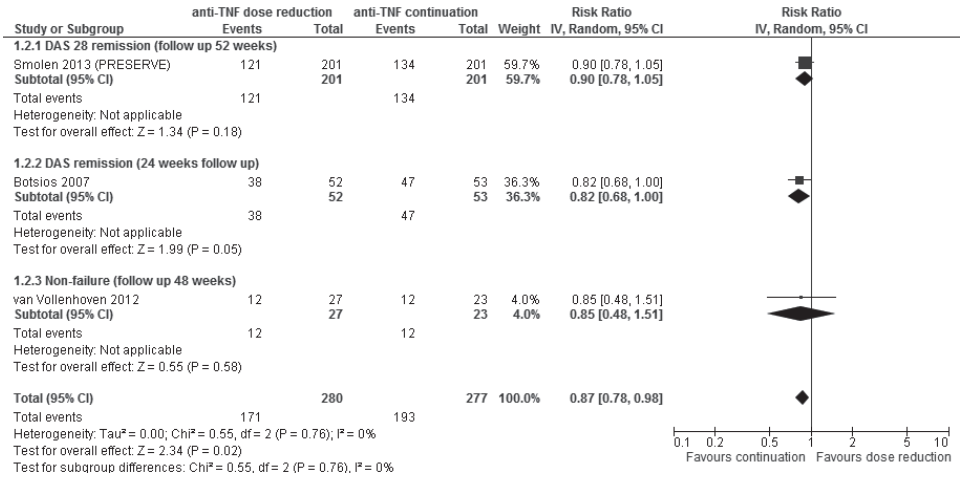


**Figure 4.** Forest plot of comparison: 2 Anti-TNF dose reduction versus anti-TNF continuation, outcome: 2.2 Proportion persistent low disease activity.

- Numbers of serious adverse events: Of the three studies included for this comparison (559 participants), only the fulltext study by Smolen 2013 (PRESERVE) provided data on this outcome, with 404 participants. No statistically significant difference was reported in the total number of adverse events between the etanercept dose reduction group and the etanercept continuation group (RR 0.58, 95% CI 0.23 to 1.45). Two deaths occurred in the group continuing etanercept 50 mg/wk. Few serious adverse events occurred (5%), and most were infections, comparable across study groups.
- Withdrawals due to adverse events: Of the three studies included for this comparison (559 participants), only the full-text study by Smolen 2013 (PRESERVE) provided data on this outcome, with 404 participants. No statistically significant difference in withdrawal due to adverse events was reported in the etanercept dose reduction group compared with the etanercept continuation group (RR 0.57, 95% CI 0.17 to 1.92).

Minor outcomes

- Proportion of participants with a flare: None of the three included studies provided data on this outcome.
- Quality of life: Of the three studies included for this comparison (559 participants), one study (Smolen 2013 (PRESERVE)) provided data on this outcome, with 404 participants. Mean EQ5D after 52 weeks' follow-up was equal in the etanercept dose reduction group and the etanercept continuation group (MD 0, 95% CI -0.04 to 0.04).
- Costs: None of the three included studies provided data on this outcome.
- Decremental cost-effectiveness ratio: None of the three included studies provided data on this outcome.

- Time to flare: Of the three studies included for this comparison (559 participants), one study (van Vollenhoven 2012) provided data on this outcome, with 50 participants. Median time to failure was 48 weeks in the etanercept 50 mg/wk continuation group and 36 weeks in the etanercept 25 mg/wk dose reduction group, but no standard deviations (SDs) were available.
- Change in other medication: None of the three included studies reported data on this outcome.





### Anti-TNF discontinuation versus anti-TNF continuation

See Summary of findings 2 (pages 68-70).

#### Major outcomes

- Mean disease activity: Of the five studies (732 participants) included in this review for this comparison, two studies provided data on mean disease activity (Smolen 2013 (PRESERVE); Harigai 2012 (BRIGHT)), with 402 and 34 participants, respectively. Data were not pooled because different outcome measures (DAS28-ESR vs DAS28-CRP) were used. In the study by Smolen 2013 (PRESERVE), the mean DAS28-ESR was higher in the etanercept discontinuation group than in the etanercept continuation group after 52 weeks (MD 1.10, 95% CI 0.86 to 1.34). In the study by Harigai 2012 (BRIGHT), the mean DAS28-CRP was also higher but this was not statistically significant in the adalimumab discontinuation group compared with the adalimumab continuation group after 52 weeks (MD 0.57, 95% CI -0.09 to 1.23).
- Persistent low disease activity: All five studies provided data on this outcome (728 participants). Chatzidionysiou 2012, Emery 2011 (OPTIMA) and Smolen 2013 (PRESERVE) reported DAS28 remission at 28 weeks and 52 weeks, respectively. Two other studies reported persistent low disease activity but used different definitions. The study by van Vollenhoven 2012 reported proportion of non-failure (with failure defined as DAS28 $\geq$ 3.2 and an increase in DAS28 $\geq$ 0.6 or disease progression as determined by investigator or participant). Data from these five studies were pooled and showed that participants who discontinued anti-TNF treatment were less likely to keep DAS28 low disease activity (RR 0.43, 95% CI 0.27 to 0.68) (Figure 5).
- Proportion of participants with persistent loss of response, refractory to reinstalment of the tapered anti-TNF: None of the five included studies provided data on this outcome. Smolen 2013 (PRESERVE) reported that no attempt was made to recapture low disease activity by reintroducing etanercept in participants whose condition had deteriorated after etanercept withdrawal, raising some ethical discussion in our view.
- Radiographic progression: Of the five studies (732 participants) included in this review for this comparison, one study provided data on this outcome (Smolen 2013 (PRESERVE)), with 351 participants. Participants who discontinued anti-TNF showed slightly more radiographic progression (mSvdH score) compared with those with anti-TNF continuation after 52 weeks (MD 0.66, 95% CI 0.63 to 0.69).

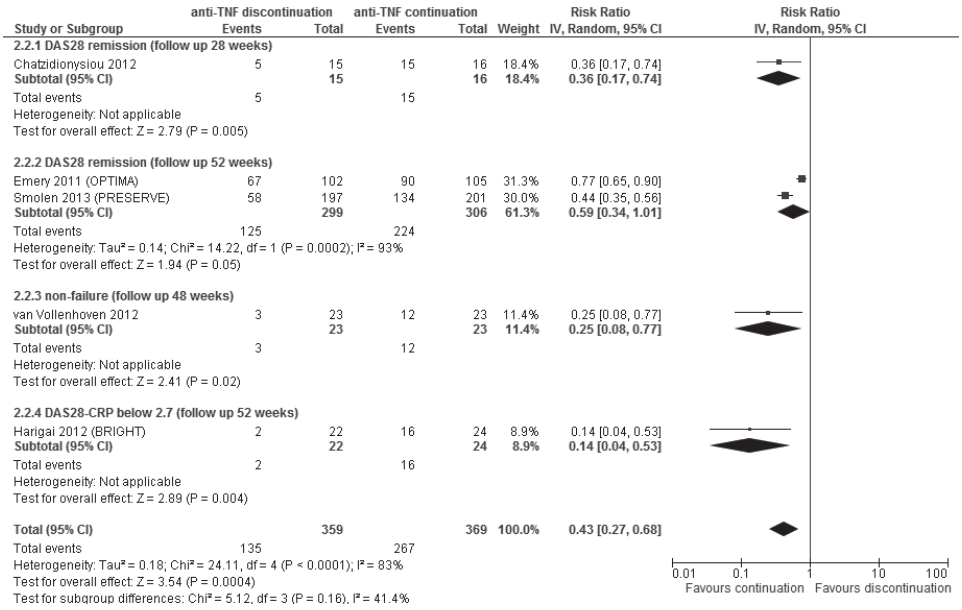


**Figure 5.** Forest plot of comparison: Anti-TNF discontinuation versus anti-TNF continuation, outcome: Proportion persistent low disease activity.

The study by Emery 2011 (OPTIMA) provided data without SDs. The mean change in mSvdH score after 52 weeks was 0.3 for the adalimumab discontinuation group compared with 0.1 for the adalimumab continuation group.

- Function: Of the five studies (732 participants) included in this review for this comparison, one study provided data on this outcome (Smolen 2013 (PRESERVE)), with 402 participants. Participants who discontinued anti-TNF treatment had a higher HAQ score after 52 weeks when compared with participants who continued anti-TNF treatment (MD 0.30, 95% CI 0.19 to 0.41). The study by Emery 2011 (OPTIMA) provided data without SDs. The mean HAQ at 52 weeks was 0.35 for the adalimumab discontinuation group compared with 0.33 for the adalimumab continuation group.
- Numbers of serious adverse events: Of the five studies (732 participants) included in this review for this comparison, only the full-text study by Smolen 2013 (PRESERVE) provided data on this outcome, with 402 participants. No statistically significant difference was reported in the total number of adverse events between the etanercept discontinuation and continuation groups (RR 1.26, 95% CI 0.61 to 2.63). Two deaths occurred in the group continuing etanercept 50 mg/wk. Few serious adverse events occurred (5%), and most were infections; this was comparable across study groups.
- Withdrawals due to adverse events: Of the five studies (732 participants) included in this review for this comparison, only the full-text study by Smolen 2013

(PRESERVE) provided data on this outcome, with 402 participants. No statistically significant difference was reported for withdrawal because of adverse events in the discontinuation group compared with the continuation group (RR 0.72, 95% CI 0.23 to 2.24).

Minor outcomes

- Proportion of participants with a flare: Of the five studies (732 participants) included in this review for this comparison, only one study provided data on this outcome (Chatzidionysiou 2012), with 31 participants. Flare in this study was defined as DAS28 > 2.6 or an increase of more than 1.2 from baseline. Proportion of flare in the adalimumab discontinuation group was not statistically significantly different from that in the adalimumab continuation group (RR 1.6, 95% CI 0.92 to 2.78)
- Quality of life: Of the five studies (732 participants) included in this review for this comparison, one study (Smolen 2013 (PRESERVE)) provided data on this outcome, with 402 participants. Mean EQ5D after 52 weeks' follow-up was lower in the etanercept discontinuation group than in the etanercept continuation group (MD 0.1, 95% CI 0.15 to 0.05).
- Costs: None of the five included studies provided data on direct or indirect costs.
- Decremental cost-effectiveness ratio: None of the five included studies provided data on this outcome.
- Time to flare: Of the five studies included for this comparison (732 participants), two studies (Chatzidionysiou 2012; van Vollenhoven 2012) provided data on this outcome, with 31 and 73 participants respectively. These two studies used different flare/failure criteria. Chatzidionysiou 2012 reported a mean relapse-free survival of 16 weeks (95% CI 10 to 21) in the adalimumab discontinuation group and 22 weeks (95% CI 18 to 26) in the adalimumab continuation group. The study by van Vollenhoven 2012 reported a median time to failure of 48 weeks in the etanercept 50 mg/wk continuation group and six weeks in the etanercept discontinuation (placebo) group, but no SDs were available.
- Change in other medication: Of the five studies included for this comparison (732 participants), only the study by Harigai 2012 (BRIGHT) provided data on this outcome, with 46 participants. Participants who discontinued adalimumab were non-significantly more likely to increase or start MTX treatment compared with participants who continued adalimumab (RR 2.18, 95% CI 0.99 to 4.81). Participants who discontinued adalimumab were also non-significantly more likely to start treatment with other DMARDs than were participants who continued adalimumab (RR 5.45, 95% CI 0.69 to 43.12)

Anti-TNF disease activity-guided dose tapering versus anti-TNF continuation

Only one study reported this down-titration strategy (Fautrel 2012 (STRASS)), with 137 participants and was published only in abstract form (Summary of findings 3, pages 71-72).

Primary outcomes

- Mean disease activity: Mean disease activity among participants who tapered adalimumab or etanercept was slightly higher after 18 months than among participants who continued adalimumab or etanercept (MD 0.50, 95% CI 0.11 to 0.89). Because of the lower than projected number of included participants, non-inferiority could not be established as expected.
- Persistent low disease activity: The abstract did not report data on this outcome.
- Proportion of participants with persistent loss of response, refractory to reinstalment of the tapered anti-TNF: The abstract did not report data on this outcome.
- Radiographic progression: Fautrel 2012 (STRASS) reported only percentage of participants with radiographic progression (progression defined as change in mSvdH score > 1) in 6.7% of those in the dose-tapering group compared with 4.5% in the continuation group. No exact data on radiographic progression were available.
- Function: Mean HAQ at 18 months' follow-up was not statistically significantly different in participants who tapered adalimumab or etanercept compared with participants who continued adalimumab or etanercept (MD 0.20, 95% CI -0.02 to 0.42).
- Number of serious adverse events: The abstract did not report data on this outcome.
- Withdrawals due to adverse events: The abstract did not report data on this outcome.

Minor outcomes

- Proportion of participants with a flare: Fautrel 2012 (STRASS) reported 81% relapse (DAS28 increase > 0.6 and DAS28 > 2.6) in the dose-tapering group compared with 56% in the continuation group.
- Quality of life: The abstract did not report data on this outcome.
- Costs: The abstract did not report data on this outcome.
- Decremental cost-effectiveness ratio: The abstract did not report data on this outcome.
- Time to flare: The abstract did not report data on this outcome.
- Change in other medication: The abstract did not report data on this outcome.

Subgroup and sensitivity analyses

We planned to do a subgroup analysis as described in Subgroup analysis and investigation of heterogeneity. Because of the small number of included studies, analyses were not informative.

We also planned to do sensitivity analyses as described in Sensitivity analysis. Because of the small number of included studies, analyses were not informative.

## SUMMARY OF FINDINGS 2

**Discontinuation of tumor necrosis factor-blocking agents compared with usual care (anti-TNF continuation) in participants with rheumatoid arthritis with low disease activity**

**Patient or population:** participants with rheumatoid arthritis with low disease activity using a standard dose of anti-TNF agents
**Settings:** clinical research centres
**Intervention:** discontinuation of anti-TNF agent
**Comparison:** usual care (anti-TNF continuation)

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | Number of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Anti-TNF continuation | Anti-TNF discontinuation | | | | |
| **Mean disease activity score**<br>Measured by DAS28 (scale from 0.9-8; higher score shows worse disease activity)<br>(follow-up 52 weeks) | Mean DAS28 in the control group was 2.4<br>Mean DAS28-CRP in the control group was 1.9 | Mean DAS28 in the intervention group was 1.1 higher (0.86-1.34 higher)<br>Mean DAS28-CRP in the intervention group was 0.6 higher (0.09 lower-1.23 higher) | | 402 (1)<br>34 (1) | ⊕⊕⊕◯ **moderate**[a]<br>⊕⊕◯◯ **low**[b] | Absolute risk difference: DAS28 14% more (95% CI from 11 % more to 17% more)<br>Relative percentage change: DAS28 52% worsening (95% CI from 41% worsening to 64% worsening)<br>Absolute risk difference: DAS28-CRP 8% more (95% CI from 1% fewer to 15% more)<br>Relative percentage change: DAS28-CRP 33% worsening (95% CI from 5% improvement to 68% worsening) |


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| | | | | | | |
|---|---|---|---|---|---|---|
| **Proportion of participants with persistent low disease activity**<br>Measured by DAS28<br>(follow-up 28-52 weeks) | 724 per 1000 | 311 per 1000 (195-492) | RR 0.43 (0.27-0.68) | 728 (5) | ⊕○○○ **very low**[c] | Absolute risk difference: 40% fewer (95% CI 54% fewer to 26% fewer)<br>Relative percentage change: 57% worsening (95% CI from 73% worsening to 32% worsening<br>NNTH = 3 (95% CI 2 to 4) |
| **Proportion of participants with persistent loss of response, refractory to reinstalment of tapered anti-TNF**<br>(follow-up 0 weeks) | See comment | See comment | Not estimable | 0 (0) | See comment | No studies |
| **Radiographic progression**<br>Measured by modified Sharp-van der Heijde score (scale from 0-448; higher score shows more radiographic joint damage)<br>(follow-up 52 weeks) | Mean radiographic progression in the control groups was -0.06 | Mean radiographic progression in the intervention groups was 0.66 higher (0.63-0.69 higher) | | 351 (1) | ⊕⊕⊕○ **moderate**[a] | Absolute risk difference: 0.14% more (95% CI from 0.14% more to 0.15% more)<br>Relative percentage change: 1.6% worsening (from 1.5% worsening to 1.6% worsening) |
| **Function**<br>Measured by HAQ (scale from 0-3; higher score shows worse functioning)<br>(follow-up 52 weeks) | Mean function in the control groups was 0.5 | Mean function in the intervention groups was 0.3 higher (0.19-0.41 higher) | | 402 (1) | ⊕⊕⊕○ **moderate**[a] | Absolute risk difference: 10% more (95% CI from 6% more to 14% more)<br>Relative percentage change: 60% worsening (95% CI from 38% worsening to 82% worsening) |

Down-titration and discontinuation strategies of tumor necrosis factor-blocking agents for rheumatoid arthritis in patients with low disease activity (Review)
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| | | | | | | |
|---|---|---|---|---|---|---|
| **Number of serious adverse events** (follow-up 52 weeks) | 59 per 1000 | 75 per 1000 (36-156) | RR 1.26 (0.61-2.63) | 402 (1) | ⊕⊕⊕○ **moderate**[a] | Absolute risk difference: 2% more (95% CI from 3% fewer to 6% more)<br>Relative percentage change: 26% improvement (95% CI from 39% worsening to 163% improvement)<br>NNTH = not applicable (not statistically significant) |
| **Withdrawals due to adverse events** (follow-up 52 weeks) | 35 per 1000 | 25 per 1000 (8-78) | RR 0.72 (0.23-2.24) | 402 (1) | ⊕⊕⊕○ **moderate**[a] | Absolute risk difference: 1% fewer (95% CI from 4% fewer to 2% more)<br>Relative percentage change: 28% worsening (95% CI from 77% worsening to 124% improvement)<br>NNTB = not applicable (not statistically significant) |

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** Confidence interval; **NNTB:** Number needed to treat for an additional beneficial outcome; **NNTH:** Number needed to treat for an additional harmful outcome; **RR:** Risk ratio.

GRADE Working Group grades of evidence.
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[a]One study (Smolen 2013 (PRESERVE)), which was sponsored by a pharmaceutical company.
[b]One study (Harigai 2012 (BRIGHT)), which had a high likelihood of bias (no allocation concealment, no blinding), a small sample size and no power analyses.
[c]Statistically significant heterogeneity, imprecision (only 1 of 5 studies with power analyses (Smolen 2013 (PRESERVE)), large proportion of participants in unclear/high risk of bias study (allocation concealment and blinding not described (Chatzidionysiou 2012; Emery 2011 (OPTIMA); Harigai 2012 (BRIGHT); van Vollenhoven 2012) (most studies published only as abstracts (Chatzidionysiou 2012; Emery 2011 (OPTIMA); van Vollenhoven 2012)).


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## SUMMARY OF FINDINGS 3

**Disease activity-guided dose tapering of tumor necrosis factor-blocking agents compared with usual care (anti-TNF continuation) in patients with rheumatoid arthritis with low disease activity**

**Patient or population:** participants with rheumatoid arthritis with low disease activity using a standard dose of anti-TNF agents
**Settings:** clinical research centres
**Intervention:** disease activity-guided dose tapering of anti-TNF agent
**Comparison:** usual care (anti-TNF continuation)

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | Number of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Anti-TNF continuation | Anti-TNF disease activity-guided dose tapering | | | | |
| **Mean disease activity score** Measured by DAS28 (scale from 0.9-8; higher score shows worse disease activity) (follow-up 18 months) | Mean DAS28 in the control group was 2.2 | Mean DAS28 in the intervention group was 0.5 higher (0.11-0.89 higher) | | 137 (1) | ⊕⊕○○ **low**[a] | Absolute risk difference[b] :6% more (95% CI from 1% more to 11% more) Relative percentage change: 28% worsening (95% CI from 6% worsening to 49% worsening) |
| **Proportion of participants with persistent low disease activity** Measured by DAS28 (follow-up 0 weeks) | See comment | See comment | Not estimable | 0 (0) | See comment | No studies |
| **Proportion of participants with persistent loss of response, refractory to reinstalment of the tapered anti-TNF** (follow-up 0 weeks) | See comment | See comment | Not estimable | 0 (0) | See comment | No studies |


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| | | | | | | |
|---|---|---|---|---|---|---|
| **Radiographic progression** Measured by modified Sharp-van der Heijde score (scale from 0-448; higher score shows more radiographic joint damage) (follow-up 0 months) | See comment | See comment | | 0 (0) | See comment | No studies |
| **Function** Measured by HAQ (scale from 0-3; higher score shows worse functioning) (follow-up 18 months) | Mean function in the control group was 0.4 | Mean function in the intervention group was 0.2 higher (0.02 lower-0.42 higher) | | 123 (1) | ⊕⊕◯◯ **low**[a] | Absolute risk difference: 7% more (95% CI from 0.7% fewer to 14% more) Relative percentage change: 50% worsening (95% CI from 5% improvement to 105% worsening) |
| **Number of serious adverse events** (follow-up 0 weeks) | See comment | See comment | Not estimable | 0 (0) | See comment | No studies |
| **Withdrawals due to adverse events** (follow-up 0 weeks) | See comment | See comment | Not estimable | 0 (0) | See comment | No studies |

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence.
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[a]One study (Fautrel 2012 (STRASS)) with unclear risk of bias (allocation concealment not described, no blinding for most outcomes) and no power analyses described/small sample size (study published only as an abstract). Projected sample size for this study was not met.
[b]Study authors used different statistical analyses: mixed linear model on repeated DAS28 measures during the study, which results in a difference between the 2 groups that is not statistically significant.

Down-citration and discontinuation strategies of tumor necrosis factor-blocking agents for rheumatoid arthritis in patients with low disease activity (Review)
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## DISCUSSION

### Summary of main results

This systematic review summarises evidence from six randomised controlled trials and one controlled clinical trial of down-titration of anti-TNF agents in patients with RA with low disease activity. Three different down-titration strategies were considered important: (1) anti-TNF dose reduction, (2) anti-TNF discontinuation and (3) anti-TNF disease activity-guided dose tapering. Available data on these strategies were presented separately.

#### Anti-TNF dose reduction compared with anti-TNF continuation

Three studies (all RCTs on etanercept) reported data on anti-TNF dose reduction compared with anti-TNF continuation. After pooling of data, it can be concluded that participants in the etanercept dose reduction group were somewhat less likely to maintain low disease activity compared with participants in the etanercept continuation group, with no statistically significant difference in mean DAS28 reported in one study. A proportion of participants remained in a low disease activity state after etanercept dose reduction. One study provided data on reinstalment of etanercept after failure of dose reduction and showed a risk of 5% of persistent flare. Participants who reduced the etanercept dose showed slightly more but clinically not meaningful radiographic progression compared with participants who continued etanercept in the study that provided data on this outcome. Function was not statistically significantly different between etanercept dose reduction and continuation. Etanercept dose reduction seems safe; however, data were available for only one study.

#### Anti-TNF discontinuation compared with anti-TNF continuation

Five studies (four RCTs and one CCT) reported anti-TNF discontinuation compared with anti-TNF continuation (adalimumab and etanercept). Different types of outcome measures were reported. Results show that participants in the anti-TNF discontinuation group had higher mean disease activity after discontinuation (data not pooled) and a lower chance of remaining in a low disease activity state (pooled data). However a proportion of participants remained in a low disease activity state after anti-TNF discontinuation. Data on radiographic progression were available from one trial and showed that participants who discontinued etanercept had slightly but statistically significantly more radiographic progression compared with participants who continued etanercept. This same study reported a higher HAQ score after etanercept discontinuation, demonstrating worse functioning. Etanercept discontinuation seems otherwise safe, but data were available for only one study.

### Anti-TNF disease activity-guided dose tapering compared with anti-TNF continuation

One study compared disease activity-guided anti-TNF dose tapering with anti-TNF continuation (adalimumab and etanercept). This study was presented only as as abstract; therefore limited data were available. Function among participants who tapered anti-TNF was reported as not statistically significantly different from that among participants who continued anti-TNF, although we calculated a significant difference in mean disease activity at study end. Of note, the study was designed as a non-inferiority study, but it failed to reach the prespecified sample size; thus non-inferiority could not be established. In a large proportion of participants, adalimumab or etanercept dose could be tapered and/or stopped.

## Overall completeness and applicability of evidence

The number of controlled studies on this matter remains limited, in spite of our effort to track down all relevant studies. We therefore chose to also include in this review studies published only in abstract format. Indeed, of the seven included studies, five were published only as one or more abstracts at the time the search was conducted for this review. Contact with study authors revealed that these studies will be or already have been submitted for publication in the near future. Thus, a future update of this review will be able to include full-text articles of studies now presented only as abstracts, as well as data from several ongoing trials that we found in different trial registries.

Most data on anti-TNF discontinuation were available. Data on dose reduction were limited exclusively for etanercept and only one study on disease activity-guided dose tapering was available. Also of note, no controlled studies on certolizumab pegol, golimumab or infliximab were found.

An important issue is that the design of all but one study does not allow conclusions to be drawn on whether it is a better strategy to attempt dose reduction or just continue the standard dosing schedule in clinical practice. This is a result of two design choices. First, disease activity-guided dose tapering and optimisation should be tested (e.g. lowering the dose up to discontinuation or flare, and in the latter case increasing the dose again to retain low disease activity). Fixed-dose reduction or stopping merely answers the question whether patients remain in low disease activity after stopping or reducing the dose, without taking into account the clinical context wherein physicians' response to flaring of the disease would of course be increasing the dose again. Second, the clinical question 'Can we maintain low disease activity with less therapy?' asks for a non-inferiority design, not a superiority design type of study, with prespecified non-inferiority margins and compatible outcomes and sample size calculations. Indeed, this was the approach used in the more recent study (Fautrel 2012 (STRASS), and this is also being done in several ongoing studies.

A last remark: Although continuous differences in radiographic progression are of interest, more relevant would be the number of participants who exceed the minimal clinically important change in the modified Sharp score, which is around five points per year (Welsing 2006) and much higher than the continuous differences that have been reported.

## Quality of the evidence

### Anti-TNF dose reduction compared with anti-TNF continuation

Using the GRADE approach, we assessed the overall quality of evidence as moderate for five of the seven 'Summary of findings' outcomes in the anti-TNF dose reduction versus continuation comparison. This was done because the single study reporting these four outcomes was determined to have low risk of bias. The only reason for downgrading was that all data were derived from one study, which was sponsored by a pharmaceutical company (high probability of publication bias). The proportion of participants with persistent low disease activity was graded as low. Reasons for downgrading this outcome were as follows: (1) A large proportion of participants were included in an unclear likelihood of bias study, and (2) only one of three studies reported that power analyses were performed (imprecision). The proportion of participants with persistent loss of response, refractory to reinstalment of the tapered anti-TNF, was graded as very low because the only study reporting this outcome had (1) an unclear likelihood of bias study (2) with no power analyses (imprecision). Also the abstract reporting this study (3) did not include an adequate description of the study population (indirectness of evidence).

### Anti-TNF discontinuation compared with anti-TNF continuation

The overall quality of the evidence was moderate for five of the seven 'Summary of findings' outcomes in the anti-TNF discontinuation versus continuation comparison. This occurred because the single study reporting these four outcomes was determined to have low risk of bias. The reason for downgrading was that all data were derived from one study, which was sponsored by a pharmaceutical company (high probability of publication bias). Mean disease activity data were not pooled because the two studies reporting this outcome used different measures (DAS28-ESR vs DAS28-CRP). Therefore the quality of the evidence was assessed separately. The study using DAS28-CRP was graded as low. Reasons for downgrading of this outcome were as follows: (1) a high likelihood of bias and (2) a small sample size combined with no power analyses (imprecision). For the proportion of participants with persistent low disease activity, the following were noted: (1) statistically significant unexplained heterogeneity, (2) imprecision and (3) a large proportion of participants in a study with unclear or high likelihood of bias; therefore the overall quality of evidence for this outcome was very low. The proportion of participants with persistent loss of response, refractory to reinstalment of tapered anti-TNF, was not reported by the included anti-TNF discontinuation studies.

### Anti-TNF disease activity-guided dose tapering compared with anti-TNF continuation

The only study comparing anti-TNF dose tapering until flare or discontinuation versus anti-TNF continuation was published as abstract. Only two of the seven ‚Summary of findings' outcomes could be graded. Mean disease activity and function were graded as low. Reasons for downgrading were as follows: (1) unclear likelihood of bias and (2) no power analyses (imprecision) described/ small sample size.

An update of this review after the included studies are published in full text will provide more information, including details on allocation concealment and methods of blinding, which will improve the quality of the evidence.

## Potential biases in the review process

Two review authors independently reviewed all titles and abstracts, extracted data and performed bias and quality assessment. Therefore, errors in extraction have been minimised.

## Agreements and disagreements with other studies or reviews

To our knowledge, no other systematic reviews have examined anti-TNF down-titration. Recently a systematic review on design and failure definitions in anti-TNF discontinuation studies was published (Yoshida 2014). The review authors concluded that heterogeneity can be seen across studies in both study design and failure definition. This is consistent with the findings reported in our review.

A number of uncontrolled studies have been conducted on downtitration. The results of this review are mostly consistent with these data. Anti-TNF discontinuation is successful in only a limited number of patients compared with dose reduction, which has a higher success rate.

# AUTHORS' CONCLUSIONS

## Implications for practice

A few clear conclusions can be drawn for clinical practice: First, halving the dose of etanercept (without disease activity-guided adaptation) in patients with RA with at least three to 12 months of low disease activity is largely comparable with continuing the standard dose, because the chance of remaining in low disease activityalthough significant-is only slightly lower than after continuation of the full dose. Also, only a non-clinically relevant increase in radiographic damage and no difference in function were found. So, an attempt to halve the dose in patients with low disease activity with RA on full-dose etanercept seems sensible in clinical practice. Second, stopping adalimumab or etanercept (again, without disease activity-guided adaptation) is an inferior strategy compared with continuing the drug in terms of disease control, radiographic damage and function. Finally, one study explored disease activity

guided tapering to stopping of adalimumab and etanercept. Although this seems a more sensible approach than fixed-dose reduction or discontinuation, this strategy is heavily dependent on optimal execution of tight control and treatment to target. In light of the significant and clinically relevant differences observed in mean disease activity at study end, this goal was not met in this study, for unknown reasons. However, functionality and radiographic damage were not different between study arms.

With respect to interpretation, two aspects should be noted: First, even when a strategy of anti-TNF down-titration results in some loss of efficacy, it could still be true that this strategy is in fact extremely cost-effective and reduces long-term adverse effects. Indeed, it is remarkable that not one of the studies presented here included assessment of the very reasons why lowering the dose or stopping of anti-TNF agents is considered in the first place, namely, cost-reduction and long-term safety. Second, in a broader sense, it should be noted that the burden of proof in this case does not lie solely with down-titration compared with continued use. To our knowledge, no controlled data are available on anti-TNF continued use after week 52, including registration studies. So, there remains equipoise on what is the best strategy after one year of treatment with anti-TNF. In this light, the design choices made for these seven trials may in some way reflect the skewed balance between industry-funded and investigator-driven research in this field.

## Implications for research

Our review highlights what is known already about anti-TNF down-titration in patients with low disease activity RA and on the other hand identifies clear gaps in our knowledge. Here we would like to mention a number of aspects that could be targeted in future studies. Of note, most of these points will be adressed already in several ongoing studies.

- For maximal generalisability, data are needed on the whole spectrum of patients with RA who are doing well while taking anti-TNF agents: early and late RA, patients with low disease activity or in deep remission, patients with and without concomitant MTX/other DMARD treatment.
- The design selected for studies comparing an anti-TNF down-titration strategy versus an anti-TNF continuation strategy should be a non-inferiority design instead of the classical superiority design, as the aim is to maintain and not improve clinical outcomes, while minimising the amount of treatment that is needed.
- The intervention should include disease activity-guided dose tapering or stopping of the anti-TNF agent using tight control/treat to target instead of fixed-dose adaptation or stopping, as the former is more compatible with clinical practice and is more likely to be non-inferior to continuation.

- The domain in which both treatment arms should be non-inferior is RA disease control. Although temporary flaring inevitably will be seen more often in the dose-tapering arm, both the incidence of more severe or prolonged flaring and mean disease activity at study end should be comparable.
- Therefore, in addition to mean disease activity, a validated RA flare criterion could be used. Use of (one of ) validated OMERACT DAS28-based flare criteria should be considered (van der Maas 2013 Flare). Use of a validated flare criterion also increases standardisation for future meta-analyses.
- Other outcomes besides disease activity that should be included are cost, quality of life, cost-effectiveness and (longterm) safety, because these constitute the reason why downtitration is contemplated in the first place.
- The drugs that are studied should also include other anti-TNF agents like certolizumab pegol, golimumab and infliximab.
- Prediction of (un)successful dose tapering would further improve outcomes of individualised disease activity-guided dose tapering, and prediction modelling should be considered, using, for example, genetics, imaging, biomarkers and drug levels. Possible gains in a good prediction rule include (1) prevention of unnecessary flaring in patients that cannot be dose reduced and (2) prevention of months of slow dose tapering in patients that can be stopped directly.
- Finally, although outside the scope of this review, efforts should be (and already are) directed toward other non-anti-TNF biologicals (abatacept, tocilizumab) and toward other inflammatory diseases in which biologicals are used, both within rheumatology (ankylosing spondylitis, psoriatic arthritis) and within other medical specialties (gastroenterology, dermatology).





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* *Indicates the major publication for the study*

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies *[ordered by study ID]*

**Botsios 2007**

| | |
|---|---|
| Methods | 24-Week, randomised controlled study in a hospital in Italy |
| Participants | Patients with RA with standard-dose etanercept (25 mg 2×/wk) in combination with methotrexate (7.5-10 mg/wk) and in remission (DAS < 1.6 throughout a 3-month period)<br>Exclusion criterion:<br>• Received other TNF blockers before etanercept enrolment |
| Interventions | Continuation of etanercept (25 mg 2×/wk) + MTX (n = 53), dose reduction of etanercept (25 mg 1×/wk) + MTX (n = 52)<br>MTX was continued at the same dosage in both groups |
| Outcomes | Primary outcome: maintained DAS remission (DAS < 1.6)<br>Secondary outcomes:<br>• HAQ<br>• DAS<br>• Regained remission in case of failure (increase in etanercept dose, switching to another biological agent) on 25 mg 1×/wk<br>• Adverse events |
| Notes | At time of review study, presented in abstract form only<br>No disclosures described |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not described in this abstract |
| Allocation concealment (selection bias) | Unclear risk | Not described in this abstract |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | No blinding described, no placebo |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not described |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | No information on missing data |
| Selective reporting (reporting bias) | Unclear risk | No study protocol available |


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**Botsios 2007** (*Continued*)

| | | |
|---|---|---|
| Other bias | Unclear risk | Difference in baseline (prognostic) data not described |

**Chatzidionysiou 2012**

| | |
|---|---|
| Methods | 52-Week, multi-centre, randomised, controlled, open-label pilot study |
| Participants | Patients with RA in stable remission (DAS28 < 2.6 for ≥ 3 months) given combination therapy with adalimumab + MTX<br>Age (median, IQR) 61 (53-65) years, 67% female, disease duration 8 (5-15) years, DAS28 1.86 (1.53-2.39) |
| Interventions | Discontinue adalimumab and continue MTX (n = 15), continue both adalimumab and MTX (n = 16)<br>MTX dose 12.5 to 20 mg/wk |
| Outcomes | Primary outcome: proportion of participants in remission (DAS28 < 2.6) at week 28 in both arms<br>Secondary outcomes:<br>• Proportion of participants with at least 1 flare (DAS28 > 2.6 or increase of more than 1.2 from baseline) during first 28 weeks<br>• Proportion of participants with at least 1 DAS28 > 2.6 during first 28 weeks<br>• Proportion of participants with at least 1 DeltaDAS28 > 1.2 during first 28 weeks<br>• Proprtion of participants with at least 1 DeltaDAS28 > 0.6 during first 28 weeks<br>• Proportion of participants with at least 1 DAS28 > 2.6 AND DeltaDAS28 > 1.2 during first 28 weeks<br>• Proportion of participants with at least 1 DAS28 > 2.6 AND DeltaDAS28 > 0.6 during first 28 weeks<br>• Relapse-free survival |
| Notes | Acronym ADMIRE<br>Pilot study<br>Funding?<br>At time of review, study presented in abstract form only<br>No disclosures described |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not described in this abstract |
| Allocation concealment (selection bias) | Unclear risk | Not described in this abstract |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | "Open-label study" |


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**Chatzidionysiou 2012** (*Continued*)

| | | |
|---|---|---|
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not described in this abstract |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | "Nonresponder imputation was performed for patients with no available DAS28 at week 28 (this included most patients who had a flare in the discontinuation group and restarted adalimumab)" |
| Selective reporting (reporting bias) | Unclear risk | Study protocol available. Not all outcome measures described in this abstract |
| Other bias | Unclear risk | Differences in baseline (prognostic) data not described |

**Emery 2011 (OPTIMA)**

| | |
|---|---|
| Methods | 78-Week, randomised, placebo-controlled trial<br>Period 1: weeks 0 through 26, rerandomisation at week 26; period 2: weeks 26 through 78 |
| Participants | Period 1:<br>• MTX-naive participants ≥ 18 years, RA < 1 year, active disease (DAS28 > 3.2, ESR ≥ 28 mm/h or CRP ≥ 1.5 mg/dL), > 1 erosion, RF positive or anti-CCP positive<br>Period 2:<br>• Adalimumab + MTX during period 1 of the study, stable low disease activity (DAS28 < 3.2) at weeks 22 and 26<br>• Mean disease duration 3.9 months |
| Interventions | Period 1:<br>• Adalimumab + MTX (n = 515), placebo + MTX (n = 517)<br>Period 2:<br>• Adalimumab + MTX (n = 105), placebo + MTX (n = 102)<br>• MTX dose not described |
| Outcomes | Primary outcome (period 2): not described<br>Outcomes:<br>• Proportion of participants with ACR20/50/70<br>• Proportion of participants with DAS28 < 3.2<br>• Proportion of participants with DAS28 < 2.6<br>• Proportion of participants with SDAI ≤ 3.3<br>• Proportion of participants with CDAI ≤ 2.8<br>• Proportion of participants with ΔmTSS ≤ 0.5<br>• Mean change in mSvdH score<br>• Mean HAQ<br>• Adverse events |




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**Emery 2011 (OPTIMA)** (*Continued*)

| | | |
|---|---|---|
| Notes | Acronym OPTIMA<br>Funding?<br>At time of review, study presented in abstract form only<br>Disclosures: P Emery: Grant/Research support from Abbott, Merck, Pfizer, Roche, BMS; consultant for Abbott, Merck, Pfizer, Roche, BMS | |
| ***Risk of bias*** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Unclear risk | Randomised trial, method not described |
| Allocation concealment (selection bias) | Unclear risk | Not described in this abstract |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Placebo controlled. No information on blinding of personnel |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not described |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | No information on missing data |
| Selective reporting (reporting bias) | Unclear risk | Study protocol available. Not all outcome measures described in this abstract |
| Other bias | Unclear risk | No baseline (prognostic) data on moment of rerandomisation |

**Fautrel 2012 (STRASS)**

| | |
|---|---|
| Methods | 18-Month, randomised, controlled study in France |
| Participants | Patients with RA according to ACR 1987 criteria, using etanercept or adalimumab > 1 year (as monotherapy or in combination), prednisone ≤ 5 mg/d, DAS28 remission (DAS28 < 2.6) for > 6 months, stable damage on X-rays<br>Age (mean, SD) 55 years, female 78%, disease duration 9.5 (8.0) years, 68% rheumatoid factor positive, 78% anti-CCP positive, DAS28 1.8 (0.6), 54% etanercept, 46% adalimumab |
| Interventions | Etanercept or adalimumab spacing (interval between 2 subcutaneous injections increased by 50% every 3 months up to a complete stop in fourth step. If DAS28 remission was not maintained, dose tapering was suspended or reversed to the previous interval based on DAS28 level) (n = 64), Etanercept or adalimumab maintenance (n = 73) |




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**Fautrel 2012 (STRASS)** (*Continued*)

| | |
|---|---|
| Outcomes | Primary outcome: disease activity, based on repeated DAS28 measures (every 3 months over 18 months) under the hypothesis of non-inferiority of the spacing group<br>Secondary outcomes:<br>• Change in DAS28<br>• Change in HAQ<br>• Relapse (DAS28 increase > 0.6 and DAS28 > 2.6)<br>• X-ray damage assessed by vdH-SHS (progression defined as change in mSvdH score > 1) |
| Notes | Acronym STRASS<br>At time of review, study presented in abstract form only<br>Disclosures: none declared |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not described in this abstract |
| Allocation concealment (selection bias) | Unclear risk | Not described in this abstract |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Open study<br>Independent X-ray readers, blinded to participant characteristics and treatment arm |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Open study<br>Independent X-ray readers, blinded to participant characteristics and treatment arm |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Not described |
| Selective reporting (reporting bias) | Unclear risk | Study protocol available. Not all outcome measures described in this abstract |
| Other bias | Unclear risk | Differences in baseline (prognostic) data not described |

**Harigai 2012 (BRIGHT)**

| | |
|---|---|
| Methods | 52-Week, non-randomised controlled clinical trial<br>(described as a retrospective study; however prospective design) |
| Participants | Patients with RA with low disease activity (DAS28-CRP < 2.7) who had participated in an adalimumab open extension trial (M03-651 or M05-775)<br>Adalimumab discontinuation (n = 22): age (mean, SD) 55.7 (14.2), 63.6% female, disease duration 10.3 (9.0) years, 81.8% rheumatoid factor positive, DAS28-CRP 1. |


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**Harigai 2012 (BRIGHT)** (*Continued*)

| | | |
|---|---|---|
| | 6 (0.3), use of MTX between weeks -26 and 0: 13.6%, use of corticosteroids between weeks -26 and 0: 40.9%<br>Adalimumab continuation (n = 24): age (mean, SD) 60.1 (12.7), 79.2% female, disease duration 10.3 (7.3) years, 87.5% rheumatoid factor positive, DAS28-CRP 1.8 (0.5), use of MTX between weeks -26 and 0: 29.2%, use of corticosteroids between weeks -26 and 0: 62.5% | |
| Interventions | Adalimumab continuation (n = 24), adalimumab discontinuation (n = 22)<br>Participants were assessed in a clinical practice setting, and treatments were adjusted accordingly. The protocol required no treatment change or modification | |
| Outcomes | Primary outcome: percentage of participants who maintained discontinuation of adalimumab for 52 weeks without incurring elevation of DAS28-CRP to > 2.7<br>Secondary outcomes:<br>• Change in disease activity<br>• Treatment change | |
| Notes | Acronym BRIGHT<br>No disclosures described | |
| ***Risk of bias*** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | High risk | Participants continued or discontinued adalimumab at the discretion of attending physicians, risk of confounding by indication |
| Allocation concealment (selection bias) | High risk | No concealment |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | No blinding |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | "The patients were assessed in a clinical practice setting and treatments were adjusted accordingly" |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | For the DAS28 outcome: discontinuation group 7/22 missing, continuation group 5/24 missing<br>For the flare outcome: discontinuation group 6 unknown (calculated as flare), continuation group 4 unknown |
| Selective reporting (reporting bias) | Unclear risk | Study protocol not available |


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**Harigai 2012 (BRIGHT)** (*Continued*)

| | | |
|---|---|---|
| Other bias | Low risk | Large difference in DMARD co-medication at baseline; however not reported to be statistically significant |

**Smolen 2013 (PRESERVE)**

| | |
|---|---|
| Methods | 88-Week, randomised, placebo-controlled trial in 80 centres in Europe, Latin America, Asia and Australia<br>Open-label period: weeks 0 through 36. Randomisation at week 36. Double-blind period: weeks 36 through 88 |
| Participants | Open-label period:<br>• Inclusion criteria: rheumatoid arthritis, aged between 18 and 70 years, moderate disease activity at screening and at baseline (DAS28 > 3.2 and ≤ 5.1), stable MTX (15-25 mg/wk) for at least 8 weeks before screening<br>• Exclusion criteria: previous/current biologicals, DMARD other than MTX within 28 days of baseline, more than 1 NSAID at baseline, prednisone > 10 mg/d or a dose that was changed within 14 days of screening, IA or IV or IM or SC glucocorticoids within 28 days of screening, live vaccine within 28 days of baseline, tuberculosis in the previous 2 years, latent tuberculosis infection and not treated according to local guidelines or not started before etanercept<br>Double-blind period:<br>• Inclusion criteria: completed the open-label stage, sustained low disease activity (mean DAS28 ≤ 3.2 from weeks 12 to 36 and DAS28 ≤ 3.2 at week 36)<br>• Exclusion criteria: dose of NSAID or prednisone changed within 14 days of randomisation, prednisone > 10 mg/d, MTX dose changed within 8 weeks of randomisation (except for reducing dose because of adverse events)<br>Etanercept 50 mg/wk (n = 202): age (mean, SD) 48.1 (12.0) years, 164 (81%) female, disease duration 6.8 (7.2) years, 147 (73%) rheumatoid factor positive, 161 (80%) anti-CCP positive, DAS28 at week 36: 2.0 (0.6)<br>Etanercept 25 mg/wk (n = 202): age (mean, SD) 46.4 (12.2) years, 157 (78%) female, disease duration 6.4 (7.1) years, 142 (71%) rheumatoid factor positive, 156 (78%) anti-CCP positive, DAS28 at week 36: 2.1 (0.6)<br>Placebo (n = 200): age (mean, SD) 48.3 (12.2) years, 167 (84%) female, disease duration 7.3 (6.7) years, 147 (74%) rheumatoid factor positive, 156 (79%) anti-CCP positive, DAS28 at week 36: 2.1 (0.6) |
| Interventions | Open-label period:<br>• Etanercept 50 mg/wk + MTX (n = 834)<br>Double blind period:<br>• Etanercept 50 mg/wk + MTX (n = 202), etanercept 25 mg/wk + MTX (n = 202), placebo + MTX (n = 200)<br>• MTX dose maximum 25 mg/wk |
| Outcomes | Primary outcome (double-blind period): proportion of participants with DAS28 ≤ 3.2 in the etanercept 50 mg/wk versus placebo group at week 88 (52 weeks after randomisation)<br>In case of significantly more low disease activity in the etanercept 50 mg/wk group compared with placebo, the conditional primary endpoint was proportion of participants |


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**Smolen 2013 (PRESERVE)** (*Continued*)

| | |
|---|---|
| | receiving etanercept 25 mg/wk who achieved DAS28 ≤ 3.2<br>Secondary outcomes:<br>• Remission (DAS28 < 2.6, SDAI ≤ 3.3, ACR/EULAR Boolean-based definition)<br>• LDA (SDAI ≤ 11)<br>• ACR20, ACR50 or ACR70 response<br>• EULAR good or moderate response<br>• Physical function HAQ-DI<br>• Change from baseline in DAS28, CDAI, SDAI<br>• Change from baseline in TJ counts, SJ counts, CRP, ESR<br>• Change from baseline in morning stiffness<br>• Change from baseline in participant global, GH and pain<br>• Change from baseline in physician global<br>• Time to loss of efficacy (loss of DAS28 LDA and change in DAS28 ≥ 0.6; discontinuation due to poor efficacy, protocol violation or another reason)<br>• Participant-reported outcomes: HAQ-DI, EuroQol-5 total, medical outcomes, study sleep scale, functional assessment of chronic illness, therapy measurement, brief pain inventory, work productivity and activity impairment scale for RA<br>• Radiographic outcome (proportion of participants-non-progressors-achieving an mSvdH score progression rate of up to 0.5 units per year or up to 2.0 units per year (smallest detectable difference))<br>• Adverse events |
| Notes | Acronym PRESERVE<br>"PRESERVE was sponsored by Wyeth, which was acquired by Pfizer in October 2009. Pfizer was responsible for data collection and analyses. The academic authors and sponsors representatives were involved in the study design, data analyses, data interpretation, writing of the report, and the final decision to submit for publication. Biostatisticians at Pfizer did and verified all data analyses. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication. "<br>Disclosures: J Smolen has received honoraria for consultations or speaking engagements or grant support or both from Abbott, Amgen, AstraZeneca, Bristol-Myers Squibb, Celgene, GlaxoSmithKline, MSD, Novo Nordisk, Pfizer, Roche, Sandoz, Sanofi and UCB |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "randomly assigned by a centralised system" |
| Allocation concealment (selection bias) | Low risk | "allocation of patients to treatment groups was done with the ICOPhone interactive voice response system on the basis of information supplied by the investigator or the study staff" |


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**Smolen 2013 (PRESERVE)** (*Continued*)

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | "patients, investigators, data-analysts and study staff were all masked to treatment allocation"<br>"etanercept packages for each patient were identical" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | "patients, investigators, data-analysts and study staff were all masked to treatment allocation" |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | "Patients who discontinued early because of poor efficacy were imputed as non-responders for all time points"<br>"Significantly more patients discontinued in group given placebo than in 50 mg and 25 mg groups" |
| Selective reporting (reporting bias) | Low risk | Study protocol available<br>Similar outcome measures in the paper compared to the protocol |
| Other bias | Low risk | No |

**van Vollenhoven 2012**

| | |
|---|---|
| Methods | 48-Week, randomised, placebo-controlled trial |
| Participants | Patients with RA, age ≥ 18 years, using etanercept 50 mg/wk plus MTX (stable dose 7.5-25 mg/wk) with low disease activity/remission (DAS28 ≤ 3.2) for ≥ 11 months, no prior biologicals except anti-TNF, no prior attempt to discontinue etanercept due to stable disease<br>Age (mean, SD) 57 (11) years, 70% female, disease duration 13.6 (8.8) years, DAS28 ≤ 2.6: 81% |
| Interventions | 73 participants randomly assigned. Number per group not described<br>Etanercept continuation (50 mg/wk) + MTX (n = 23), etanercept dose reduction (25 mg/wk) + MTX (n = 27), etanercept discontinuation (placebo) + MTX (n = 23) |
| Outcomes | Primary outcome: proportion of non-failures for etanercept 50 mg/wk versus placebo (failure defined as DAS28 ≥ 3.2 and an increase in DAS28 ≥ 0.6 or disease progression as determined by investigator or participant)<br>Secondary outcomes:<br>• Comparison of non-failures<br>• Comparison of DAS28<br>• Time to failure<br>• Predictors for failure<br>• Adverse events |




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**van Vollenhoven 2012** (*Continued*)

| | | |
|---|---|---|
| Notes | Acronym DOSERA<br>At time of review, study presented in abstract form only<br>This study was sponsored by Pfizer Inc<br>Disclosures: R van Vollenhoven: Grant/Research support from Abbott, BMS, GSK, MSD, Pfizer, Roche, UCB; consultant for Abbott, BMS, GSK, MSD, Pfizer, Roche, UCB | |
| ***Risk of bias*** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Unclear risk | Not described in this abstract |
| Allocation concealment (selection bias) | Unclear risk | Not described in this abstract |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Placebo controlled. No information on blinding of personnel |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not described |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | No information on missing data |
| Selective reporting (reporting bias) | Unclear risk | Study protocol available. Not all outcome measures described in this abstract |
| Other bias | Unclear risk | Differences in baseline (prognostic) data not described |

ACR: American College of Rheumatology.
CCP: Cyclic citrullinated peptide.
CDAI: Clinical Disease Activity Index.
CRP: C-reactive protein.
DAS28: Disease activity score in 28 joints.
DMARD: Disease-modifying antirheumatic drugs.
ESR: Erythrocyte sedimentation rate.
EULAR: European League Against Rheumatism.
GH: Growth hormone.
HAQ-DI: Health Assessment Questionnaire-Disability Index.
IQR: Interquartile range.
LDA: low disease activity
mSvdH score: modified Sharp-van der Heijde score
mTSS: modified total Sharp score
MTX: Methotrexate.
NSAID: Nonsteroidal anti-inflammatory drug.
RA: Rheumatoid arthritis.
RF: Rheumatoid factor.
SDAI: Simplified Disease Activity Index.
SJ: swolen joint
TJ: tender joint
TNF: Tumor necrosis factor.

# five

## DOSE REDUCTION STRATEGY OF SUBCUTANEOUS TNF INHIBITORS IN RHEUMATOID ARTHRITIS: DESIGN OF A PRAGMATIC RANDOMISED NON INFERIORITY TRIAL, THE DRESS STUDY

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## ABSTRACT

### Background

Preliminary, mostly uncontrolled studies suggest that dose reduction or discontinuation of tumour necrosis factor blockers can be achieved in a relevant proportion of patients with RA without loss of disease control. However, long term safety, cost effectiveness and feasibility in clinical practice remain uncertain.

### Methods/Design

This study is a 18-months pragmatic, non-inferiority, cost minimalisation, randomised controlled trial on dose reduction and discontinuation of the subcutaneous tumour necrosis factor (TNF) blockers adalimumab and etanercept in RA patients with low disease activity. 180 RA patients with low disease activity (DAS28 < 3.2 or clinical judgment of the rheumatologist) are randomised 2:1 to either increased spacing and eventually discontinuation after 6 months of the TNF blocker, and usual care. Implementation is done in routine daily care, using treat to target and feedback implementation in both treatment arms. The primary outcome is non-inferiority (NI margin 20%) in cumulative incidence of persistent (> 3 months) RA flare, according to a recently validated DAS28 based flare criterion (DAS28 change > 1.2, or DAS28 increase of 0.6 and current DAS28 ≥ 3.2). Secondary outcomes include mean disease activity, function, radiographic progression, safety and cost effectiveness. Cost per quality adjusted life year (QALY) differences between groups are expressed as a decremental cost effectiveness ratio (DCER), i.e. saved costs divided by (possible) loss in QALY.

### Discussion

The design of this study targeted several clinical and methodological issues on TNF blocker dose de-escalation, including how to taper the TNF blockers, the satisfactory control condition, how to define flare, implementation in clinical practice, and the choice of the non-inferiority margin. Pragmatic cost minimalisation studies using non-inferiority designs and DCERs will become more mainstream as cost effectiveness in healthcare gains importance.

### Trial registration

Dutch Trial Register NTR3216, The study has received ethical review board approval (number NL37704.091.11).

## BACKGROUND

Tumour necrosis factor blocking agents (TNF-blockers) have proven to be effective and safe pharmacological interventions in the treatment of rheumatoid arthritis (RA). As these agents improve clinical, functional and radiographic outcome, TNF-blockers have become an integral part of the standard of care of RA. However, TNF-blockers are also associated with (sometimes dose dependant) adverse effects including injection site reactions, increased risk of infections and non melanoma skin cancer/lymphomas, rare severe adverse events and high costs [1-3]. Optimal use of these drugs is therefore warranted, including the right dose for the right patient [4]. Elective dose reduction in the context of low disease activity is however up to recently very uncommon in daily clinical practice [5].

Emerging data, mostly uncontrolled, has indicated that dose reduction or discontinuation of TNF blockers [6-20] can be achieved in a relevant proportion of patients with RA without loss of disease control. This seems similar between the three most used anti-TNF agents infliximab, adalimumab and etanercept (no data are available on certolizumab and golimumab), although the proportion of patients in whom the drug can be safely tapered seems to depend on the design of the study and context (especially authorised or higher than authorised dosage, dose reduction or stopping, and in early or established RA).

The fact that dose reduction or discontinuation can be successful could be expected for several reasons [4]. In clinical phase II/III studies, lower than registered anti-TNF dosages have been shown to result in good response in sizable proportions of patients [21-23]. So, maintenance of clinical efficacy on lower dosages is to be expected in many patients. In addition, patients sometimes improve independently of the installed treatment, as witnessed by the improvement that is found in placebo arms of clinical trials [21-23]. This improvement is in part spontaneous improvement (regression to the mean) or due to concomitant DMARD or glucocorticoid therapy, but also caused by the placebo effect (expectation bias) [24].

Although data on dose reduction is increasing, a number of aspects of dose tapering strategies in TNF blockers are still not well known thus far. Is reinstallment of the TNF blocker safe and effective? Is reducing the dose while maintaining clinical response associated with more radiographic joint damage in the long-term? Can these strategies be implemented in daily clinical care, and what is the cost effectiveness compared to usual care? To answer these questions, we designed a pragmatic RCT, the results of which will be presented in a separate paper. The primary aim of this study is to demonstrate non-inferiority of a dose reduction strategy compared to usual care with regard to persistent disease flare.

During the design of this RCT, a number of issues had to be addressed and in this paper we would like to describe in detail the study design, and motivate and discuss some of the design choices that were made.

## METHODS/DESIGN

This pragmatic, open, randomised, controlled, stratified non-inferiority strategy trial with cost effectiveness analysis is currently being performed (inclusion finished October 2012) at the departments of rheumatology of the Sint Maartenskliniek in the cities of Nijmegen and Woerden, the Netherlands. The study has received ethical review board approval (number NL37704.091.11) and has been registered (Dutch Trial Register NTR3216). A data safety monitoring board (DSMB) is installed. Every three months data on recruitment, efficacy, safety, protocol adherence and protocol updates and all aspects concerning GCP are reviewed with three independent DSMB members, an internal medicin physician, a pharmacist and an epidemiologist.

We made a distinction in an induction phase (months 0-9 after the first dose reduction) and a maintenance phase (months 6-18), because the cost effectiveness is very different between these two time periods [14] (Figure 1). In the induction phase, medication costs are still high, patients are sometimes seen more often, and quality of life might be compromised by temporary flares. Therefore, the cost effectiveness ratio found in the stable maintenance phase can be better interpreted for subsequent years.

### Objectives

The aim of the study is to test whether a tight control strategy with protocollised dose reduction and discontinuation in RA patients using TNF blockers is non-inferior with regard to disease control compared to a strategy without dose reduction attempt, and superior with regard to cost effectiveness. This translates in the following research questions:

*Primary objective*

- To assess whether the difference in cumulative incidence in persistent RA flares with a duration > 3 months between the intervention group and the usual care group of RA patients does not exceed the non-inferiority margin of 20% after 18 months of follow up.

*Secondary objectives*

- To compare the cumulative incidence of patients fulfilling flare criteria in the intervention and the usual care group after 9 months and after 18 months of follow up.
- To compare the cumulative incidence of patients with persistent RA flare resulting in change of biological between the intervention and the usual care group after 9 months and after 18 months of follow up.
- To compare the proportion of patients with a DAS28 < 3.2, DAS28 < 2.6 and fulfilling remission criteria according to ACR/EULAR criteria between the intervention and usual care group at 9 and 18 months follow up.

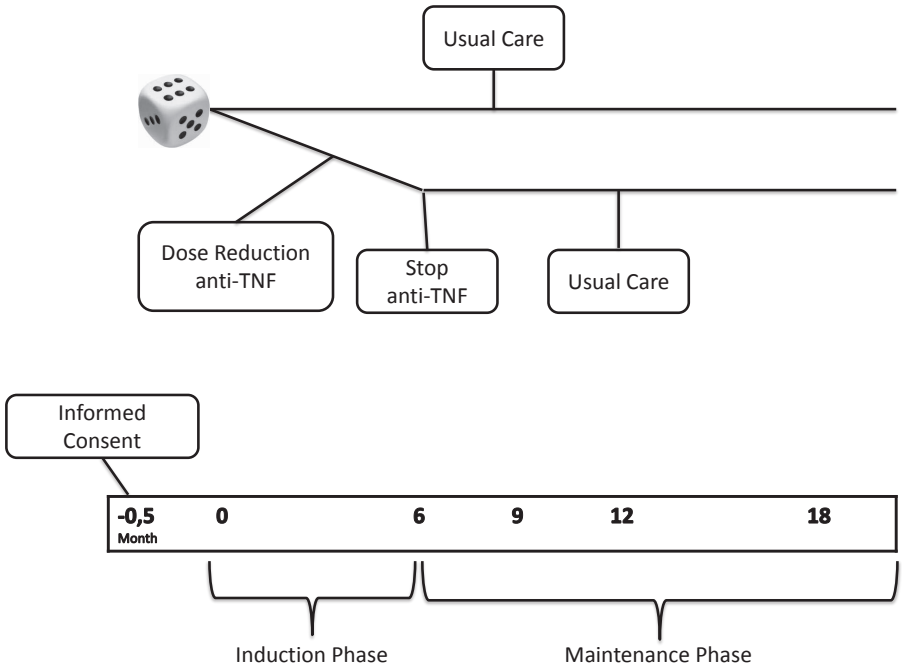


**Figure 1.** Design of the induction and maintenance phase.

- To compare the mean DAS28 and the mean time averaged DAS28 between the intervention and usual care group at 9 and 18 months follow up.
- To compare the proportion of patients using NSAIDs, glucocorticoids or DMARDs between the intervention and usual care group at 9 and 18 months follow up.
- To compare the mean Health assessment questionnaire disability index (HAQ-DI) between intervention and usual care group at 9 and 18 months follow-up.
- To compare the proportion of patients with a change in modified Sharp-van der Heijde Score exceeding the minimal clinical important change (MCIC) between the intervention and usual care group at 18 months.
- To compare the proportion of patients developing adverse events with special attention for allergic/ injection reactions between the intervention and usual care group.
- To estimate the decremental cost effectiveness ratio of a protocollised dose reduction/ withdrawal strategy of adalimumab or etanercept compared to usual care for the 9 months induction phase and for the 12 months maintenance phase.

*Study design rationale*

The comparison made in this study is between usual care and an alternative strategy (dose reduction) that aims to preserve, but not improve, disease control, whilst

minimising the amount of TNF blocker. Therefore, a non-inferiority design („can we achieve the same effect with less effort") instead of the classic superiority RCT design („can we do better with more effort") was chosen. Of note, this is an adaptation of the original registered research protocol.

*Study outcome rationale*

As disease control is the domain that should remain non-inferior, an outcome measure of disease control had to be selected as primary outcome. Several options come to mind, each with specific advantages and drawbacks.

A straightforward option would be a comparison of disease activity at study end, like for example mean DAS28 with non-inferiority margin of 0.3 DAS28 points. However, it can be expected that at study end no difference is found between the two strategies because patients are treat-to-target, but that flaring is much more frequent during the study in the dose reduction arm. Comparison of time integrated DAS28 might be therefore a better alternative, with the bonus of lower sample size requirements due to the repeated measurements [18]. However, disease activity AUC values are harder to interpret and less informative for a practising clinician than percentage of patients with a flare.

Another option would therefore be to use cumulative incidence of flares as primary outcome, and this is chosen in the majority of dose reduction and discontinuation studies. However, temporary flares that improve after reinstallment of therapy and without a large impact on overall disease control will inevitably occur more frequent in a dose reduction arm, but are clinically less relevant than persisting flares. We therefore chose to assess non-inferiority with respect to cumulative incidence of persisting flare, which is defined as a flare according to the DAS28 based OMERACT validated flare criterion persisting for at least 3 months (independent of treatment changes). The latter also facilitates the calculation of numbers needed to treat/ harm (NNT/NNH), thus making results easier to interpret and communicate to patients and physicians alike.

An interesting alternative for a primary outcome of non-inferior disease control would be to prove superior cost effectiveness of the alternative strategy. This would require proving that either the alternative strategy does not lead to loss of Quality Adjusted LifeYears (QALY) but saves costs (dominant strategy), or that the ratio of saved costs and loss of QALY is favourable. Of note, instead of the common term incremental cost effectiveness ratio (ICER), this approach results in a decremental cost effectiveness ratio (DCER), that states the amount of costs saved per lost QALY. The use of this kind of analyses as primary research question is however challenging due to several issues, and therefore very infrequently employed [25]. Firstly, due to the bootstrapping methods that are used to calculate the DCER, a formal sample size calculation is not possible. Secondly, quality of life is only moderately correlated with RA disease activity, posing a real chance of false reinsurance when quality of life

does not seem to be compromised. Thirdly, although ICERs of under 40,000 euro per gained QALY are widely accepted as cost-effective, no such clear-cut threshold is available for DCERs. Although the symmetry of using also 40,000 as threshold for DCER seems attractive, as these saved cost can be used elsewhere in health care system to get more quality of life improvement than was lost, it seems awkward to provide suboptimal therapy in relatively low cost effectiveness ranges. However, it can be argued that when the situation was reversed, e.g., when usual care would be to attempt dose reduction, the alternative of continuing medication would not be considered cost-effective when data shows an ICER clearly over 40,000. Interpretation of DCER seems therefore coloured by anchoring to either the existing and/or the alternative strategy. Anyway, a high DCER of for example > 100,000 saved per lost QALY would probably meet wide acceptance from a cost effectiveness point of view [25].





## Patients, eligibility and generalisability

All patients are eligible to enter the study if they are diagnosed with rheumatoid arthritis (either 2010 ACR RA and/or 1987 RA criteria and/or clinical diagnosis of the treating rheumatologist, fulfilled at any time point between start of the disease and inclusion), and of any disease duration, use etanercept or adalimumab in any stable dose for at least 6 months, and are in low disease activity state [26,27]. Previous dose reduction of the TNF blocker is allowed when more than 6 months ago. All background medication including DMARDs (either monotherapy or in combination) and prednisone equivalent up to 5 mg are allowed during the study and have to be stable for at least four weeks before inclusion. Consenting patients are randomly allocated in a ratio of 2:1 to the intervention or the control group, stratified for TNF blocker (adalimumab and etanercept).

We have chosen to operationalise low disease activity state by either a DAS28CRP < 3.2 or judgment of low disease activity by the rheumatologist at two subsequent visits at least 3 month apart. This means also patients with a DAS28 ≥ 3.2, but judged to have a low disease activity by their treating rheumatologist, are eligible for inclusion. This is firstly because several biologic registries show that mean DAS28 in TNF Blocker treated patients in clinical practice is around 3.2 [28]. This means that over 50% of the patients has a DAS28 ≥ 3.2, and even more are not in remission, but that both the patient and rheumatologist judge the disease activity to be low enough not to warrant switch of treatment. Limiting inclusion to only patients with DAS28 < 3.2 or even < 2.6 would therefore limit generalisability to current treatment practices. It might be rebutted that these higher disease activity scores reflect undertreatment and thus result in suboptimalisation. A DAS28 can however be inflated by OA associated joint pain, concomitant fibromyalgia or spuriously elevated ESR. This is also the rationale for use of DAS28CRP instead of DAS28 ESR. Another important consideration is that we treat RA patients for two reasons: firstly

to improve current signs and symptoms, and secondly to prevent joint damage. With respect to the first reason, it is important to note that the patient acceptable symptom state of the DAS28, has been found to be around 3.5 to 3.9, clearly higher than the currently advocated treatment aims of 2.6 or 3.2 [29]. For prevention of joint damage it is important to realize that not all patients have high risk of erosive disease and a need for prognosis modification [30]. Therefore, accepting somewhat higher disease activity can be legitimate and is indeed part of clinical practice. Of note, per October 19, 2012, all patients (n = 180) have been enrolled and randomised. Mean DAS28CRP is 2.2, and 8% of patients had a DAS28 > 3.2.

Because we aimed for maximal generalisability, we chose to only exclude patients if they have co morbidity which also requires treatment with anti-TNF and thus prevents dose reduction (e.g. Crohns disease), or when it is to be expected that the outcome cannot be measured (short life expectancy, planned major surgery).

## Interventions

*Control*

Patients in the usual care group will continue treatment by their own rheumatologist, following a standardised protocol based on the tight control/treat-to-target principle and aiming to maintain low disease activity. Visits are planned every 3 months and patients are encouraged to contact the outpatient clinic if they experience more complaints in between visits. CRP based DAS28 measurements are provided on the day of the outpatient visit to the treating rheumatologists. The standardised protocol offers protocollised treatment suggestions when there is a flare, including a treatment algorithm and dosing of the drugs. The research physician monitors protocol adherence of the rheumatologists and will - where needed - give feedback and advice to the rheumatologist. Treatment choices, however, are left to the discretion of the treating rheumatologist. This way it is ensured that positive study results can be achieved also in clinical practice. Treatment will be changed in case of a confirmed flare (the definition of flare will be discussed separately). A one time flare will be, if necessary, bridged with glucocorticoids. Also, dose reduction or stopping, for any reason, was allowed in the control arm, as this is sometimes-although infrequent-also part of usual care (5). In summary, the control condition exist of tight control by patients own rheumatologist, and all treatment choices are allowed.

Of note, although called usual care, tight control care has thus far not consistently been implemented in clinical care in the Netherlands [31]. However, opting for a standard care arm without tight control would result in underestimation of possible drawbacks of dose reduction, as these effects would be ameliorated by the difference in tight control.

*Intervention*

The intervention group receives identical care as the control group, with addition of a dose reduction and withdrawal strategy protocol and feedback and advice to treating rheumatologist. This strategy is directly adapted from the Dutch Society of Rheumatology biological guideline [32]. If a patient uses adalimumab, the interval will be stepwise increased every three months from 14 to 21 to 28 days, after that the adalimumab will be stopped. For etanercept, the interval will be increased from 7 to 10 to 14 days and stopped thereafter. If a patient uses a different dose regimen at start, an alternative dose reduction strategy is used. Patients already on a longer dosing interval will step in at the nearest dosing interval. Patients on a shorter dosing interval will also stepwise increase the interval to stop after 6 months using an accelerated strategy. The three month interval is based on data that shows that most of the flaring after dose reduction occurs within 3 months [14].

The dose reduction steps from 100% to 66% and 50% and thereafter stop are based on the notion that relatively small dose reduction seems to be feasible in a large proportion of patients, and therefore will lead to sizable reduction in total volume and costs of the TNF blocker [14,20]. Indeed, although stopping the TNF blocker obviously saves more drug per patient than dose reduction, the total volume of saved drugs is the same in patients that stop or are only dose reduced, because the latter group is much larger [14]. Also, although we cannot substantiate this, dose reduction until stop feels more appropriate for patients than just stopping the drug.

When a confirmed flare occurs, the interval is decreased back to the last effective interval. When there is still no improvement of disease activity eventually after reintroduction of the original interval and dose, the patient will be advised to switch to the next biologic or DMARD according to the treatment protocol.

## Outcome measures

The outcome measures used in this study include disease activity (DAS28CRP based RA Flare criterion, mean and time integrated DAS28CRP), function (HAQ DI), radiological damage (Modified Sharp van der Heijde score, MSvdH), Adverse events (CTC 4.0 criteria), utility (Euroqol 5D 5 L) and costs [33-39].

*Definition of flare*

RA Flare in this study is defined in both treatment arms as a DAS28 increase compared to baseline of more than 1.2 or a DAS28 increase of more than 0.6 with a current DAS28 $\geq$ 3.2 at two separate timepoints at least 4 weeks apart. This criterion has been validated recently, and has been shown to have the optimal tradeoff between sensitivity and specificity, and the best construct and criterion validity [40]. As it has been shown that flares are frequently temporary and occur and disappear without regimen change, a flare is only considered a flare if it is confirmed after at least 4 weeks [11]. Patients are however not left untreated, and when a flare in disease

activity occurs, all bridging therapy including i.a. or im steroids or NSAID can be given and are allowed. Of note, flares are defined with change compared to baseline, not compared to the last visit, to prevent undertreatment in patients with a slight increase in disease in subsequent visits.

When the flare is confirmed after 4 weeks, in both treatment arms patients receive optimal treatment for the flare, for example protocollised reinstallment or dose increase of the TNF blocker or change to another biologic or DMARD. Only patients in whom the flare persist longer than three months (in spite of all treatment intensivation) are classified as having persistent flare, the primary outcome of this study.





*Secondary outcomes*

Cost effectiveness A separate calculation will be made for the 9 months induction phase and the 12 months maintenance phase for the reasons described above. The cost analysis includes both direct and indirect costs, from a society perspective, and consist of two main components: determination of volumes of care and determination of cost prices for each volume of consumption. Volumes of care (registered out-patient clinic visits, medication use, and work-related absenteeism) are multiplied with the cost prices to calculate costs. Cost prices for medication are retrieved from the Dutch National tariff list provided by the Dutch Board of Health Insurances. The standard cost prices from the, Dutch Guideline for Cost Analyses' are used for valuation of hospital related care and work-related absenteeism.

Radiographic damage Change in radiographs of hands and feet between baseline and study end are compared between intervention and usual care by calculating the change in MSvdH score, scored chronologically in random order [35]. The smallest detectable difference (SDD) within this 18 months timeframe in this group of patients with established RA is expected to be 8 points, comparable with the widely validated minimal clinical important change (MCIC) of 5 point per year [38,39,41]. Proportions of patients showing radiographic joint damage progression exceeding the MCIC are then calculated.

## Assessments

Regular visits are planned at baseline and every 3 months thereafter up to month 18. When a flare occurs, patients are seen within two days, but at least within a week, and additionally an extra visit is planned after 4 weeks.

## Randomisation, allocation concealment and blinding

Allocation is stratified for adalimumab and etanercept using stratified block randomisation in random sized blocks and a ratio of 2:1. Patients will be randomised by the research physician using a computer-generated randomisation list, which has been transferred to paper sheets and put in sealed envelopes.

This study uses a controlled and randomised, but only partly blinded design, as patients and physicians are not blinded for allocation. Blinding of the assessor performing the joint scores was strived for, and this was done by instructing both patients and the independent joint assessor to first score the DAS28CRP, before assessing medication changes and adverse effects.

Although triple blinding (patients, physicians, researcher) would methodologically be preferable, this is unfeasible because dose reduction in this study is done via increasing the interval instead of decreasing the dosage per injection. The latter would not be sensible, since TNF blockers are given using prefilled injection pens. Blinding of patient and physician is possible when using interval widening, but would be very difficult. The unblinded nature of the study could result in information and attribution bias, as flares in patients in whom the dose is reduced would possible be reported sooner because they would be attributed to the intervention. This bias can however fortunately only lead to overestimation of the drawbacks of a dose reduction strategy, not underestimation, and therefore the higher risk of bias was accepted.



## Sample size

The null hypothesis in this study is that the intervention is inferior compared to the control arm by more than the non-inferiority margin δ (H0: μ1-μ2 > δ). The alternative hypothesis rejects this null hypothesis (H1: μ1-μ2 ≤ δ), thus proving non-inferiority. The sample size calculation is motivated as follows [42] using the fomula as shown.

$$n_1 = kn_2$$

$$n_2 = \frac{(Z_a + Z_\beta)^2}{(\varepsilon - \delta)^2}\left[\frac{p_1(1-p_1)}{k} + p_2(1-p_2)\right]$$

We estimated that 15% (p1 = 0.85) of patients will experience the primary outcome in the usual care arm (persistent flare), with an estimated 20% (p2 = 0.80) of patients with this outcome in the intervention arm. Applying one sided testing, an alpha of 0.05 ($Z_\alpha$ = 1.64, noninferiority testing one sided), power 1-beta 0.8 ($Z_\beta$ = 0.84), an inferiority margin of 20% (δ = –0.2), and randomisation ratio of 2:1 intervention versus control (k = 2) resulted in n = 114 and n = 57 for intervention and control arm. Accounting for a 10% drop-out, we choose to include 180 patients in total.

The estimation of proportion of primary outcome in both groups and magnitude of the non-inferiority margin (δ) are motivated as follows. Although clear data are absent, based on the few dose reduction studies that included a control group, and on previously published drug survival curves for adalimumab and etanercept in our population, we estimated that after 18 month in the usual care group 15%

of patients would have changed their biologic therapy due to insufficient disease control [12,15,16,28]. We furthermore assumed that 15% of patients in the intervention group can ultimately stop the drug (without persistent flare), resulting in cumulative incidence of 85% flares in the group of patients with partial dose decrease. Of these patients, we estimate that 5% will not respond to reinstallment of the TNF blocker and experience a persistent flare. Thus, we expect a cumulative incidence of persistent flare of 15 + 5 = 20% in the intervention arm.

A difference in persistent flare of over 20% between usual care and dose reduction would constitute a clinical relevant non-inferiority margin in our opinion. The underlying reasoning is, that it is to be expected that half of the patients who start another biologic for a flare will show response again within three months (21-23). Half of 20% of the patients would therefore experience a persistent flare, a more prolonged period with uncontrolled disease activity, resulting in a NNH of 10. In our clinical view, this seems to balance nicely with an expected chance of being able to reduce the dose or stop the drug of approximately 60 and 15% respectively (NNT 1.5 and 6 respectively), as much more patients are expected to benefit than to be harmed using this non-inferiority margin. The ratio of 2:1 for intervention and control sample size is chosen to be able to include more determinants in a prediction model for successful dose reduction.





## Planned data analysis

All statistical analyses are performed using STATA/IC 10.1 for Windows. Analyses will be done on intention to treat (ITT) basis and also per protocol basis, the latter because ITT analyses might underestimate differences between treatment arms in non-inferiority studies, resulting in a false positive study [25]. Number and reasons for exclusion and dropout are reported to ensure internal validity. Missing data on determinants/covariates will be described using descriptive analyses and missing data mechanisms will be studied. Missing values will be imputed using multiple imputation when meeting the assumption of missing (completely) at random, as imputation will increase precision and possibly reduce bias. Logistic regression models with the indicator variable as outcome and the other variables as covariates will be used to check these assumptions. Multiple imputation using chained equations will then be used to estimate missing values. Descriptive statistics will be provided using mean +/–SD, median (p25-p75) or frequencies/percentages depending on the type distribution of the data.

The primary outcome, cumulative incidence of persistent flare is calculated in both groups. The two proportions are then compared using Fisher exact testing. The cost and quality of life are compared between intervention and usual care group for the induction phase and for the maintenance phase separately. Direct costs and indirect cost will be calculated, as will utility based on EUROQOL-5D-5 L. Thereafter, when the intervention is not a clearly dominated or dominant strategy, a decremental

cost effectiveness ratio will be estimated using bootstrapping, expressed as saved costs divided by loss in quality of life.

## DISCUSSION

The development of the current study protocol induced a number of clinical and methodological issues that had to be targeted, and that are specific for the context of this research area. These choices include how to taper the TNF blockers, the satisfactory control condition in light of current treatment practices, how to define flare, implementation in clinical practice, and the choice of the non-inferiority margin. This resulted in a clinical study design that differs in many respects from previously published and ongoing studies in this field.

In addition to the methodological issues mentioned above, some medico-legal issues also arose. According to new legislation based on GCP II, the 2001 EU directive and the subsequent Dutch law on medical research (WMO 2006), clinical studies that study patients using medication, even when given according to current registration demands and not initiated or changed for study purposes, are considered interventional medication studies [43,44]. This label results in a large administrative burden (EUDRACT registration, investigators brochure, increases monitoring demands, and responsibility for medication cost), making investigator driven clinical pharmacological research difficult or even nearly impossible to perform. Paradoxically, this results in less safe and (cost) effective care for the very people these laws are meant to protect, the patients. Inspired by the discussion amongst clinical researchers concerning practical implications of this legislation, medical ethical review boards have developed more lenient approaches to these kind of studies [45,46]. Indeed, because our study does not directly specify what medication to give, but provides a comprehensive treatment strategy and feedback as intervention, because the drugs are given for standard indication, and as the intervention is withdrawal of the drug, the study was considered not an interventional medication study.

In conclusion, healthcare in the next decades will not only be driven by improving outcomes, but also by achieving the same results with less effort and less risk for adverse effects. Non-inferiority studies combined with decremental cost effectiveness analyses - although thus far seldom done and challenging [25]-are the preferential design to achieve this. The widespread and long term use of expensive and sometimes toxic biologicals in chronic inflammatory conditions seems an excellent field to start with improving the cost effectiveness of our current high cost healthcare system. Future research in this topic should include expansion to other biologics and other diseases.

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# six

## RANDOMISED CONTROLLED NON-INFERIORITY STUDY OF DISEASE ACTIVITY GUIDED DOSE REDUCTION AND WITHDRAWAL OF ADALIMUMAB AND ETANERCEPT COMPARED TO USUAL CARE IN RHEUMATOID ARTHRITIS

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*Submitted*

## ABSTRACT

### Objectives

To evaluate whether a disease activity guided dose reduction strategy of adalimumab or etanercept is non inferior in maintaining disease control in patients with RA as continuing usual care.

### Design

Randomised controlled, open label, non-inferiority strategy trial.

### Setting

Two rheumatology outpatient clinics in the Netherlands

### Participants

180 patients with RA and low disease activity using adalimumab or etanercept. 121 were allocated to the dose reduction strategy, 59 to usual care.

### Interventions

Disease activity guided dose reduction strategy (advice to stepwise increase the injection interval every three months, until flare of disease activity or discontinuation) or usual care (no dose reduction advice). In case of flare (DAS28-CRP increase >1.2 or DAS28-CRP increase >0.6 and current DAS28-CRP ≥3.2), the TNFi was restarted or escalated.

### Main outcome measures

The primary outcome was the difference in proportions of patients with major flare between the two groups at 18 months, compared against a non-inferiority (NI) margin of 20%. Secondary outcomes include functioning, quality of life, radiographic progression, adverse events and cost-effectiveness.

### Results

Dose reduction was non-inferior to usual care (12% and 10%; difference = 2% in major flare, 95% confidence interval (CI) -12 to 12). TNFi could successfully be stopped in 20% (95% CI 13 to 28) of patients, the interval successfully increased in 43% (95% CI 34 to 53). In 37% (95% CI 28 to 46) of patients no dose reduction was possible. Functional status, quality of life and radiographic progression were not different between the groups. During the 18 months, mean costs were € 9,038 lower in the dose reduction group, (QALY difference -0.02, ns), resulting in a cost effectiveness ratio of € 390,493 per QALY.

### Conclusions

A disease activity guided TNFi dose reduction strategy is non-inferior to usual care in clinical outcome, while being clearly superior in cost-effectiveness.
Trial registration Dutch trial register, www.trialregister.nl, number NTR 3216.

## INTRODUCTION

Tumour necrosis factor inhibitors (TNFi) are effective in the treatment of rheumatoid arthritis (RA), improving clinical, functional and radiographic outcomes.[1] Different TNFi are widely used, with adalimumab (40 mg every two weeks) and etanercept (50 mg weekly / 25 mg biweekly) being the two most used,[2] and among the highest selling drugs worldwide.[3]

Treatment with TNFi is not without drawbacks: they are associated with (dose dependent) adverse effects, including increased risk of infections and skin cancer.[4-6] Furthermore, TNFi treatment is costly: approximately 15,000 euro yearly per patient.[7] Optimising the use of TNFi is therefore warranted. Previous research indeed suggested that dose reduction or discontinuation of TNFi without deterioration of disease activity is possible in a relevant proportion of patients, although unfortunately successful dose reduction cannot be predicted in individual patients.[8-10] A promising strategy might therefore be slowly tapering the TNFi until it is stopped, while carefully monitoring the disease, and increase the dose or restart when necessary. However, some important questions regarding the feasibility and applicability of dose reduction in individual patients in clinical practice remain unanswered. For example, it has not been demonstrated that a disease activity guided strategy, i.e. a strategy of monitoring the disease activity and restarting the TNFi or increasing the dose again in case of disease worsening after dose reduction results in equally good care as just continuing treatment unaltered. Flares that occur after dose reduction might be short lived and easily treated, or could be prolonged, compromising quality of life, or resulting in radiologic damage.[11] Also, although titrating patients to the lowest dose may save medication costs, it may also lead to increased number of patient contacts and consequent costs. Interestingly, none of the previous controlled dose reduction and discontinuation studies used the appropriate non-inferiority design, included a disease activity guided strategy or cost-effectiveness analyses.[8-10]

The aim of this study was therefore to demonstrate non-inferiority with regard to efficacy and safety between a disease activity guided TNFi dose reduction strategy and usual care (continuing TNFi) in daily clinical practice, and assessing possible benefits in terms of cost-effectiveness. A secondary aim was to identify possible predictors for successful dose reduction.

## METHODS

### Study design and participants

The Dose REduction Strategy of Subcutaneous TNF inhibitors (DRESS) study was a pragmatic, open label, randomised, controlled, non-inferiority (NI) trial, stratified by TNFi. The rationale and design have been described extensively elsewhere,[12], chapter 5, and are summarised here. Consenting RA Patients (either 2010 and/

or 1987 ACR RA criteria and/or clinical diagnosis of treating rheumatologist) using adalimumab or etanercept in any stable dose and interval for at least six months, with stable low disease activity at two subsequent visits, were enrolled. Low disease activity was determined by rheumatologist and measured using the DAS28-CRP. This validated composite disease activity measure (range 0.9-9, < 3.2 indicating low disease activity) includes 28 swollen and tender joint counts, patients' judgment of global disease activity and CRP. The study was performed at the Sint Maartenskliniek in Nijmegen and Woerden, the Netherlands, from December 2011 through May 2014, and was approved by the local ethics committee (CMO region Arnhem-Nijmegen, NL37704.091.11).





## Randomisation and masking

Allocation was stratified for TNFi using block randomisation in random sized blocks (block size 3 to 12), and in a ratio of dose reduction versus usual care of 2:1. This ratio was chosen to be able to include more determinants in a prediction model for successful dose reduction or discontinuation. A research physician randomised patients using a computer-generated randomisation list. To conceal the sequence until treatment strategy was assigned, sequentially numbered sealed opaque envelopes that contained the randomly assigned allocations were used.

## Procedures

Patients allocated to the usual care group continued a standardised treat-to-target treatment protocol, aimed at maintaining at least low disease activity. Visits were planned three monthly and patients were encouraged to contact the outpatient clinic when experiencing more symptoms. Nurse assessed DAS28-CRP was provided to the treating rheumatologists. Nurses had been trained and calibrated repeatedly to minimise measurement error. Treatment was changed in case of a disease activity flare. A flare was defined using a validated criterion: as a DAS28-CRP increase >1.2 or a DAS28-CRP increase >0.6 and current DAS28-CRP ≥3.2 compared to baseline DAS28-CRP.[13] In case of flare, a new visit after four weeks was advised. Intra-muscular and intra-articular corticosteroid injections were allowed.

In the dose reduction group, patients received identical care as the usual care group, with addition of a dose reduction advice given to the treating rheumatologist. The dose reduction strategy consisted of stepwise increasing the interval between injections every three months. For adalimumab the steps were: 1) 40 mg every 21 days, 2) 40 mg every 28 days, 3) stop. For etanercept the steps were: 1) 50 mg every 10 days, 2) 50 mg every 14 days, 3) stop. In case of flare, the last effective interval was reinstated. If despite this the flare persisted, TNFi was increased until the shortest registered interval, thereafter treatment was switched. Only one attempt at dose reduction was done.

## Outcomes

Primary outcome was the difference in cumulative incidence of major flare between the dose reduction and the usual care group at 18 months follow up.[12] Major flare was defined as a DAS28-CRP based flare, with a duration > three months, independent of treatment changes.[12] Cases with major flare were reviewed by two physicians for more in-depth clinical interpretation.

Secondary outcomes included cumulative incidence of patients with flare (duration < three months), change in DAS28-CRP, change in functioning, measured with the Health Assessment Questionnaire-Disability Index (HAQ-DI) (range 0-3, higher score indicating worse functioning), and quality of life, measured with the EuroQol-5D5L (EQ5D-5L) (range 0-1, higher score indicating better quality of life). Percentages of patients who could successfully taper or stop were described, as well as change in use of glucocorticoids, change in Disease Modifying Antirheumatic Drugs (DMARDs), and occurrence of (severe) adverse events.

Radiographs of hands and feet (baseline and 18 months) were assessed in chronological order by two blinded, trained readers, using the modified Sharp-van der Heijde (SvdH) score (range 0-448, higher scores indicating more joint damage, sub scores including erosion score (range 0-280) and joint space narrowing score range 0-168)).[14] The proportion of patients with a change in SvdH score exceeding the Minimal Clinical Important Change (MCIC) of 8 points in 18 months was compared between groups.[15-16] As a sensitivity analysis, the smallest detectable change (SDC) was calculated and used as cut-off value, as well as a third cut-off of, 0.5 SvdH units.[17]

EQ5D-5L based quality-adjusted life years (QALYs) were calculated. Volumes of care were determined, including (telephone) consultations with the rheumatologist or rheumatology nurse, RA related hospital admissions, medication use and RA related work absenteeism. Volumes were multiplied by the cost prices (retrieved from the Dutch national tariff list).[18] Prices were indexed for 2014, when necessary, using the general Dutch price index rate (May 2014).[19]

## Statistical Analysis

The assumption was made that 20% of patients would experience the primary outcome in the dose reduction arm and 15% in the usual care arm. With one sided testing, (alpha 0.05, 1-beta 0.8), a NI margin of 20%, and randomisation ratio of 2:1 dose reduction versus usual care and accounting for 5% drop-out, 180 patients were calculated to be necessary to reject the null-hypothesis of inferiority.[12] No interim analyses or stopping rules were defined prior to study start.

Analyses were done per-protocol by including only patients who: 1) completed follow up, 2) actually started TNFi dose reduction in the dose reduction arm, and 3) had not stopped or reduced TNFi at 18 months follow up in the usual care arm. Additional intention to treat (ITT) analyses were done. For the primary outcome,

the point estimate and confidence interval (CI) of the difference in cumulative incidence of major flare between both groups was calculated, and the upper limit of the CI compared to the NI margin. A t-test was used to compare mean (and mean time averaged) DAS28-CRP, HAQ-DI and EQ5D-5L. Difference in cumulative incidence in flare was tested with $\chi^2$. To identify predictors, two univariate logistic regression analyses were performed with the two main outcomes - successful dose reduction and stopping - as dependent variables, and baseline patient-, clinical- and treatment variables as independent variables. Multivariate analyses were planned in case more than one variable was significantly associated with one of the outcomes.

Costs, quality of life and cost-effectiveness were calculated for the whole duration of the study. A decremental cost-effectiveness ratio (DCER) was calculated by dividing the difference in costs by the difference in QALYs between the groups, expressed as savings per QALY lost. 95% uncertainty boundaries in the DCER were determined non-parametrically using bootstrapping (1000 replications). The Net Monetary Benefit (NMB) per patient for the dose reduction strategy was calculated for different levels of willingness to pay (WTP) in euro's per QALY, using the formula: WTP * effect (difference in QALY) - costs. This results in the net amount of money saved, when the possible loss of QALY is corrected for, using different WTP levels per QALY.[20]





## RESULTS

### Patients

A total of 180 patients were enrolled, 121 patients in the intervention group and 59 patients in the usual care group (Figure 1). Baseline characteristics were similar between the two groups, except for higher prevalence of DMARD co-medication in the usual care group (Table 1). Almost no data was missing; 2% of the planned visits, and 3% to 7% missing per variable, thus multiple imputation was deemed unnecessary.

### Primary outcome, disease activity and function outcomes

Using the primary per protocol analysis (Figure 1 for number and reasons for excluded patients), the difference in cumulative incidence of major DAS28-CRP flare was 14/119 patients (12%) and 5/50 patients (10%) in the dose reduction and usual care groups respectively. The upper limit of the 95% confidence interval around the difference was lower than 20% (2%, 95% CI -12 to 12) showing that the dose reduction strategy was non-inferior to usual care. Additional ITT analyses showed very similar results (Figure 2). No relevant between drug differences were found in the stratified analysis. Therefore, further analyses were all done ITT. Review of patients with major flare (n=21, Figure 2) revealed three clinically distinct subgroups: 1/ formal flare criterion fulfilled, but clinically no flare (spurious high

CRP, co morbidity, social context (n=8)), 2/ clinical flare, the treatment of which was suboptimal due to, for example, adverse events or patient's wish (n=8) and 3/ clinical flare, and no improvement after re-instalment of previous TNFi treatment (n=5, 4 of which in dose reduction group).

The cumulative incidence of short-lived flares was significantly higher in the dose reduction group compared to the usual care group: 88/121 (73%, 95% CI 64-80) versus 16/59 (27%, 95% CI 17-40), respectively (p <0.001). The number of flares per patient with at least one flare during the study is shown in figure 3. Mean DAS28-CRP remained low in both groups, with a temporary small but significant increase in the dose reduction group at 9 months (Figure 4A), also resulting in a higher mean time averaged DAS28-CRP in this group (p< 0.01). Mean (time averaged) functioning and quality of life remained stable and not significantly different between the two groups. (Figure 4B and 4C).



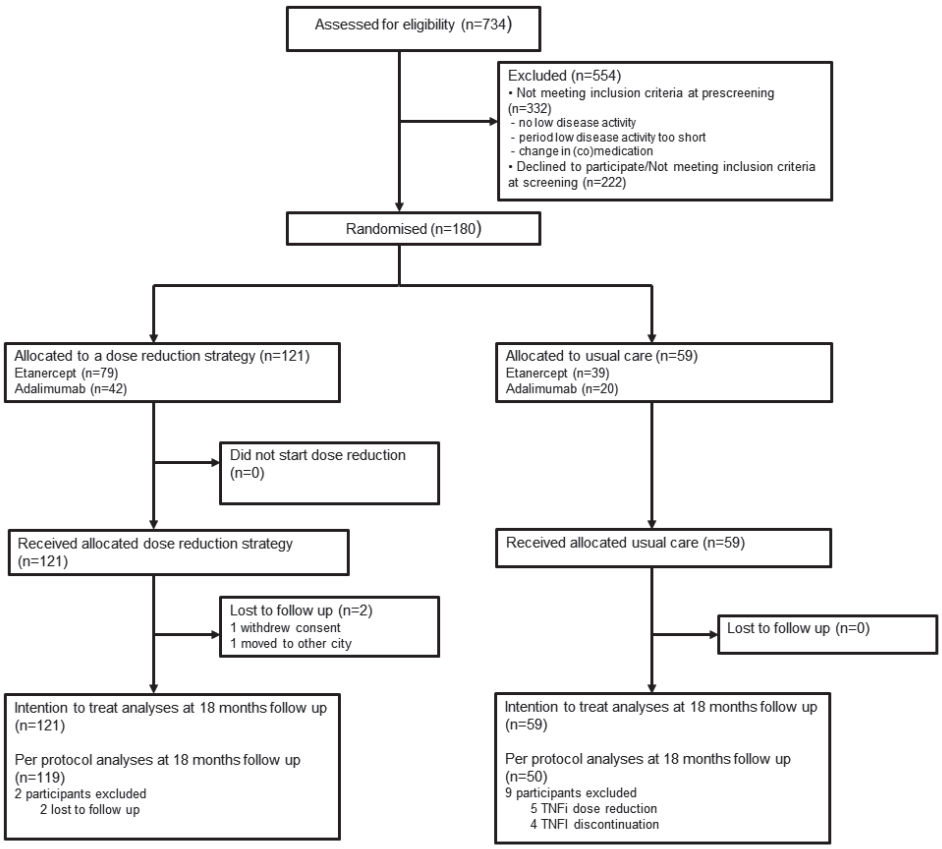


**Figure 1.** Flowchart of patient recruitment and drop out.

**Table 1.** Baseline patient characteristics

| | Dose reduction (n=121) | Usual care (n=59) |
|---|---|---|
| Age, years (SD) | 59 (10.5) | 58 (9.3) |
| Female, n (%) | 75 (62) | 41 (69) |
| Current smoking, n (%) | 29 (24) | 18 (31) |
| BMI (SD) | 27 (4.9) | 26 (4.0) |
| Diagnosis according to 2010 and/or 1987 ACR criteria, n (%) | 114 (94) | 58 (98) |
| Disease duration, years median [p25-p75] | 10 [6-17] | 10 [6-16] |
| RF positive, n (%) | 94 (78) | 49 (83) |
| ACPA positive, n (%) | 77 (64) | 39 (68) |
| Erosive disease, n (%) | 99/116 (85) | 54 (92) |
| SvdH score, median [p25-p75] | 23 [6-50] | 17.5 [8.5-46.5] |
| Disease activity | | |
| Swollen joints, number median [p25-p75] | 0 [0-0] | 0 [0-1] |
| Tender joints, number median [p25-p75] | 0 [0-1] | 0 [0-0] |
| Erythrocyte sedimentation rate, mm/hour (SD) | 17 (14) | 16 (10) |
| C-reactive protein, mg/litre (SD) | 4 (4) | 4 (4) |
| DAS28-CRP (SD) | 2.2 (0.6) | 2.1 (0.7) |
| DAS28-ESR (SD) | 2.5 (0.7) | 2.5 (0.8) |
| 2011 ACR/EULAR Boolean-based remission, n (%) | 31 (26) | 21 (36) |
| Treatment | | |
| Etanercept/adalimumab, n (%) | 79/42(65/35) | 39/20 (66/34) |
| Duration of current TNFi therapy, years (SD) | 3.5 (2.5) | 3.6 (2.3) |
| Previous dose reduction attempt current TNFi, n (%) | 21 (17) | 11 (19) |
| Previous DMARDs, median [p25-p75] | 2 [1-3] | 2 [1-3] |
| Previous TNFi, median [p25-p75] | 0 [0-1] | 0 [0-1] |
| Concomitant therapy | | |
| DMARD, n (%) | 73 (60) | 47 (80) |
| MTX, n (%) | 58 (48) | 41 (69) |
| MTX dose, mg (SD) | 15·8 (5.7) | 16.1 (5.5) |
| glucocorticoid, n(%) | 6 (5) | 3 (5) |
| NSAID, n (%) | 65 (54) | 35 (59) |
| Employment, n (%) | 44 (36) | 21 (36) |
| Travel distance (one way) to hospital, kilometres median [p25-p75] | 30.4 [13.5-47.2] | 33.2 [17.3-50] |

BMI= Body Mass Index; RF= rheumatoid factor; ACR= American College of Rheumatology; ACPA= anti-Citrullinated Peptide Antibodies; SvdH= modified Sharp van der Heijde; DAS28= 28 joints disease activity score; EULAR= European League Against Rheumatism; TNFi= Tumor Necrosis Factor inhibitor; DMARD= Disease Modifying Antirheumatic Drug; MTX= Methotrexate; NSAID= Non-Steroidal Anti Inflammatory Drug

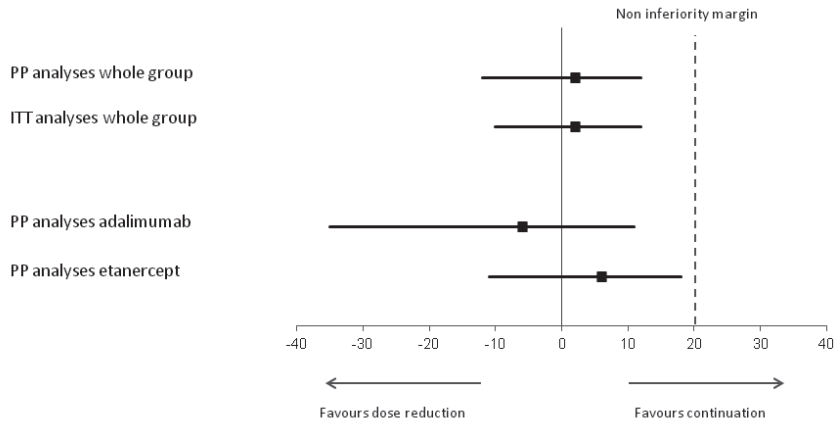


**Figure 2.** Primary outcome analyses

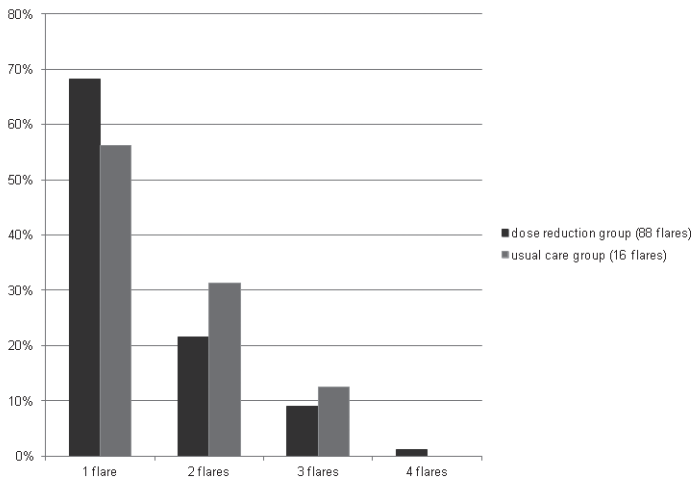


**Figure 3.** Numbers of flares in patients with a flare during the study in the dose reduction and usual care group

## Medication and prediction modelling

At 18 months, in the dose reduction group TNFi was successfully discontinued or tapered in 24/121 (20%, 95% CI 13-28) and 52/121 (43%, 95% CI 34-53) of patients respectively, whereas in 45 (37%, 95% CI 28-46) of patients no dose reduction was possible. For patients using adalimumab, at 18 months 26% and 36% had successfully discontinued or tapered and 38% could not reduce the dose. For etanercept this

was 17%, 47% and 36% respectively. All table 1 characteristics were tested for their predictive value. No clinical, laboratory or co-medication variables were significantly associated with successful dose reduction or discontinuation of TNFi. In the usual care group, four patients (7%, 95% CI 2-17) discontinued TNFi (all because of adverse effects), five patients (8%, 95% CI 3-19) tapered TNFi because of low disease activity, 50 patients did not dose reduce (85%, 95% CI 73-92).

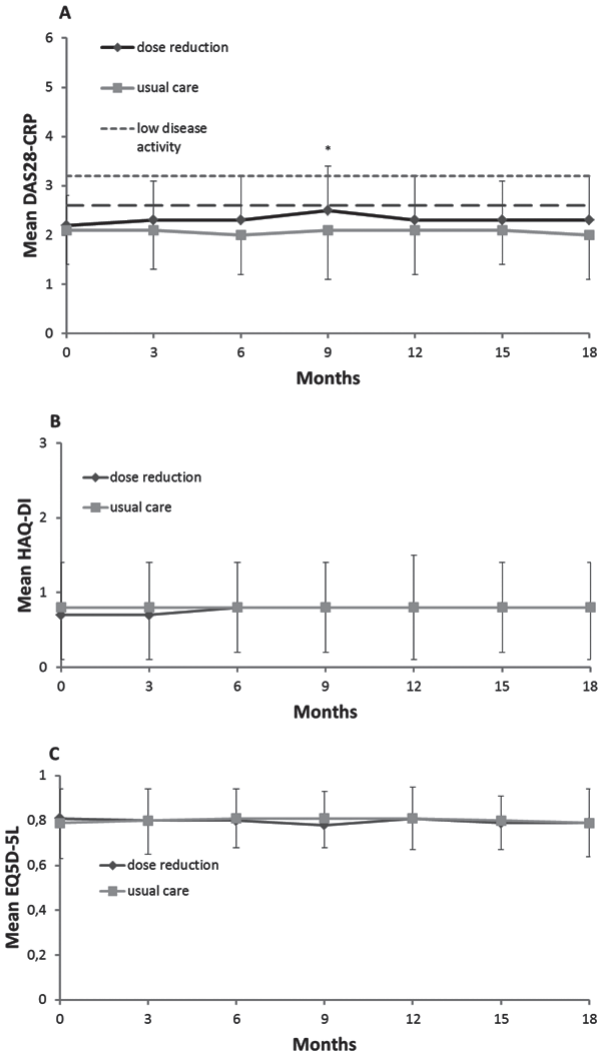


**Figure 4.** Mean **A**: Disease activity (measured with DAS28-CRP) **B**: Functioning (measured with HAQ-DI) and **C**: Quality of life (measured with EQ5D-5L) during planned study visits for the dose reduction and usual care group

Intra-muscular and/or intra-articular glucocorticoid injections were given to 43/121 patients (35%, 95% CI 27-45) in the dose reduction group and in 14/59 patients (24%, 95% Ci 14-37) in the usual care group (ns). The number of injections per patient receiving parenteral glucocorticoids at least at one occasion is shown in figure 5. At 18 months, 8/121 (7%, 95% CI 3-13) and 6/59 (10%, 95% CI 4-22) of patients in the dose reduction and usual care group respectively used oral glucocorticoids (ns). DMARDs were reduced or discontinued more often in the usual care group compared to the dose reduction group, 16/59 (27%, 95% CI 17-40) versus 12/121 (10%, 95% CI 5-17), ($p<0.01$), while DMARD initiation or dose escalation occurred more often in the dose reduction group compared to the usual care group (16/121, 13%, 95% CI 8-21 versus 2/59, 3%, 6-13, $p<0.05$). At 18 months, the percentage of patients using a DMARD remained lower for the dose reduction group (74/121, 61%, 95% CI 52-70) compared to the usual care group (41/59, 69%, 95% CI 56-80) (ns).





## Radiological outcomes and safety

Radiographs were available for 175 patients (Table 2). In neither group did any of the patients have a SvdH progression score exceeding the MCIC of 8 points. The sensitivity analyses showed no difference when the SDC (4.1 points) was used as cut-off. More patients in the dose reduction arm exceeded the 0.5 units progression compared to patients in the usual care arm (Figure 6). The difference in mean progression between groups was small but significant and was mainly due to difference in joint space narrowing, as progression in erosion scores was similar.

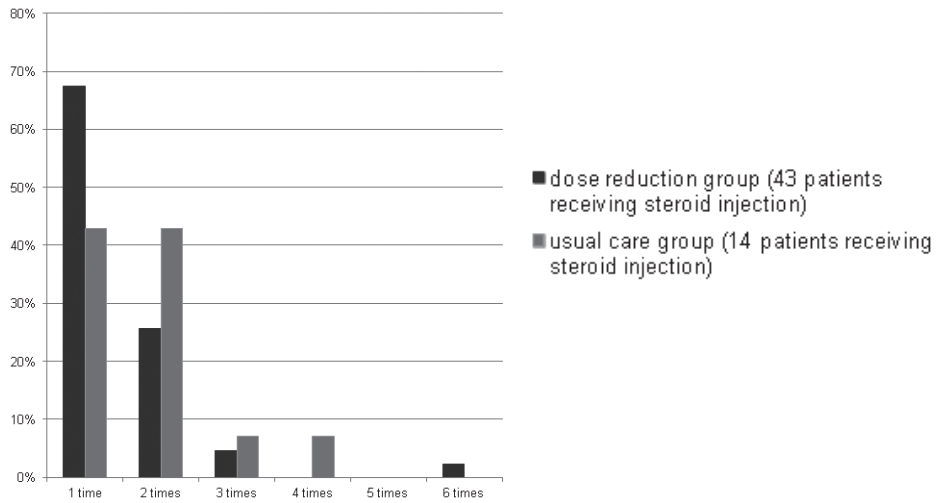


**Figure 5.** Numbers of injections in patients receiving parenteral glucocorticoids

**Table 2.** Radiographic outcomes (n=175)

| | Dose reduction (n=116) | Usual care (n=59) | Difference (95% CI) |
|---|---|---|---|
| Progression total SvdH | 0.75 (1.5) | 0.15 (1.1) | 0.60 (0.17-1.0) |
| Progression erosion score | 0.29 (0.8) | 0.12 (0.7) | 0.17 (-0.07-0.41) |
| Progression joint space narrowing | 0.46 (1.2) | 0.03 (0.9) | 0.43 (0.08-0.78) |
| Progression > MCIC | 0 (0%) | 0 (0%) | 0% (-8 – 4) |
| Progression > SDC | 5 (4%) | 0 (0%) | 4% (-4 – 10) |
| Progression > 0.5 | 37 (32%) | 9 (15%) | 17% (2 – 29) |

Progression = in units per 18 months
Data are mean (SD) or n (%)
SvdH: modified Sharp-van der Heijde score; MCIC: Minimal Clinical Important Change (8 units)
SDC: Smallest Detectable Change (4.1 units)





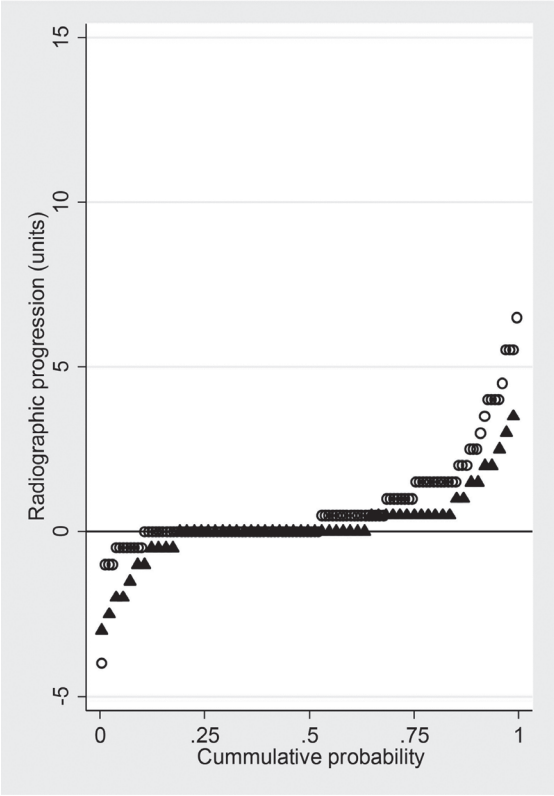


**Figure 6.** Probability plot for radiological progression in the dose reduction and usual care group
O = dose reduction group
▲ = usual care group

The occurrence of adverse events was similar between the groups (Table 3). The, non-significant, higher incidence of overall serious adverse events was caused by more (mostly orthopaedic) elective surgery. Frequency of serious infections, cardiovascular events and malignancies was similar between groups.

## Costs, quality of life and cost-effectiveness

RA related work absenteeism occurred in 2/59 (3%, 95% CI 1-13%) and 6/121 (5%, 95% CI 2-11) patients in the usual care and intervention group, resulting in 7 and 25 days work lost respectively (ns). The mean total costs were €12,223 in the dose reduction group and €21,261 in the usual care group (p<0.001). The mean QALY for this same period was 1.23 for the dose reduction group and 1.25 for the usual care group (ns), resulting in a DCER of €390,493 (Figure 7A). The NMB of dose reduction is shown in figure 7B. When using a WTP level of €80,000 per QALY, often considered the upper limit the society is willing to pay per gained QALY, the NMB is around 7,000 euro per patient per 18 months.

**Table 3.** Safety summary

| | Dose reduction (n=121) | Usual care (n=59) |
|---|---|---|
| Flares | | |
| All flares* | 88 (73) | 16 (27) |
| Major flares | 15 (12) | 6 (10) |
| Other adverse events | | |
| Adverse events | 95 (79) | 45 (76) |
| Serious adverse events** | 30 (28) | 7 (12) |
| Planned surgery | 11 (9) | 1 (2) |
| PET/CT related † | 4 (3) | - |
| Cardiovascular event | 5 (4) | 1 (2) |
| Infectious adverse event | 3 (2) | 3 (5) |
| Malignancy | 6 (5) | 2 (3) |
| Allergic (injection) reaction | 0 | 0 |
| Death | 0 | 0 |

Data are n (%); Cumulative incidence at 18 months: number of patients with at least 1 event in the study period.
* statistically significant p<0.001
** 4 patients had 2 serious adverse events
† Patients allocated to the dose reduction group were asked for a sub-study which included a whole body PET/CT. Four patients were diagnosed with extra-articular abnormalities that needed explorative surgery

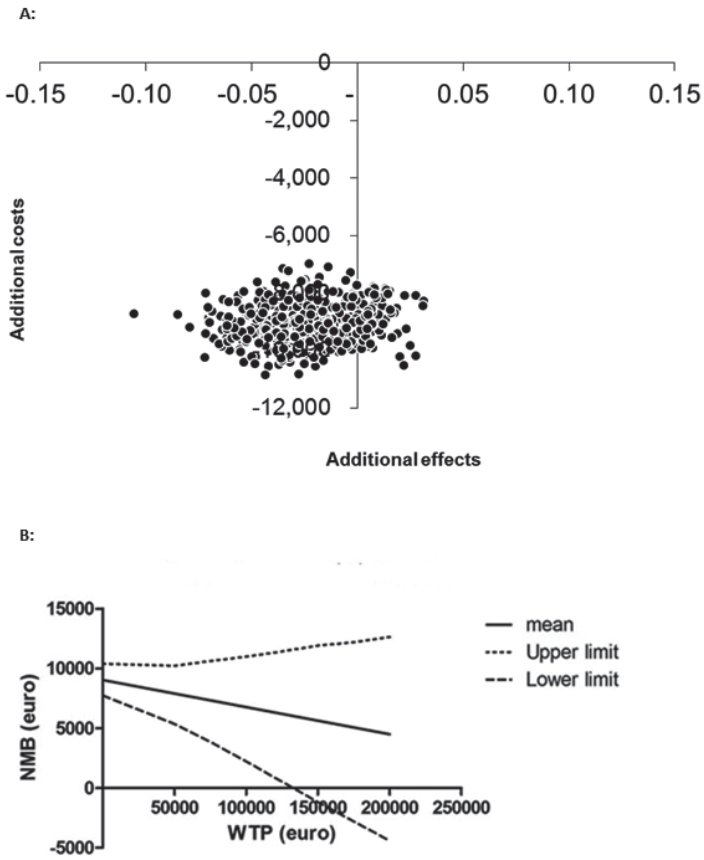


**Figure 7.** Cost effectiveness analysis. A: Results of the 1000 bootstrapped replications, presented in cost-effectiveness planes. It graphically presents the uncertainty around the cost-effectiveness ratio. B: Net Monetary Benefit on the y-axis, plotted against different levels of euro per QALY that could be chosen as WTP on the x-axis.
NMB= Net Monetary Benefit; WTP= Willingness To Pay

## DISCUSSION

This is the first study to show that a disease activity guided dose reduction strategy of adalimumab or etanercept in RA is non-inferior to usual care for occurrence of major flare, but clearly superior in cost-effectiveness. In the majority of patients, TNFi intervals could be increased or TNFi could be discontinued without a difference in major flares, disease activity after 18 months, functioning, clinically relevant radiographic progression, quality of life, side effects, or other treatment between the dose reduction strategy and usual care, although short lived flares were more frequent in the dose reduction group. Unfortunately, no predictive factors for successful dose reduction or discontinuation could be found.

The internal validity of our study was strengthened by the randomised design, use of validated outcome measures and comparable treatment strategy in both arms, with exception of the dose reduction advice. The number of patients needed according to our sample size calculation was met and loss to follow up and missing data were kept to a minimum. Our study was based on some methodological choices that can be challenged. Firstly, the pre-planned NI margin we chose was to some extent arbitrary, as only four non inferiority studies have ever been done focusing on DMARDs/biologicals in RA, and none of these were a strategy study or used flare as primary outcome. Our NI margin was considered clinically reasonable, as the resulting minimum number needed to harm of one in five (20% difference between groups in major flare) seems a fair trade-off with the expected number needed to benefit of lower than one in two (50% difference between groups in successful dose reduction). This study was also not blinded. However, the direction of the expectation bias that might have occurred would be towards overestimation of short lived flares, and parallel underestimation of proportion of patients who can successfully taper in the intervention group, because both patients and physicians would expect a high risk of flare. This is contrary to regular RCTs in which treatment is started, as in these trials, expectation of response can lead to inflated measures for effectiveness. A blinded study would thus probably have resulted in the same estimates with regard to major flares (no difference), lower incidence of short lived flares, and higher proportion of successfully tapered patients. This is indeed corroborated by the PRESERVE study, that showed a higher percentage of patients who could dose reduce and stop than in our study.[8] Whether we chose the optimal primary outcome can be debated. Several non-validated flare criteria have been used in dose reduction and discontinuation research.[21] Our DAS28 based flare criterion has been validated, correlating well with patient and physician judgement of disease worsening, and showing good construct validity. However, the optimal definition of flare is still under debate, with work in progress to also develop patient reported flare criteria.[22]

There were some interesting differences in baseline characteristics and treatment during follow-up between the dose reduction and usual care group. Lack of DMARD co-medication and higher level of radiological damage at baseline were for example more prevalent in the dose reduction group, but these differences would have caused bias in the conservative direction. This baseline imbalance in DMARD medication is probably a reason for DMARDs being more often escalated or initiated in the dose reduction group, while dose reduction and discontinuation of DMARDs was more frequent in the usual care group. Another reason for the latter could be that patients in the usual care group desired to dose reduce other RA medication while TNFi was continued. However, use of DMARDs and oral glucocorticoids at study end was still more prevalent in the usual care group. We therefore think that these between group differences do not invalidate our conclusions of non-inferiority with regard to the clinical outcome and clear superiority in cost effectiveness.

How should our study results be interpreted in light of the existing evidence on tapering and stopping TNFi? There are a number of studies on dose reduction and discontinuation of TNFi. However, most are relatively small, uncontrolled and heterogeneous in design and outcomes, or compare fixed dose reduction or discontinuation, without the possibility to increase the dose, which makes it difficult to compare results.[10] Also of importance is how to interpret the difference in short lived flares and minimal radiographic progression. Higher incidence of short lived flares in the dose reduction group is inevitable when using a disease activity guided dose reduction strategy. However, in our view, the clinical impact of these short lived flares is limited, and worth the trade-off with much lower TNFi exposition, including fewer injections, and probably lower risk for long term side effects.

Although not statistically significant, the number of SAEs was higher in the dose reduction group. This was however mostly caused by higher incidence of elective surgery (joint replacement, arthrodesis, joint prosthesis revision). A possible reason for this could be that surgeons are more likely to operate when patients are using less or no TNFi. Also, as part of a sub-study whole body PET/CT scans were performed in the dose reduction group, leading to four patients with abnormalities requiring surgery. As no PET/CT scans were performed in the usual care group, this seems a case of information bias.

An important aspect of generalizability of our dose reduction strategy is the use of treat-to-target, which is important in the treatment of RA,[23,24] but especially when following a disease activity guided dose reduction strategy, as risk of flaring is increased. In this study, implementation of treat-to-target was satisfactory, as witnessed by the low DAS28-CRP during the study in both groups. However, implementation of this strategy on a large scale and in other health care systems and countries could be challenging, for example due to large travel distance for patients.[25,26]

In conclusion, we demonstrated the non-inferiority of a feasible dose reduction strategy of adalimumab or etanercept compared to usual care in patients with RA and low disease activity. Implementation of this strategy would further improve the cost-effectiveness of RA treatment. Future research should include longer follow up studies confirming persistence of non-inferiority for clinical and radiographic outcomes and assessing possible superiority for adverse events. Other potential predictors for successful dose reduction and discontinuation (biomarkers, ultrasound, PET/CT) could be investigated to further minimise the risk of flaring.

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# seven

## PREDICTION OF SUCCESSFUL DOSE REDUCTION OR DISCONTINUATION OF ADALIMUMAB OR ETANERCEPT USING SERUM DRUG LEVELS AND ANTIDRUG ANTIBODY MEASUREMENT

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*To be submitted*

## ABSTRACT

### Objectives

To evaluate if adalimumab and etanercept serum (anti)drug levels can predict successful dose reduction or discontinuation in rheumatoid arthritis (RA) patients with low disease activity. Central hypotheses being that: 1) a patient with no/low serum levels and/or anti-drug antibodies should be able to successfully stop and 2) a patient with high serum levels should be able to reduce the dose.

### Methods

RA patients, included in the intervention arm of a randomised controlled study of a dose reduction strategy of adalimumab or etanercept (n=118) were analysed. Serum anti(drug) levels were measured before start of dose reduction. Receiver-operator-curves (ROC) and optimal cut-off serum drug levels were calculated. Sensitivity analyses were done for timing of serum sampling.

### Results

Mean drug levels were not different per subgroup (successful discontinuation, successful dose reduction, or no dose reduction possible at 18 months). ROC analyses showed no predictive value of drug levels for outcome, except for an unexpected inverse association between lower etanercept levels and higher chance for successful dose reduction (Area Under the Curve (AUC) 0.36, 95% CI 0.23-0.49). High adalimumab trough levels predicted successful dose reduction (AUC 0.86, 95% CI 0.58-1.00). Anti-drug antibodies were rare (adalimumab 10%, etanercept 0%) and not predictive for successful discontinuation.

### Conclusions

We could not confirm predictive value of random timed sampling of adalimumab and etanercept serum drug levels for successful dose reduction or stopping in RA patients, with the possible exception of high adalimumab trough levels for successful dose reduction. Anti-drug antibodies have no predictive value in this context.

## INTRODUCTION

Tumour necrosis factor inhibitors (TNFi) have proven to be effective in clinical, functional and radiographic outcomes in patients with rheumatoid arthritis (RA).[1] However, TNFi are associated with (dose-dependent) side effects, like infections and skin cancer, and are also costly.[2, 3] Optimal use of these drugs is therefore warranted, amongst others using the lowest effective dose in the individual patient, and discontinuing treatment when this is no longer necessary.

A number of studies in patients who achieve persistent low disease activity demonstrated that dose reduction and discontinuation is possible in a relevant proportion of patients without increase in disease activity.[4] However, disease activity guided dose reduction in a patient already using the most optimal dose, will lead to (temporary) flare of disease activity. Although fortunately, dose escalation or restart of the drug is effective in the majority of patients,[4] and short lived flares do not seem to compromise quality of life, functioning or radiological outcome,[5] they can still present a burden for patients.

Prediction of successful dose reduction or discontinuation in addition to a disease activity guided type of dose reduction could have two advantages: 1/ in patients in whom TNFi cannot be dose reduced, flares caused by dose reduction can be prevented and 2/ when successful discontinuation can be predicted, no dose tapering phase is necessary, thus saving time and drugs.

Possible predictors for successful dose reduction or discontinuation could be TNFi serum levels and anti-drug antibodies. Clinical scenarios have been proposed in which measurement of drug levels or anti-drug antibodies is expected to be valuable in patients doing well.[6-8] Following these scenarios, decision rules were composed, sharing two central hypotheses: 1) a patient with no/low serum levels and/or anti-drug antibodies should be able to successfully stop the TNFi as clinical effect is not to be expected and 2) a patient with high serum levels should be able to reduce the dose, as the same clinical effect is to be expected with a lower dose. Although logically sound at face value, these hypotheses have not been tested before.[9] One previous study testing these hypotheses in patients down titrating infliximab could not confirm a predictive effect of (anti)infliximab trough levels for successful dose reduction or discontinuation.[10] For adalimumab and etanercept (the most frequently used TNFi) there is, to our knowledge currently no data available.

Therefore, the aim of this study was to investigate whether serum drug levels and anti-drug antibodies can predict successful dose reduction or withdrawal of adalimumab or etanercept in RA patients with low disease activity.

## METHODS

### Study population and design

Patients included in the intervention arm of an open randomised clinical trial investigating non-inferiority of a dose reduction strategy of adalimumab or etanercept compared to usual care (DRESS-study, chapter 6), with 18 month follow up were included for these analyses.[11]

Patients with RA (either 2010 ACR RA and/or 1987 RA criteria and/or clinical diagnosis of the treating rheumatologist) using either adalimumab or etanercept in any stable dose for at least 6 months, with stable low disease activity were included. Patients were treated according to the tight control principle. Visits were planned every 3 months and patients were encouraged to contact the outpatient clinic if they experienced more complaints. Patients in the intervention arm were treated using a dose reduction and withdrawal strategy consisting of stepwise increasing the interval between injections every three months. For adalimumab the steps were: 1) 40 mg every 21 days, 2) 40 mg every 28 days, 3) stop. For etanercept the steps were: 1) 50 mg every 10 days, 2) 50 mg every 14 days, 3) stop. In case of flare, the last effective interval was reinstated. If despite this the flare persisted, TNFi was increased until the shortest registered interval, thereafter treatment was switched. A flare was defined using a DAS28 based flare criterion: a DAS28-CRP increase of > 1.2 or a DAS28-CRP increase of >0.6 and current DAS28-CRP ≥ 3.2.[12]

### Assays

Serum samples were collected at baseline (before start dose reduction) at a regular visit, thus unrelated to time of injection, for pragmatic reasons. The time of the previous and next adalimumab or etanercept injection was noted. Serum adalimumab and etanercept levels were measured using enzyme-linked immunosorbent assay (ELISA) based on their ability to bind TNF.[13, 14] Adalimumab levels have been proposed to be therapeutically low when below 5 mg/l and high when over 8 to 12 mg/l,[8, 15, 16] for etanercept previously published thresholds were low when below 2.1 mg/l and high when over 4.7 mg/l,[13] both on a group level.

Anti-adalimumab antibodies were assessed using a validated antigen-binding test (Radio Immuno Assay(RIA)). Anti-adalimumab antibodies were considered positive based on the lower limit of detection if both the value was > 12 arbitrary units/ml and the adalimumab level was < 5mg/l.[14] Anti-etanercept antibodies were assessed using different assays.[13]

### Statistical analyses

Our study has six separate null hypotheses, three for each TNFi. These are, that 1/ there is no association between high drug levels with successful dose reduction, 2/no association between low drug levels and successful stopping, and 3/no

association between the presence of anti-drug antibodies and successful stopping. The associations are analysed using Receiver Operator Curve (ROC) analyses and calculation of the point estimate of the area under the curve (AUC) and surrounding confidence interval, to test whether the lower limit of the confidence interval is above 0.5. Sample size calculation show that, with a null hypothesis of a ROC AUC of 0.5, an expected AUC of 0.75, an event rate of 20% (being able to stop) to 40% (being able to dose reduce), a total of 65 to 43 patients per drug (adalimumab or etanercept) respectively are needed to be able to reject the null hypotheses with a power (1-beta) of 0.8 and alpha of 0.05.

Descriptive statistics were used for demographic/clinical data. Percentages of patients were calculated for three different outcomes at 18 months: successfully stopped, successfully dose reduced (lower dose/higher interval than baseline) or no dose reduction possible of adalimumab or etanercept, and differences were tested using a t-test. ROC were created for adalimumab and etanercept levels, and for the presence of anti-drug antibodies, versus the outcomes successful discontinuation and successful dose reduction separately, compared to the 'no dose reduction possible' group. The optimal cut-off values were identified using the most optimal Youden index. Finally, because sampling was done at random time in relation to injection instead of trough level timing, sensitivity analyses were done for three groups of patients with peak sampling (adalimumab day 1-4 and etanercept day 1-2 after last injection), trough sampling (adalimumab 11-14 days and etanercept 6-7 days after last injection) and intermediate sampling. No correction for multiple testing was applied.

## RESULTS

### Patient characteristics and baseline (anti) drug levels

Baseline serum samples and outcome were available for 118 of 121 patients (Table 1). TNFi could be successfully stopped in 19% (95%CI 12-27) of patients, the interval successfully increased in 44% (95%CI 35-53). In 37% (95%CI 29-47) of patients no dose reduction was possible without loss of disease control. All patients had adalimumab or etanercept levels above the lower limit of detection.[13, 16] Mean drug levels and anti-drug antibodies were not significantly different between subgroups (Table 2). Anti-adalimumab antibodies (low titres, 15 to 46 U/ml) were detected in 4 patients (10%), two patients used methotrexate co-medication, the other two patients used adalimumab monotherapy. No anti-etanercept antibodies were detected.

**Table 1.** Baseline patient characteristics

| | Dose reduction (n=118) |
|---|---|
| Age, years (SD) | 59 (9.9) |
| Female, n (%) | 73 (62) |
| Current smoking, n (%) | 27 (23) |
| BMI (SD) | 27 (4.9) |
| Diagnosis according to 2010 and/or 1987 ACR criteria, n (%) | 111 (94) |
| Disease duration, years median [p25-p75] | 10 [5-16] |
| RF positive, n (%) | 92 (78) |
| ACPA positive, n (%) | 83 (70) |
| DAS28-CRP (SD) | 2.2 (0.6) |
| DAS28-BSE (SD) | 2.5 (0.7) |
| Etanercept/adalimumab, n (%) | 76/42 (64/36) |
| Duration of current TNFi therapy, years (SD) | 3.5 (2.5) |
| Previous DMARDs, median [p25-p75] | 2 [1-3] |
| Previous TNFi, median [p25-p75] | 0 [0-1] |
| Concomitant therapy | |
| DMARD, n (%) | 72 (61) |
| MTX, n (%) | 57 (48) |
| glucocorticosteroid, n(%) | 5 (4) |
| NSAID, n (%) | 65 (55) |

BMI= Body Mass Index; RF= rheumatoid factor; ACPA= anti-Citrullinated Peptide Antibodies; DAS28= 28 joints disease activity score; TNFi= Tumor Necrosis Factor inhibitor; DMARD= Disease Modifying Antirheumatic Drug; MTX= Methotrexate; NSAID= Non-Steroidal Anti Inflammatory Drug

## Prediction of successful dose reduction or discontinuation

The ROC analyses showed no significant predictive value of adalimumab or etanercept serum levels for successful dose reduction or discontinuation (Figure 1), except for a significant but small association between lower etanercept levels and higher chance for successful dose reduction (AUC 0.36, 95% CI 0.23-0.49). Presence of anti-adalimumab antibodies was not predictive for successful discontinuation, with none of the 4 patients with adalimumab antibodies being able to successfully stop adalimumab.

## Sensitivity analyses for timing of serum sampling

Mean serum drug levels for the different serum sampling times show somewhat lower levels with increasing time after injection, although the differences are not large and mostly non-significant (Table 3). A sensitivity analyses showed that for

**Table 2.** Mean drug levels and antidrug antibodies at baseline

**A: adalimumab**

| Outcome at 18 months | Mean drug level at baseline mg/l (SD) | | Anti-drug antibodies (%) |
|---|---|---|---|
| Successfully stopped (n=11) | 8.5 (2.8) | | 0 |
| Successfully dose reduced (n=15) | 8.1 (5.2) | ns | 1 (7) |
| No dose reduction possible (n=16) | 6.8 (4.1) | | 3 (19) |

**B: etanercept**

| Outcome at 18 months | Mean drug level at baseline mg/l (SD) | | Anti-drug antibodies (%) |
|---|---|---|---|
| Successfully stopped (n=11) | 2.7 (1.3) | | 0 |
| Successfully dose reduced (n=37) | 2.0 (0.9) | ns | 0 |
| No dose reduction possible (n=28) | 2.4 (1.0) | | 0 |

SD=standard deviation; ns= not statistically significant

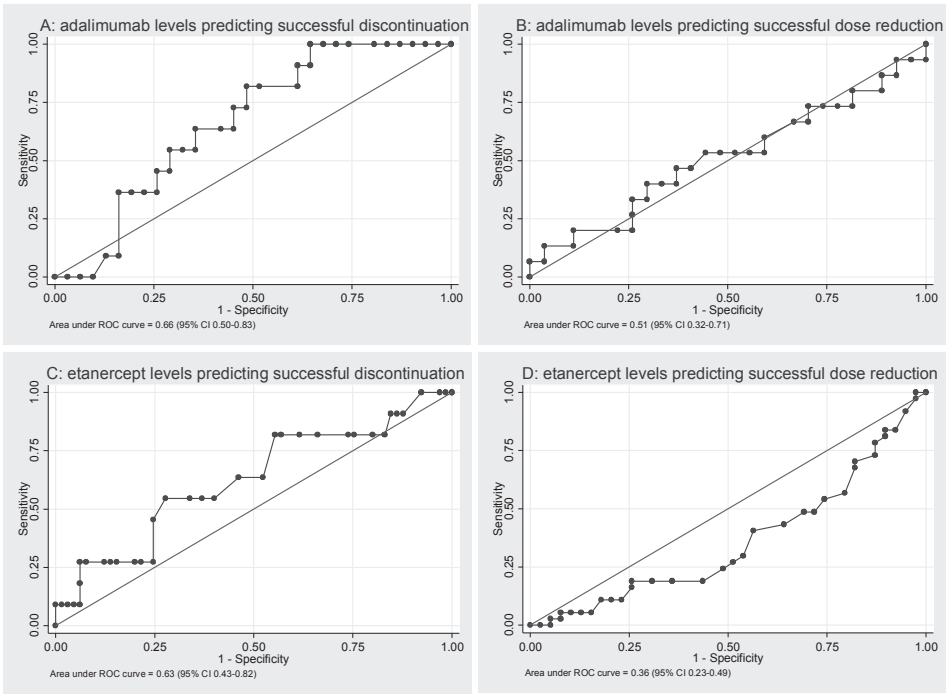


**Figure 1.** Receiver Operator Curves (ROC)

**Table 3.** Mean serum levels for different sampling times

**A: adalimumab n=42**

| Sampling time | Mean drug level at baseline mg/l (SD) | |
|---|---|---|
| Peak (n=11) | 8.5 (5.6) | |
| Intermediate (n=22) | 7.7 (4.2) | ns |
| Trough (n=9) | 6.7 (2.0) | |

**B: etanercept n=76**

| Sampling time | Mean drug level at baseline mg/l (SD) | | |
|---|---|---|---|
| Peak (n=25) | 2.4 (1.2) | ns | * |
| Intermediate (n=28) | 2.5 (1.0) | * | |
| Trough (n=23) | 1.7 (0.6) | | |

SD=standard deviation; ns= not statistically significant
*p<0.05

intermediate timed serum etanercept level, low levels were associated with a higher chance of successful dose reduction (AUC 0.28 95% CI 0.08-0.47), with levels lower than 2.5 mg/l showing a sensitivity of 77% and a specificity of 67%. For adalimumab, high trough timed levels were associated with successful dose reduction (AUC 0.86, 95% CI 0.58-1.00), with trough levels higher than 7.8 mg/l showing a sensitivity of 100% and a specificity of 86%. None of the patients had adalimumab trough levels ≥ 12 mg/l.

## DISCUSSION

With the results of our study we could not confirm that random timed sampling of (anti)drug levels of adalimumab and etanercept can predict whether an RA patient can successfully reduce the dose or stop the TNFi treatment. With regard to antidrug antibodies we could also not confirm predictive value for successful discontinuation.

An important design choice in our study was to perform random sampling of serum levels, instead of sampling just before the next injection or fixed time after last injection (trough level sampling), because it can be argued that this might have led to underestimation of the association between (anti)drug level and outcome. This might be the case, although it should be noted that the differences between peak and trough levels (peak to trough ratio's) - as also shown in our data - in subcutaneous TNFi are not very high.[17] So, the benefits of trough sampling over random timed sampling can be questioned. Also, the requirement for trough level sampling might hamper the use in daily clinical practice. The random timed sampling did enable us to do exploratory sensitivity analyses. These analyses showed an association

between high adalimumab trough levels and successful dose reduction, suggesting a predictive value of trough levels above 7.8 mg/l in this scenario. However, this should be interpreted with caution and validation is required, as previously different cut-offs for supra-therapeutical adalimumab trough levels have been suggested, ranging from 8 mg/l to 12 mg/l.[8, 15, 16] In addition, analyses for etanercept showed the opposite; a small inverse relation between (intermediate timed) etanercept serum levels and successful dose reduction. These perhaps contra intuitive and contradictive findings suggest that this might be false positive findings.

Another finding important to discuss is the lack of predictive value due to low percentage of patients with anti-adalimumab antibodies (10%) compared to other studies (17-30% RIA measured anti-adalimumab antibodies) in RA patients.[6] This difference might be explained by the fact that the included RA patients had been treated with tight control for a long time, with patients not doing well (sometimes possibly due to anti-adalimumab antibodies) being switched to other treatments. This selection does not invalidate our findings, however, as it is a sign of good RA care and therefore a relevant study population. Also, none of the four patients with anti-adalimumab antibodies was able to stop without deterioration in disease activity.

A potential limitation of this study is the limited number of patients, especially for the sub-analyses. However, any clinically relevant association would have still been detected with the above mentioned analyses, as witnessed by the significant adalimumab trough level analysis.

Although disappointing, our results are not directly conflicting with the established body of evidence. One study with a comparable design (i.e. prediction of successful tapering of infliximab in RA) failed to show predictive value of (anti) infliximab trough levels on successful dose reduction or discontinuation.[10] Two other studies in related scenarios (prediction of response after golimumab dose escalation by means of golimumab trough levels in ankylosing spondylitis patients, and prediction of response after start of infliximab by means of infliximab trough levels in RA) could also not confirm a strong predictive value.[18, 19] On the other hand, a number of cross-sectional or non-interventional studies did find (weak to moderate) positive correlations between TNFi serum levels and response on a group level.[6]

So, how can we reconcile these seemingly conflicting results? Two main factors might play a role. Firstly, although on a group level a dose response curve has been demonstrated, the same curves show high inter-individual variation in effective serum drug levels.[13, 14] This means that a serum drug level of for example 5 mg/l can be too low for one patient, but supra-therapeutical for another, and recently data supporting this view have been published.[20] Secondly, patients that are doing well even without TNFi cannot be identified by their serum drug levels, as their low disease activity is of course unrelated to the drug level. Both effects result in low or no associations between drug levels and the result after tapering.

All in all, the hypothesis that random timed serum TNFi levels can straightforwardly be used for prediction of successful dose reduction or discontinuation in RA patients doing well on adalimumab or etanercept could unfortunately not be confirmed. The same seems true for antidrug levels as they are not prevalent and not associated with successful discontinuation. High adalimumab trough levels might be predictive for successful dose reduction. However, this should be replicated first, especially as for etanercept the inverse was found.

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# eight

SUMMARY AND GENERAL DISCUSSION

## OPTIMISING BIOLOGIC DMARD TREATMENT

In the treatment of rheumatoid arthritis (RA), optimal individual dosing of biologic disease modifying antirheumatic drugs (bDMARDs) is warranted, because of their increased risk of (dose dependent) adverse effects and high costs. To achieve optimal effect and minimise adverse effects and costs, these drugs should be used in the lowest effective dose/longest effective interval and the drug should be stopped when possible. The different bDMARDs available for RA have their own pharmacological characteristics and subsequently need different strategies to reach the lowest effective dose/longest interval. This thesis discussed dosing strategies for rituximab, tocilizumab and anti-Tumor Necrosis Factor (TNF) agents.

### Rituximab

The optimal treatment strategy of rituximab in patients with RA remains a point of discussion. Different strategies are being used in clinical practice. The classically used on demand treatment strategy, in which a patient is retreated in case of flare in disease activity, is an individualised approach based on the large variation in response duration to rituximab (usually 6-12 months). However, a disadvantage of this strategy is the (temporary) worsening in disease activity before retreatment. This can be a burden for patients and might lead to worse radiological outcome.[1] A variation of this strategy, the treatment strategy with a predefined target (for example DAS28 based low disease activity) might minimise the chance of worsening in disease activity. Lastly, the fixed schedule treatment strategy, with retreatment for example every 6 months, will prevent flare in disease activity and leads to superior disease control. However, due to the large variation in response duration, it is difficult to recommend a specific interval, with a short interval leading to overtreatment in a group of patients and a longer interval leading to a flare of disease activity before planned retreatment in some patients.

In chapter 2 of this thesis we investigated another possible rituximab treatment strategy; retreatment when there is loss of response (LoR), and thereafter using a fixed interval based on the first response duration. Therefore, the intra-individual variation in response duration after two subsequent rituximab courses in RA patients was determined. In seventy RA patients treated with at least three rituximab courses, differences in first and second interval between infusions and between duration until LoR were analysed. Mean interval in days was 301 (Standard Deviation (SD) 95 days) and 341 (SD 123) days for the first and second rituximab infusion interval. Mean interval between infusions until LoR was 252 (SD 93) and 307 (SD 126) days respectively. Limits of agreement between intervals were large (-190 to 272 days). We therefore concluded that duration of response after the first rituximab course is not a useful parameter in timing of retreatment, because of the large intra-individual variation in response duration.

So, what treatment strategy should best be used in clinical practice? Only a limited number of studies comparing the different rituximab treatment strategies

are available. One small study showed no difference in clinical, functional and radiographic outcomes after one year between a fixed treatment strategy (every 24 weeks) and on demand retreatment.[2] However a large registry study comparing on demand versus fixed retreatment in patients with at least 3 rituximab treatment cycles showed better clinical and functional outcomes in patients with fixed retreatment.[3] Another study comparing a treatment-to-target strategy (retreatment after at least 24 weeks, when DAS28-ESR ≥ 2.6) to a treatment as needed strategy (retreatment after at least 24 weeks, based on physician's discretion) showed better clinical and functional response in patients in the treatment-to-target strategy group.[4] No studies comparing a treatment-to-target with a fixed strategy are available. Analysis of a Swiss database showed a gradual deterioration in DAS28 from six months after rituximab treatment in patients eventually needing retreatment and observed that physicians usually delayed retreatment until disease activity was at pre-rituximab level and the authors concluded that this is suboptimal for patients.[5] Also important to take into account, is the time needed with rituximab retreatment to regain low disease activity again when using a treatment-to-target strategy, as a long time to response might lead to suboptimal disease control. However, time to response for rituximab does not seem longer than for example time to response after start of anti-TNF.[6] Also, bridging in case of non-low disease activity is feasible and effective. In this sense, treating to target with rituximab retreatment resembles the successful strategy of treating to target whilst tapering anti-TNF used in our DRESS study, as waiting for the right timing of retreatment is de facto tapering of rituximab.

Considering all evidence, a treatment-to-target strategy seems the most optimal strategy at this moment. Indeed, in a recent international consensus statement, a treatment-to-target strategy, with retreatment after at least 6 months in patients who do not achieve remission, is advocated.[7] Of note, our study showed a mean interval duration of 10 months and an increase in response duration in the second interval compared to the first interval. Therefore, a fixed strategy, with retreatment every 6 months would lead to (increasing) overtreatment. A treatment-to-target strategy enables a more individualised approach and prevents overtreatment.

## Tocilizumab

Only limited data exists on dose reduction of tocilizumab in patients with RA and low disease activity. Therefore, the aim of **chapter 3** was to investigate the feasibility of reducing the dose of tocilizumab in patients with RA and low disease activity from 8mg/kg to 4mg/kg every 4 weeks. Retrospectively, data were collected of 22 patients successfully treated with tocilizumab 8mg/kg for about 6 months and thereafter tapered to 4 mg/kg because of low disease activity. Mean DAS28 at time of dose reduction was 2.3 (SD 0.9). After 3 and 6 months follow up, 77% (95% Confidence Interval (CI) 54-91) and 55% (95% CI 32-76) of patients had successfully reduced the dose without losing disease control, respectively. DAS28 at 3 and 6 months was

somewhat higher than baseline, 2.7 (SD 1.2) and 2.5 (SD 1.0) respectively. All patients who experienced worsening of disease activity after dose reduction regained low disease activity after dose escalation. We therefore concluded that disease activity guided dose reduction of tocilizumab seems to be feasible in a relevant proportion of patients.

Our results are comparable with the other two existing tocilizumab dose reduction studies, that also found that dose reduction is possible without deterioration in disease activity in a number of patients.[8, 9] They are also compatible with the, only small, differences in response between these two dosages in the clinical randomised induction trials.[10-13]

All in all, dose reduction of tocilizumab seems promising in patients with RA and low disease activity. However, all existing studies on tocilizumab dose reduction are small retrospective studies. Larger studies investigating non-inferiority of disease activity guided dose reduction and also discontinuation of tocilizumab compared to continuing treatment unaltered with regard to flares, patient functioning and radiological progression will give more insight in the merits of the former strategy. These studies should also address the availability of tocilizumab as subcutaneous injections.[14] Although dose reduction by widening of the injection interval seems a practical strategy, this has still to be studied.

### Anti-TNF agents

To summarise the research previously performed on dose reduction and discontinuation of anti-TNF agents we conducted a systematic literature review of randomised controlled trials and controlled clinical trials comparing down titration of anti-TNF agents to usual care/no down titration in RA patients and a low disease activity state, described in **chapter 4.** We identified three different down titration strategies i.e. fixed anti-TNF dose reduction, fixed anti-TNF discontinuation and disease activity guided anti-TNF tapering. Seven studies (total 1203 patients) reporting anti-TNF down titration were included. Only two of these studies were published full text at the time of this review. We concluded, mostly based on moderate quality evidence, that non-disease activity guided dose reduction of etanercept 50 mg weekly to 25 mg weekly, after at least 3 to 12 months of low disease activity, seems as effective as continuing the standard dose with respect to disease activity and function outcome, although dose reduction significantly induces minimal but not clinically meaningful differences in radiological progression. Discontinuation (also without disease activity guided adaptation) of adalimumab and etanercept is inferior to continuation of treatment with respect to disease activity, radiological outcome and function. Disease activity guided dose tapering of adalimumab and etanercept seems slightly inferior to continuation of treatment with respect to disease activity, with no difference in function. However the only study investigating this comparison included lower than projected number of patients. An interesting

finding in this review was the lack of cost-effectiveness and long term safety as outcome measures in the included studies, as these are the main reasons dose reduction and discontinuation are considered. Most included studies were industry funded studies that used a (non-disease activity guided) fixed dose reduction or treatment protocol without the possibility to escalate or restart therapy, which does not reflect clinical practice.

Partly based on the results of this systematic review we designed a pragmatic, non-inferiority, randomised controlled trial on dose reduction and discontinuation of the subcutaneous anti-TNF agents adalimumab and etanercept in RA patients with low disease activity (the DRESS study). **Chapter 5** targets several clinical and methodological issues on anti-TNF agent dose reduction, including how to taper anti-TNF agents, the satisfactory control condition, how to define flare, implementation in clinical practice, and the choice of the non-inferiority margin. The results of the DRESS study are described **in chapter 6**. We randomly assigned 180 patients with RA and low disease activity using adalimumab or etanercept to a disease activity guided dose reduction strategy or usual care (2:1). Dose reduction consisted of stepwise increases of the interval between injections every 3 months until flare in disease activity or discontinuation, with the possibility to escalate or restart in case of flare of disease activity. A flare was defined as a DAS28-CRP increase >1.2 or DAS28-CRP increase >0.6 and current DAS28-CRP ≥3.2, compared to baseline DAS28-CRP. The primary outcome was the difference in proportions of patients with major flare (flare > 3 months) between the two groups at 18 months. Dose reduction was shown to be non-inferior to usual care, with the difference in major flare being 2% (95% CI -12% to 12%). Anti-TNF agent could successfully be stopped in 20% (95% CI 13 to 28) of patients, the interval successfully increased in 43% (95% CI 34 to 53). In 37% (95% CI 28 to 46) of patients no dose reduction was possible. Functional status, quality of life and clinically relevant radiographic progression were not different between the groups. During the 18 months, mean costs were €9,038 lower in the dose reduction group, (Quality Adjusted Life Year (QALY) difference -0.02, ns), resulting in a cost effectiveness ratio of €390,493 per QALY. We therefore concluded that a disease activity guided dose reduction strategy of adalimumab and etanercept is non-inferior to usual care for major flare, while being clearly superior in cost-effectiveness.

The DRESS study was performed in a daily clinical practice setting showing that the disease activity guided strategy is a feasible approach. One study also investigated non inferiority of a disease activity guided dose reduction of adalimumab and etanercept.[15, 16] This study showed comparable results, with 35,9% and 37,5% of patients being able to dose reduce or discontinue, respectively. Also, no difference in functioning and radiographic progression was found in this study. Disease activity based on DAS28 measurement using a mixed linear model showed no statistical difference between dose reduction and continuing treatment, however non-inferiority could not be proven.

Thus, combining the existing evidence on (disease activity guided) dose reduction and discontinuation of anti-TNF agents and the results of our research we can conclude that it is feasible, safe and cost-effective in RA patients with (at least) low disease activity and should be part of guidelines on biologic DMARD treatment in RA. The European League against rheumatism (EULAR) recommendations on the use of bDMARDs in patients with RA indeed includes a recommendation to taper bDMARDs in patients with persistent remission.[17] Other guidelines on treating patients with RA with bDMARDs, including the Dutch guideline and the National Institute of Health and Care Excellence (NICE) guideline also contain recommendations on tapering of bDMARDs.[18, 19]

## CHALLENGES IN OPTIMISING BIOLOGIC DMARD TREATMENT

While more and more evidence on optimising bDMARDs is available, different points of discussion remain; including 1) the choice of outcome measure in dose tapering studies and long term follow up questions, 2) challenges in implementation in clinical practice and, 3) the possibility of prediction.

### Outcome measures

The right primary outcome to assess the possibility for dose tapering can be debated. During a dose reduction strategy, the risk of flare in disease activity is increased and correctly identifying patients who flare is important. Although, different flare criteria have been used in anti-TNF dose reduction and discontinuation studies, none of the used criteria have been validated.[20] In our trial we used a validated DAS28 based flare criterion.[21] This criterion correlates well with opinion of both patient and physician, and shows good construct validity. In addition, we chose to use DAS28-CRP instead of DAS28-ESR, because the former is more sensitivity to short-term change in disease activity and less influenced by confounding factors.[22] However, previous studies have showed that DAS28-CRP values of disease activity are lower than DAS28-ESR (range 0.2-0.7 points).[23, 24] Measuring change using DAS28 results in difference between DAS28-ESR and DAS28-CRP as well, with DAS28-CRP use resulting in more improvement compared to DAS28-ESR.[25, 26] It is thus advocated that, when using DAS28-CRP, different cut-off points for low disease activity and remission should be used.[24] Whether this is also true for the DAS28-CRP based flare criterion, has to be studied further. In our DRESS study, number of (major) flares was increased when measured with DAS28-ESR compared to DAS28-CRP, however the difference between dose reduction and usual care group remained the same.

Long term outcome effects of anti-TNF dose reduction and discontinuation have yet to be studied. Our study was with 18 months follow up the longest study, as most other studies followed patients for a maximum of 1 year.[27, 28] However, it can be argued that some questions should be answered with the study horizon even further away. These questions include whether radiographic joint damage does

not increase after longer follow up. Also, the question to what extend can patients, who are able to reduce or discontinue their medication, remain on that regimen, i.e. the persistence on that regimen has to be established. Another question concerns whether patients who are not able to reduce their therapy, should ever retry tapering again? And if so, what would be the time after the first attempt to retry? Finally, the risk/benefit between possible increase in cardiovascular risk and possible reduction in, incidence of, infections, antibody formation and malignancies should also be studied further.

## Implementation

With this thesis we increased the body of evidence that dose reduction and discontinuation of biologic agents is feasible, safe and cost-effective in a relevant proportion of patients. However, implementation of a dose reduction strategy in daily clinical practice could be challenging for a number of reasons. First of all, patients and physicians should be convinced that dose reduction is part of good treatment. Fear of flare in disease activity when starting dose reduction could be a barrier for both patient and physician to start such a strategy. Indeed, in the DRESS study fear of flare was reason for not participating in the study for a number of patients. Therefore, patient and physician perspective on dose reduction are needed to identify possible barriers and solutions to overcome these barriers. Secondly, during dose reduction, close monitoring of disease activity with additional change in treatment is important due to an increased risk in flare. This tight control or treat-to-target principle has previously been demonstrated to be superior to usual care treatment.[29] However, implementation of tight control in clinical practice has been shown to be difficult, due to different reasons including long travel distance for patients and rheumatologist's hesitant attitude towards using composite scores.[30, 31]

While this thesis focusses on dose reduction and discontinuation of biologic DMARDs (bDMARDs), discontinuation of conventional synthetic DMARDs (csDMARDs) has also been studied previously.[32] The use of combination therapy with both csDMARDS and bDMARDs is advocated for the treatment of RA. This raises the question which drug to taper when a patient uses combination therapy and is doing well. Due to costs, dose reduction of bDMARDs might be more cost effective. Other motives for dose reduction of either bDMARD or csDMARDs are side effects and patient's preference. Therefore, the choice which drug to taper might be an individual choice made by physician and patient. Future research is necessary on this subject and these kind of studies are currently being done in fact.[33]

One of the reasons dose reduction of bDMARDs is advocated are the high costs, with the yearly costs being approximately 15,000 euro.[34] A relatively new phenomenon in rheumatology is the biosimilars (biological product highly comparable with the reference biological regarding molecular structure, quality, efficacy and safety).

The first two infliximab biosimilars have recently been approved by the European Medicines Agency (EMA).[35] Biosimilars for adalimumab, etanercept and rituximab are currently being developed. The costs of these biosimilars are expected to be much lower than the existing biologicals. However, due to production complexity it is expected that also the biosimilar drugs will carry a significant price tag, as can be seen with previous biosimilar introductions (growth hormone, erythropoietin) and existing price levels in other countries.[34] As also adverse effects and practical reasons (including less frequent injections) are reasons for dose reduction and discontinuation the need for dose tapering remains present.

### Prediction

For timing of rituximab retreatment, prediction of duration of response can be helpful. Determinants that have been found to be associated with a longer duration of response to rituximab are older age, fewer prior DMARDs, lower baseline DAS28 and rheumatoid factor positivity.[5, 36] Other research suggested that the detectability of B cells 6 months after rituximab treatment may predict loss of response after 6 months.[37] Also ultrasound maybe helpful in detecting inflammation before the onset of clinical symptoms and therefore predict flare.[38] However, because of the weak associations with all these variables and loss of response, no clinically relevant prediction model exists so far.

Predicting successful anti-TNF agent dose reduction or discontinuation could provide two improvements over an individualised dose reduction strategy. Firstly, in patients in whom the anti-TNF agent cannot be dose reduced, flares caused by dose reduction can be prevented when dependency on anti-TNF could be predicted. Secondly, when successful discontinuation can be predicted, the dose tapering phase can be skipped and the drug can be stopped directly, thus saving time and drugs. Prediction of successful tapering has been subject of research. Some clinical determinants previously found to be (somewhat) associated with successful discontinuation of anti-TNF agents include shorter disease duration, less radiographic joint damage, lower disease activity before discontinuation and anti-TNF treatment duration, although none of these are consistently and strongly correlated.[39-44] Interestingly, in both the DRESS study and tocilizumab dose reduction study we could not find clinical predictive factors for successful dose reduction or discontinuation.

Because clinical prediction seems not helpful, some - although not much research - has focussed on other predictors, especially imaging and biomarkers. For ultrasound for example, the predictive value for successful tapering has been investigated, however different and conflicting results were found.[41, 42, 45] MRI and PET scanning have not been examined thus far, but might be seen as promising. However, all imaging techniques measure the domain of disease activity and it can be questioned whether the level of disease activity is predictive for successful

tapering, as clinically this seems not to be the case. In conclusion, more research is needed to determine the value of these techniques. Biomarkers have also been investigated in predicting response to biological therapy in RA,[46] and could have some value in predicting successful dose reduction or discontinuation, although this has not been tested so far. Again however, like with imaging techniques, the question what domain the biomarker should cover should be answered first before candidate biomarkers are selected. In the context of predicting successful tapering, we want to be informed not about disease activity per se, but about the relation between treatment and disease activity in this particular patient, and it seems hard to imagine any biomarker to fit this profile.

Another fruitful approach might be, - and is often mentioned in literature - measurement of anti-TNF agent serum (anti)drug antibodies.[47-49] The underlying rationale is that 1) a patient with no/low serum levels and/or anti-drug antibodies should be able to successfully stop the TNFi as effect is not to be expected and 2) a patient with high serum levels should be able to reduce the dose as preservation of the same clinical effect is to be expected with a lower dose. In a sense, by the way, this is the reverse approach as mentioned before, as now not the *disease activity* is measured, but a proxy for the exposition to the biological *treatment*. The same problem also arises again, that measuring the treatment does not inform us about the relationship between treatment and disease activity. In **chapter 7**, we investigated the predictive value of random timed adalimumab and etanercept serum (anti) drug levels for successful dose reduction or discontinuation in patients included in the intervention arm of the DRESS study. In 118 patients serum (anti)drug levels of adalimumab or etanercept were measured before start of dose reduction. Mean drug levels were not different per subgroup (successful discontinuation, successful dose reduction, or no dose reduction possible at 18 months), and receiver operator analyses showed no predictive value of drug levels for outcome, except for an unexpected inverse association between lower etanercept levels and higher chance for successful dose reduction (Area Under the Curve (AUC) 0.36, 95% CI 0.23-0.49). Sub-analyses for timing of sampling showed the opposite, with high adalimumab trough levels predicting successful dose reduction (AUC 0.86, 95% CI 0.58-1.00). Finally, anti-drug antibodies were rare (adalimumab 10%, etanercept 0%) and not predictive for successful discontinuation.

How to interpret these findings? Firstly, we were unable to confirm that random timed adalimumab and etanercept serum levels and antidrug antibodies have predictive value for successful dose reduction or discontinuation in RA patients with low disease activity. Also, anti-drug antibodies have no predictive value in this context, as they are too infrequent and seem not related with higher chance of successful stopping. We feel that high adalimumab trough levels might be predictive for successful dose reduction. However, this should be replicated first, as this could well be a false positive finding. The reason for this cautious conclusion

being that A/ number of patients were very low, resulting in low precision, B/ for etanercept to our surprise the reverse relation was found and C/the cut off value was somewhat different than suggested before. Our findings seem to replicate the disappointing findings of other prospective prediction cohort studies, including lack of predictive value for response to infliximab in RA,[50] no predictive value for successful tapering infliximab in RA,[51] and no association between serum golimumab levels for effect of dose increase in ankylosing spondylitis.[52] However, a number of cross-sectional or non-interventional longitudinal studies did find positive correlations between anti-TNF serum levels and response on a group level.[47] This difference is probably real, and might be explained by the fact that when measuring serum drug levels in responding patients, the relation between serum levels and response is absent because of two effects. Firstly, although on a group level a dose response curve has been demonstrated, the same curves show high inter-individual variation in effective serum drug levels.[53] This means that a serum drug level of for example 5 mg/l can be too low for one patient, but supra-therapeutical for another, and recently data supporting this view have been published.[54] Secondly, patients that are doing well even without anti-TNF agent cannot be identified by their serum drug levels, as their low disease activity is of course unrelated to the drug level.

In conclusion, no predictors are available yet that can help us to improve our treating to target approach. This furthermore implicates that, when a rheumatology practice strives to adopt a dose tapering strategy, utmost care should be taken to implement high quality care to prevent prolonged flaring and minimise the burden for the patients.

## CLINICAL IMPLICATIONS AND FUTURE RESEARCH

### Clinical implications

The results of this thesis have a number of implications for the more individualised use of the investigated bDMARDs in RA patients in clinical practice.

1. A rituximab strategy using the first interval as a reference for future retreatment is not useful as the intra-individual response duration to rituximab is too high.
2. Dose reduction of tocilizumab from 8mg/kg to 4mg/kg every 4 weeks seems to be possible in a relevant number of patients with low disease activity without loss of disease control.
3. A disease activity guided dose reduction strategy of adalimumab and etanercept is non-inferior to continuing these treatments unaltered and leads to a large reduction in costs without loss of function and radiologic deterioration.
4. Random timed etanercept and adalimumab (anti)drug level measurement is thus far not an evidence based diagnostic aid when deciding on dose reduction or discontinuation or not.

## Future research

This thesis also raises a number of topics that could be addressed in future research. These include:

- Comparison of the effectiveness of different treatment strategies of rituximab, for example a fixed treatment strategy versus treatment-to-target strategy.
- Identification of predictors for individual response duration to rituximab.
- Testing disease activity guided dose reduction and discontinuation strategies in other biologic DMARDs, including tocilizumab and abatacept and other rheumatic diseases including ankylosing spondylitis and psoriatic arthritis.
- Exploration of patient and physician perspective on dose reduction and discontinuation and ways to optimise this.
- Assessment of long term (un)intended effects of dose reduction and discontinuation of bDMARDs, including radiographic outcomes and adverse effects.
- Studying whether bDMARD or csDMARDs should be prioritised for tapering in patients with RA using combination therapy and doing well.
- Assessment of predictive value of adalimumab trough levels for successful dose reduction.



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# nine

NEDERLANDSE SAMENVATTING

## Hoofdstuk 1: inleiding

Reumatoïde artritis (RA) is een chronische ontstekingsziekte, waarvan de oorzaak niet bekend is. De meeste patiënten hebben een symmetrische gewrichtsontsteking, meestal van de handen en voeten. Dit leidt tot pijn, stijfheid en zwelling met als gevolg verlies van functionaliteit, kwaliteit van leven en bij een groot deel van de patiënten ook schade aan de gewrichten.

De laatste jaren zijn de behandelingsmogelijkheden van RA enorm toegenomen. Door een beter begrip van het ziekteproces konden de zogenaamde biologische reumaremmers (biologic Disease Modifying Anti-Rheumatic Drugs, bDMARDs) worden ontwikkeld. Deze biologische reumaremmers grijpen aan op afweercellen of ontstekingseiwitten. De meest gebruikte biologische reumaremmers voor RA zijn de TNF-blokkers, zoals adalimumab en etanercept. Andere biologische reumaremmers die worden gebruikt bij de behandeling van RA zijn onder andere rituximab en tocilizumab.

De biologische reumaremmers hebben echter een aantal nadelen. De belangrijkste zijn bijwerkingen, zoals een iets verhoogd risico op (ernstige) infecties en huidkanker. Daarnaast zijn deze middelen erg duur vergeleken met de originele reumaremmers zoals Methotrexaat, namelijk rond de 15.000 euro per patiënt per jaar. Het is daarom belangrijk individuele patiënten te behandelen met de voor hen optimale dosering van biologische reumaremmers. Dit houdt in: het geven van de laagst mogelijke dosering of een lange tijd tussen injecties, en eventueel stoppen als dit mogelijk is. Op deze manier wordt het maximale effect bereikt met zo min mogelijk bijwerkingen en kosten. In dit proefschrift is gekeken naar deze meest optimale dosering in individuele RA patiënten die rituximab, tocilizumab of TNF-blokkers gebruiken.

## Hoofdstuk 2: rituximab interval

De behandeling met rituximab is anders dan de overige biologische reumaremmers. Het wordt gegeven als infuus, wat na 2 weken wordt herhaald. Deze infusen werken lang, gemiddeld 6-12 maanden, maar dit wisselt sterk per patiënt. Het optimale behandelschema voor rituximab bij patiënten met RA is nog niet duidelijk. In de praktijk worden verschillende strategieën gebruikt. De belangrijkste zijn: 1) een vast schema, waarbij patiënten bijvoorbeeld om de 6 maanden behandeld worden met rituximab en 2) een "wanneer nodig" schema, waarbij patiënten pas weer worden herbehandeld met rituximab als de RA opvlamt. Beide strategieën hebben nadelen: bij de behandeling elke 6 maanden krijgen patiënten die het minder vaak nodig zouden hebben wat te vaak het infuus, en bij de "wanneer nodig" aanpak zal de RA telkens weer opvlammen. Een alternatieve strategie zou kunnen zijn om de eerste keer te herbehandelen volgens het "wanneer nodig" schema en de keren daarna volgens een vast schema gebaseerd op de duur van respons op het eerst infuus. Dit werkt echter alleen als binnen één individuele patiënt het infuus steeds even

lang effect heeft. In dit hoofdstuk hebben we gekeken of de duur van respons op rituximab na de eerste kuur, voor een individuele patiënt ongeveer even lang is als na de tweede, in patiënten die werden behandeld volgens het "wanneer nodig" schema. We vonden grote verschillen tussen de responsduur na het eerste en het tweede infuus binnen één patiënt en concludeerden dan ook dat responsduur na het eerste infuus niet gebruikt kan worden voor het plannen van herbehandelen. Een vast doseringsschema is wellicht de beste strategie derhalve.

### Hoofdstuk 3: tocilizumab afbouwen

Tocilizumab is een biologische reumaremmer die in een dosering van 8 mg per kg lichaamsgewicht wordt gegeven elke vier weken. Een lagere dosering van 4 mg per kg is echter ook effectief in een groot deel van de patiënten. De geregistreerde dosering voor tocilizumab bij patiënten met RA in Europa is 8 mg per kg elke 4 weken, maar in de Verenigde Staten 4 mg per kg, eventueel op te hogen naar 8 mg per kg. Het is niet bekend of en in hoeveel patiënten het mogelijk is om de dosering van 8 mg per kg te verlagen naar 4 mg per kg als de RA rustig is. In dit hoofdstuk werd bij 22 patiënten die 8 mg per kg tocilizumab gebruikten en hiermee een rustige ziekte hadden, gekeken of de dosering kon worden afgebouwd naar 4 mg per kg. We zagen dat 6 maanden na het verlagen van de dosering 55% van de patiënten nog steeds op 4 mg per kg zat. Van alle patiënten die helaas wel een opvlamming van de ziekte kregen na het verlagen van de dosering, behaalde iedereen weer lage ziekteactiviteit na ophogen van de dosering. We concludeerden daarom dat afbouwen van de dosering tocilizumab van 8mg per kg naar 4 mg per kg haalbaar is bij een groot deel van de patiënten met RA en lage ziekteactiviteit.

### Hoofdstuk 4: systematische review afbouwen/stoppen tnf-blokkers

De meest gebruikte biologische reumaremmers in RA betreffen TNF blokkers. Naar het optimaal doseren van deze middelen zijn een aantal onderzoeken gedaan. Om de eerdere onderzoeken op het gebied van afbouwen en stoppen van TNF-blokkers bij patiënten met RA en een lage ziekteactiviteit samen te vatten en te onderzoeken welke data nog missen, hebben we in hoofdstuk 4 een systematische literatuurstudie uitgevoerd naar gerandomiseerde en gecontroleerde klinische trials.

Zeven studies met in totaal 1203 patiënten werden gevonden. Hiervan waren maar 2 studies als volledig artikel gepubliceerd. We identificeerden 3 verschillende strategieën die gevolgd werden: 1) niet ziekteactiviteit gestuurd afbouwen, 2) niet ziekteactiviteit gestuurd stoppen en 3) ziekteactiviteit geleid afbouwen tot stop. Op basis van deze studies concludeerden we dat niet ziekteactiviteit gestuurd verlagen van etanercept van 50 mg naar 25 mg per week even effectief lijkt als doorgaan met etanercept 50 mg per week als gekeken wordt naar ziekteactiviteit en functioneren. Er is echter wel mogelijk een klein, niet klinisch relevant, verschil in toename van gewrichtsschade op röntgenfoto's. Niet ziekteactiviteit gestuurd stoppen van

adalimumab of etanercept lijkt minder goed dan doorgaan met adalimumab 40 mg per 2 weken of etanercept 50 mg per week, met betrekking tot ziekteactiviteit, functioneren en toename van radiologische gewrichtsschade. Ziekteactiviteit geleid afbouwen van adalimumab of etanercept tot stop tenslotte, lijkt iets minder goed dan doorgaan met deze middelen wat betreft ziekteactiviteit, zonder dat er een verschil lijkt te zijn in functioneren. Echter, de enige studie die deze laatste strategie uitvoerde haalde niet het beoogde aantal patiënten voor de studie en was niet optimaal uitgevoerd.

Een paar zaken in ontwerp en uitvoering van de onderzoeken vielen op. Opvallend was het ontbreken van kosteneffectiviteit analyses en analyses naar bijwerkingen in deze studies, terwijl dit juist de redenen zijn waarom afbouwen van TNF-blokkers wordt gesuggereerd. Ook werd er gefixeerd afgebouwd of gestopt, zonder de mogelijkheid om op te hogen of te herstarten bij opvlamming van de ziekte. Dit is niet een strategie die in de dagelijkse praktijk gebruikt zal worden. Tenslotte werd zelden de correcte onderzoeksaanpak gekozen, namelijk het zogenaamde non- inferioriteit design. Overigens waren de meeste studies gesponsord door de farmaceutische industrie. Deze aspecten tezamen leiden tot onderschatting van de voordelen en overschatting van de nadelen van op proef afbouwen en stoppen van TNF blokkers.





## Hoofdstuk 5: design dress studie

Mede gebaseerd op basis van de resultaten uit de systematische literatuurstudie in hoofdstuk 4 hebben we een gerandomiseerde, niet geblindeerde, pragmatische non-inferioriteit studie naar ziekteactiviteit geleid afbouwen van adalimumab of etanercept bij patiënten met RA en lage ziekteactiviteit opgezet (de Dose REduction Strategies for Subcutaneous TNF inhibitors (DRESS) studie). Dit hoofdstuk beschrijft de keuzes die we hebben gemaakt tijdens het ontwerpen van de studie. Onder andere het afbouwproces, de keuze voor de controlegroep, definiëren van opvlamming van de ziekte (flare), de implementatie in de klinische praktijk en de non-inferioriteit marge.

## Hoofdstuk 6: de dress studie

Dit hoofdstuk beschrijft de belangrijkste resultaten van de DRESS studie. In deze studie hebben we 180 patiënten met RA, die adalimumab of etanercept gebruikten en hiermee een rustige ziekte hadden, gerandomiseerd in een afbouwgroep of een controlegroep in een verhouding van 2:1. Afbouwen bestond uit stapsgewijs iedere 3 maanden de tijd tussen de injectie vergroten tot opvlamming van ziekteactiviteit of tot stop. Als er sprake was van een opvlamming werd de medicatie weer opgehoogd of herstart. De belangrijkste uitkomstmaat van de studie was het verschil in percentage van langdurige opvlamming van de RA (>3 maanden) gedurende de studie (18 maanden) tussen de twee groepen. Hierbij vonden we afbouwen non-inferieur (even

goed) aan doorgaan als het verschil en de onzekerheid hieromheen onder de 20% zou liggen (non-inferioriteit marge). We vonden in deze studie een verschil van 2% tussen de twee groepen en konden concluderen dat afbouwen non-inferieur is aan doorgaan met TNF blokkers met betrekking tot langdurige opvlamming van de RA. Kortdurende opvlamming (<3 maanden) kwam wel vaker voor in de groep die adalimumab of etanercept afbouwden. Op 18 maanden was in de afbouwgroep 20% succesvol (met behoud van lage ziekteactiviteit) gestopt met adalimumab of etanercept, bij 43% van de patiënten was het interval succesvol verlengd. Bij 37% van de patiënten kon de dosering niet worden verlaagd. Functioneren, kwaliteit van leven en klinisch relevante toename in gewrichtsschade op röntgen foto's waren niet verschillend tussen de groepen. Gedurende de 18 maanden waren de kosten in de afbouwgroep per patiënt ruim 9.000 euro lager vergeleken met de controlegroep.

Al met al was het op proef afbouwen en stoppen van de TNF blokker even goede zorg als doorgaan met het middel, en werden veel kosten bespaard.

### Hoofdstuk 7: voorspellen succesvol afbouwen/stoppen

Hoewel we in de DRESS studie geen verschil vonden tussen de afbouwgroep en de controlegroep wat betreft langdurige opvlamming van de ziekte, functioneren, kwaliteit van leven en toename in gewrichtsschade op röntgenfoto's vonden we wel duidelijk meer kortdurende opvlammingen in de controlegroep. Het kunnen voorspellen van succesvol afbouwen of stoppen zou deze kortdurende opvlammingen kunnen voorkomen, door niet af te bouwen bij patiënten waar dit volgens de voorspellende factoren niet gaat lukken. Daarnaast hoeven patiënten waarvan vooraf bekend is dat ze direct zouden kunnen stoppen niet het hele afbouwproces te doorlopen, wat tijd en kosten scheelt.

Tot nu toe zijn er echter geen duidelijke voorspellende factoren gevonden voor succesvol afbouwen of stoppen van TNF-blokkers. In de literatuur worden medicatiespiegels in het bloed en antistoffen gericht tegen de medicatie als mogelijke voorspellers van succesvol afbouwen en stoppen genoemd. Het idee is dat patiënten met hogere medicatiespiegels in het bloed een grotere kans hebben dat ze kunnen afbouwen, en dat mensen die geen medicatie in het bloed hebben (eventueel door antistofvorming tegen het medicijn) kunnen stoppen.

In dit hoofdstuk onderzochten we de mogelijkheid om het succesvol afbouwen of stoppen van adalimumab of etanercept te voorspellen met behulp van medicatiespiegels van en antistoffen tegen deze middelen. In 118 patiënten uit de afbouwgroep van de DRESS studie werd serum afgenomen vóór start van afbouwen. We vonden dat de gemiddelde medicatiespiegel niet verschilde tussen de groepen (succesvol afgebouwd, succesvol gestopt of niet kunnen afbouwen bij 18 maanden). Medicatiespiegels konden niet voorspellen wie er succesvol kon afbouwen of stoppen, hoewel er wat verrassend wel een relatie werd gevonden tussen *lage* etanercept spiegel en succesvol afbouwen. Dit is namelijk tegenstrijdig aan de

hypothese dat hoge spiegels succesvol kunnen afbouwen voorspellen. Subanalyses van verschillende momenten waarop de medicatiespiegel meting was gedaan liet geen andere resultaten zien behalve een mogelijke relatie tussen hoge adalimumab spiegels afgenomen vlak voor de volgende injectie (dalspiegel) en succesvol afbouwen. Antistoffen tegen adalimumab waren zeldzaam en niet voorspellend voor succesvol kunnen stoppen. Er werden geen etanercept antistoffen gevonden.

We concludeerden dat we niet hebben aangetoond dat medicatiespiegels en antistoffen kunnen voorspellen welke patiënt succesvol kan afbouwen of stoppen. Mogelijk zijn hoge adalimumab dalspiegels wel voorspellend voor succesvol afbouwen, dit zal echter in een grotere studie moeten worden onderzocht, omdat de aantallen in deze studie te laag zijn voor een duidelijke conclusie en we bij etanercept de omgekeerde relatie vonden.

### Hoofdstuk 8: discussie

In dit hoofdstuk worden de resultaten van de onderzoeken besproken en bediscussieerd. Ook worden de resultaten vergeleken met andere vergelijkbare onderzoeken. Aan het einde van het hoofdstuk worden een aantal implicaties voor de klinische praktijk aangegeven en suggesties voor verder onderzoek.

De belangrijkste conclusies uit dit proefschrift zijn:

- Een behandelstrategie met rituximab, waarbij de responsduur van het eerste interval gebruikt wordt voor het plannen van herbehandeling is niet zinvol, omdat de variatie in responsduur op (her) behandelingen met rituximab binnen één RA patiënt te groot is. (Hoofdstuk 2)
- Afbouwen van tocilizumab van 8mg/kg naar 4 mg/kg iedere 4 weken bij patiënten met RA en lage ziekteactiviteit lijkt mogelijk bij de meerderheid van de patiënten met behoud van lage ziekteactiviteit. (Hoofdstuk 3)
- Een ziekteactiviteit gestuurde afbouwstrategie van adalimumab of etanercept is non-inferieur aan doorgaan met adalimumab of etanercept en leidt tot een flinke kostenbesparing zonder verlies van functioneren of relevante verslechtering van gewrichtsschade op röntgenfoto's. (Hoofdstuk 6)
- Het is op dit moment onvoldoende bewezen dat het meten van adalimumab en etanercept medicatiespiegels of antistoffen zinvol is om succesvol afbouwen of stoppen van adalimumab en etanercept te kunnen voorspellen. (Hoofdstuk 7)

LIST OF PUBLICATIONS

## Articles

van Herwaarden N, den Broeder AA, Jacobs W, van der Maas A, Bijlsma JW, van Vollenhoven RF, van den Bemt BJF. Down-titration and discontinuation strategies of tumor necrosis factor-blocking agents for rheumatoid arthritis in patients with low disease activity. Cochrane Database Syst Rev. 2014 Sep 29;9.

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## Conference abstracts

Can response duration after the first rituximab treatment be used in timing of rituximab retreatment? Najaarsdagen Reumatologie Papendal 2012 and ACR 2012 Washington (poster presentation)

Dose reduction of tocilizumab in rheumatoid arthritis patients with low disease activity is feasible. Najaarsdagen Reumatologie Papendal 2012 (oral presentation) and ACR 2013 San Diego (poster presentation)

Randomised Controlled Non-Inferiority Study of Dose Reduction and Withdrawal of Adalimumab and Etanercept in Rheumatoid Arthritis. Najaarsdagen Reumatologie Papendal 2014 and ACR 2014 Boston (oral presentation) *Beste presentatie najaarsdagen 2014*

Prediction of Successful Dose Reduction or Discontinuation of Adalimumab or Etanercept Using Serum Drug Levels and Antidrug Antibody Measurement. Najaarsdagen Reumatologie Papendal 2014 and ACR 2014 Boston (poster presentation) *Best abstract nvza/nvpf ziekenhuisfarmaciedagen 2014*

CURRICULUM VITAE

Noortje van Herwaarden werd op 10 april 1985 geboren te Nijmegen. In 2003 behaalde ze haar VWO diploma op het Lindenholt College in Nijmegen waarna ze in datzelfde jaar aan de Radboud Universiteit Nijmegen begonnen is met de studie Geneeskunde. Tijdens deze opleiding deed ze in het kader van de wetenschappelijke stage onderzoek naar sekseverschillen bij jicht in de huisartsenpraktijk, onder begeleiding van van Prof. dr. A.L.M. Lagro-Janssen. Begin 2010 behaalde ze haar artsexamen (cum laude).

Op 1 januari 2010 begon ze als arts-assistent niet in opleiding op de klinische afdeling reumatologie in de Sint Maartenskliniek in Nijmegen onder supervisie van dr. Maurice Jeurissen, dr. Henk Martens en dr. Marcel Franssen. Toen de mogelijkheid ontstond voor het doen van wetenschappelijk onderzoek, startte ze in april 2011 met haar promotietraject, begeleid door dr. Alfons den Broeder, dr. Aatke van der Maas, dr. Bart van den Bemt, Prof. dr. Hans Bijlsma en Prof. dr. Ronald van Vollenhoven, met dit proefschrift als resultaat.

Vanaf 1 oktober 2014 is ze begonnen met haar vooropleiding interne geneeskunde in het Canisius Wilhelmina Ziekenhuis te Nijmegen (opleider dr. A.S.M. Dofferhof) in het kader van de opleiding tot reumatoloog (opleider dr. A.E. van Ede).

# DANKWOORD

De tijd tijdens mijn promotietraject is voorbij gevlogen. Ik had nooit gedacht dat onderzoek doen iets voor mij zou zijn, laat staan een heel promotietraject. Dat ik nu toch ondertussen dit laatste hoofdstuk van mijn proefschrift aan het schrijven ben, heb ik dan ook aan heel veel mensen te danken.

Het begon allemaal toen ik in de Sint Maartenskliniek op G1 kwam werken. Wat een heerlijke plek om als jonge dokter aan de slag te gaan! Ik heb het enorm naar mijn zin gehad en erg veel geleerd. In het bijzonder wil ik Maurice Jeurissen, Henk Martens en Marcel Franssen bedanken voor de fijne begeleiding en het veilige leerklimaat. Door jullie wist ik zeker dat ik reumatoloog wilde worden. Tijdens mijn tijd op G1 kreeg ik in de rustige momenten ook de mogelijkheid om met onderzoek aan de slag te gaan. Dat dit uiteindelijk uitgroeide tot promotieonderzoek was met name mogelijk door de fijne begeleiding.

Mijn dank gaat dan ook uit naar dr. A. van der Maas mijn co-promotor. Beste Aatke, ook al was je niet vanaf het begin als co-promotor betrokken, je hebt me vanaf het begin begeleid en bent steeds een voorbeeld voor mij geweest. Je kan op een erg fijne manier kritisch zijn, zonder het gevoel te geven dat iets prut is. En ook al vind je jezelf misschien geen gestructureerd persoon, qua begeleiding gaf je me die structuur zeker wel. Daarnaast hebben we ook de nodige lol gehad, zoals tijdens mijn eerste congreservaring in Londen.

Dr. B.J.F. van de Bemt, mijn tweede co-promotor. Beste Bart, we hebben met name veel samengewerkt aan de systematische review. Het was erg fijn dat ik kon terugvallen op je eerdere ervaring met deze vorm van onderzoek. Als mijn mede co-promotor moest ik aanvankelijk best wennen aan je manier van werken. Ik werd soms gek van jouw zin: "daar moeten we het nog eens over hebben" (als ik iets de volgende dag wilde submitten). Voor jou was ik soms denk ik wat kort door de bocht. Maar ik ben onze discussies en je enthousiasme erg gaan waarderen.

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Het reumacentrum van de Sint Maartenskliniek was wat mij betreft een ideale plek om onderzoek te doen. Graag wil ik dan ook dr. F.H.J. van den Hoogen, directeur reumacentrum, bedanken. Beste Frank, bedankt voor je vertrouwen en de mogelijkheid om als jonge arts-onderzoeker te kunnen werken. De combinatie van ruim de tijd voor onderzoek, maar ook voor (poli)klinische werkzaamheden maakte het voor mij extra leuk. Ook de reumastaf wil ik bedanken voor de leuke, leerzame tijd en fijne begeleiding.

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