Disease activity guided dose reduction and withdrawal of adalimumab or etanercept compared with usual care in rheumatoid arthritis: open label, randomised controlled, non-inferiority trial

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ABSTRACT

OBJECTIVE
To evaluate whether a disease activity guided strategy of dose reduction of two tumour necrosis factor (TNF) inhibitors, adalimumab or etanercept, is non-inferior in maintaining disease control in patients with rheumatoid arthritis compared with usual care.

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

SETTING
Two rheumatology outpatient clinics in the Netherlands, from December 2011 to May 2014.

PARTICIPANTS
180 patients with rheumatoid arthritis and low disease activity using adalimumab or etanercept; 121 allocated to the dose reduction strategy, 59 to usual care.

INTERVENTIONS
Disease activity guided dose reduction (advice to stepwise increase the injection interval every three months, until flare of disease activity or discontinuation) or usual care (no dose reduction advice). Flare was defined as increase in DAS28-CRP (a composite score measuring disease activity) greater than 1.2, or increase greater than 0.6 and current score of at least 3.2. In the case of flare, TNF inhibitor use was restarted or escalated.

MAIN OUTCOME MEASURES
Difference in proportions of patients with major flare (DAS28-CRP based flare longer than three months) between the two groups at 18 months, compared against a non-inferiority margin of 20%. Secondary outcomes included TNF inhibitor use at study end, functioning, quality of life, radiographic progression, and adverse events.

RESULTS
Dose reduction of adalimumab or etanercept was non-inferior to usual care (proportion of patients with major flare at 18 months, 12% *v* 10%; difference 2%, 95% confidence interval −12% to 12%). In the dose reduction group, TNF inhibitor use could successfully be stopped in 20% (95% confidence interval 13% to 28%), the injection interval successfully increased in 43% (34% to 53%), but no dose reduction was possible in 37% (28% to 46%). Functional status, quality of life, relevant radiographic progression, and adverse events did not differ between the groups, although short lived flares (73% *v* 27%) and minimal radiographic progression (32% *v* 15%) were more frequent in dose reduction than usual care.

CONCLUSIONS
A disease activity guided, dose reduction strategy of adalimumab or etanercept to treat rheumatoid arthritis is non-inferior to usual care with regard to major flaring, while resulting in the successful dose reduction or stopping in two thirds of patients.

TRIAL REGISTRATION
Dutch trial register (www.trialregister.nl), NTR 3216.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Tumour necrosis factor (TNF) inhibitors adalimumab and etanercept are effective in rheumatoid arthritis, but are associated with some side effects and high costs

Dose reduction or stopping (tapering) of TNF inhibitor use is feasible in many patients, although it cannot be predicted which patient can be tapered

In general, disease activity guided strategies to treat rheumatoid arthritis have resulted in optimal clinical outcomes

WHAT THIS STUDY ADDS

A treat-to-target based TNF inhibitor tapering strategy, consisting of increases in intervals between injections until the patient flares or the drug can be stopped, is non-inferior to usual care (a treat-to-target strategy without dose reduction), with regard to occurrence of major flare

Although short lived flares and minimal radiographic progression occurred more frequently with dose reduction, it showed similar outcomes to usual care after 18 months for functioning, quality of life, adverse events, and clinically relevant radiological joint damage

Dose reduction or stopping was successful in two third of patients

Introduction

Tumour necrosis factor (TNF) inhibitors are effective in the treatment of rheumatoid arthritis, improving clinical, functional, and radiographic outcomes.[1 2] Different TNF inhibitors are widely used, with adalimumab (40 mg every two weeks) and etanercept (50 mg every week or 25 mg twice a week) being the most used,[3] and among the highest selling drugs worldwide.[4]

Treatment with TNF inhibitors is not without its drawbacks: they are associated with (dose dependent) adverse effects, including increased risk of infections and skin cancer.[5–7] Furthermore, such treatment is costly, at about €14 000 per year per patient.[8] Optimising the use of TNF inhibitors is therefore warranted. Previous research has suggested that dose reduction or discontinuation of these inhibitors

without the deterioration of disease activity is possible in a relevant proportion of patients, although successful dose reduction cannot be predicted in individual patients.[9–11] Therefore, a promising strategy might be to slowly taper the use of TNF inhibitors 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 is not known whether a disease activity guided strategy—that is, a strategy of monitoring the disease activity and restarting the use of TNF inhibitors or increasing the dose again if the disease worsens after dose reduction—results in care that is equally as good as just continuing treatment unaltered. Flares in disease activity that occur after dose reduction might be (1) short lived and easily treated or (2) prolonged, compromising quality of life or resulting in radiological damage.[12] Also, although titration to the lowest dose might save treatment costs, it could also lead to an 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 reported cost effectiveness analyses.[9–11]

Therefore, this study aimed to demonstrate non-inferiority with regard to efficacy and safety between a disease activity guided strategy of dose reduction in TNF inhibitors and usual care (that is, continuing TNF inhibitor use), in daily clinical practice for patients with rheumatoid arthritis. We also planned to assess the possible benefits of decreasing TNF inhibitor use. 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 trial, stratified by the TNF inhibitor used. The rationale and design have been described extensively elsewhere,[13] and are summarised here. We enrolled consenting patients with rheumatoid arthritis (based on 2010 or 1987 American College of Rheumatology criteria, or clinical diagnosis by the treating rheumatologist) using adalimumab or etanercept at any stable dose and interval for at least six months, with stable low disease activity at two subsequent visits. Low disease activity was determined by the rheumatologist and measured using the DAS28-CRP score. This validated composite score measures disease activity (range 0.9–9) and includes 28 swollen and tender joint counts, patients' judgment of global disease activity, and C reactive protein level. The study was performed at the Sint Maartenskliniek in Nijmegen and Woerden, the Netherlands, from December 2011 to May 2014, and was approved by the local ethics committee (Commissie Mensgebonden Onderzoek region Arnhem-Nijmegen, NL37704.091.11). The study was registered with the Dutch trial register (www.trialregister.nl, NTR 3216) one week after study inclusion started, owing to temporary incapacitation of the research doctor.

Randomisation and masking

Allocation was stratified by TNF inhibitor using block randomisation in random sized blocks (block size 3–12), and in a ratio of dose reduction versus usual care of 2:1. This ratio was chosen to include more determinants in a prediction model for successful dose reduction or discontinuation. A research physician allocated patients using a randomisation list generated by computer. 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 every three months and patients were encouraged to contact the outpatient clinic if they experienced more symptoms. DAS28-CRP scores were assessed by nurses and provided to the treating rheumatologists. Nurses had been trained and their joint assessment skills were calibrated repeatedly to optimise inter-rater reliability. Treatment was changed in case of a disease activity flare. We defined a flare using a validated criterion: an increase in DAS28-CRP score of more than 1.2, or a score increase of more than 0.6 compared with baseline score, where the current score was at least 3.2.[14] If a flare occurred, a new visit after four weeks was advised. Intramuscular and intra-articular glucocorticoid 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 for that particular patient to the treating rheumatologist. The dose reduction strategy consisted of stepwise increases of the time interval between injections every three months. For adalimumab, the steps were (1) 40 mg every 21 days, (2) 40 mg every 28 days, and (3) stop. For etanercept, the steps were (1) 50 mg every 10 days, (2) 50 mg every 14 days, and (3) stop. In the instance of a flare, the last effective interval was reinstated; if the flare persisted, TNF inhibitor use was increased up to the shortest registered interval, and treatment was switched thereafter in case of persisting flare. Only one attempt at dose reduction was done, and in the case of flare and treatment escalation, no further attempts at reduction were made.

Outcomes

Primary outcome was the difference in cumulative incidence of major flare between the dose reduction and usual care groups at 18 month follow-up.[13] Major flare was defined as a DAS28-CRP based flare with a duration of longer than three months, independent of treatment changes.[13] We initially planned the primary outcome to be the cumulative incidence of all flares (now a secondary outcome). The reason for the switch of primary

outcome was the developing insight that transient flaring is an inherent trait of all dose tapering strategies based on disease activity. However, when a flare can be treated easily, and does not lead to loss of function, quality of life, persistent increase of disease activity, increase of other treatment, clinically relevant radiographic damage, and prolonged major flare, in our view this can be reasonably viewed as non-inferior care. The outcome change took place after study start but before outcomes were available, as has been published elsewhere.[13] Patients with major flare were reviewed further by two doctors.

Secondary outcomes included cumulative incidence of patients with short lived flare (duration >three months); change in DAS28-CRP score; change in functioning, as measured by the health assessment questionnaire-disability index (HAQ-DI; range 0–3, higher score indicating worse functioning); and quality of life, as measured by EuroQol-5D-5L (EQ5D-5L; range 0–1, higher score indicating better quality of life). These outcomes were assessed at nine and 18 months' follow-up. We recorded the proportions of patients who could successfully taper or stop treatment, as well as any change in the use of glucocorticoids or disease modifying antirheumatic drugs (DMARDs), and the occurrence of severe adverse events.

Radiographs of hands and feet (at 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 indicate more joint damage). These values included subscores for erosion (range 0–280) and joint space narrowing (range 0–168).[15] The proportion of patients with a change in SvdH score exceeding the minimal clinical important change of eight points in 18 months was compared between groups.[16 17] As a sensitivity analysis, the smallest detectable change was calculated and used as cut-off value, as well as a third cut-off value of 0.5 SvdH units.[18] We calculated quality adjusted life years based on EQ5D-5L scores to analyse quality of life differences.

We also assessed costs, cost effectiveness, and the predictive value of serum drug levels and whole body PET/CT scanning (positron emission tomography combined with computed tomography) scans. These results will be published in separate publications.

Statistical analysis

We assumed 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 (α=0.05, 1–β=0.8), a non-inferiority margin of 20%, and randomisation ratio of 2:1 dose reduction versus usual care and accounting for 5% dropout, we calculated that 180 patients would be necessary to reject the null hypothesis of inferiority.[13] No interim analyses or stopping rules were defined before study start.

The chosen non-inferiority margin is to some extent arbitrary, because no non-inferiority studies on rheumatoid arthritis have used major flare as outcome. However, in our opinion, a difference in persistent flare of over 20% between the usual care and dose reduction groups would constitute a clinically relevant non-inferiority margin. The underlying reasoning is that half of patients who start another biologic to treat a flare are expected to show a response again within three months.[1 2] Therefore, half of 20% of the patients would experience a persistent flare—that is, a more prolonged period with uncontrolled disease activity—resulting in a number needed to harm of 10. In our clinical view, this number seems to balance well with an expected chance of being able to reduce the dose or stop the drug of about 60% and 15% respectively (numbers need to treat 1.5 and 6, respectively), because many more patients are expected to benefit than be harmed using this non-inferiority margin.

Primary analyses were done per protocol by including only patients who (1) completed follow-up, (2) actually started dose reduction of TNF inhibitors in the dose reduction arm, and (3) had not stopped or reduced TNF inhibitor use at 18 months' follow-up in the usual care arm. Additional intention to treat analyses were also done. For the primary outcome, we calculated the point estimate and confidence interval of the difference in cumulative incidence of major flare between both groups, and compared the upper limit of the confidence interval with the non-inferiority margin. A *t* test compared mean values (and mean time averaged) for DAS28-CRP, HAQ-DI, and EQ5D-5L. We used the x^2 test to analyse the difference in cumulative incidence of flares, and the levels of disease activity at baseline, nine months, and 18 months. The different timepoints were tested separately, with no repeated measure analyses performed.

To identify predictors, we performed two univariate logistic regression analyses. The two main outcomes—successful dose reduction and stopping—were dependent variables, and patient, clinical, and treatment variables at baseline were independent variables. We planned multivariate analyses in case more than one variable was significantly associated with one of the outcomes.

Results

Patients

We enrolled 180 patients, 121 in the intervention group and 59 in the usual care group (fig 1). Baseline characteristics were similar between the two groups, except for higher prevalence of DMARD cotreatment in the usual care group (table 1). Almost no data were missing (2% of the planned visits, and 3–7% missing per variable); thus multiple imputation was deemed unnecessary. There were no differences in missing levels by randomisation group.

Primary outcome, disease activity, function, and quality of life outcomes

Using the primary per protocol analysis (fig 1 for numbers and reasons for excluded patients), the cumulative incidence of major DAS28-CRP flare was 14 (12%) of 119 patients in the dose reduction group and five (10%) of 50 patients in the usual care group. The upper limit of

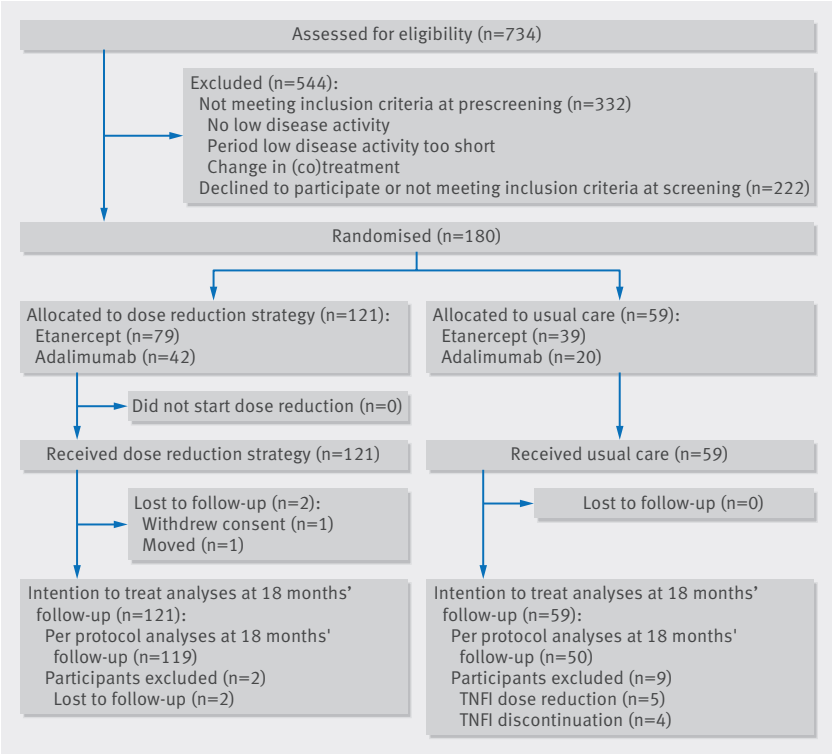

Fig 1 | **Flowchart of patient recruitment and dropout. TNFI=TNF inhibitor**

the 95% confidence interval around the difference was lower than the non-inferiority margin of 20% (2%, 95% confidence interval –12% to 12%), showing that the dose reduction strategy was non-inferior to usual care. Additional intention to treat analyses showed similar results (fig 2). We found no relevant between drug differences in the stratified analysis. Therefore, all further analyses were done according to intention to treat. The cumulative incidence of major flare at nine months was seven (6%) of 121 patients in the dose reduction group and two (3%) of 59 patients in the usual care group. In-depth clinical review of all intention to treat patients with major flare (n=21) showed three clinically distinct subgroups. The first group (n=8) showed no flare clinically, but fulfilled the formal flare criterion due to spuriously high C reactive protein, incident comorbidity, or social context (for example, psychosocial stress). The second group had a clinical flare, but treatment was suboptimal owing to, for example, adverse events or the patient's wishes (n=8). The third group also had clinical flare, but showed no improvement after optimal treatment including reinstallment of previous TNF inhibitor treatment (n=5, of whom four patients were in the dose reduction group).

The cumulative incidence of short lived flares was significantly higher in the dose reduction group than the usual care group (66/121 patients (55%, 95% confidence interval 45% to 64%) *v* 12/59 (20%, 11% to 33%) at nine months' follow-up; 88 (73%, 64% to 80%) *v* 16 (27%, 17% to 40%) at 18 months' follow-up (both P<0.001)). Figure 3 shows the number of flares per patient with at least one flare during the study. Mean DAS28-CRP scores remained low in both groups, with a temporary small but significant increase in the dose reduction group at nine months (fig 4A), also resulting in a higher mean time averaged DAS28-CRP in this group (P<0.01). Table 2 shows proportions of patients with DAS28CRP scores below 3.2, 2.6, or in remission (according to 2011 American College of Rheumatology/European League Against Rheumatism Boolean based criteria). Mean (time averaged) functioning and quality of life remained stable and did not differ significantly between the two groups (figs 4B and 4C).

Treatment and prediction modelling

In the dose reduction group (n=121), TNF inhibitor use at 18 months was successfully discontinued in 24 patients (20%, 95% confidence interval 13% to 28%) and tapered in 52 (43%, 34% to 53%). No dose reduction was possible in 45 patients (37%, 28% to 46%). For patients using adalimumab at 18 months, 26% and 36% had successfully discontinued or tapered inhibitor use, and 38% could not reduce the dose; corresponding proportions for etanercept at 18 months were 17%, 47%, and 36%.

In the usual care group (n=59), four patients (7%, 95% confidence interval 2% to 17%) discontinued TNF inhibitor use (all because of adverse effects), five (8%, 3% to 19%) tapered use because of low disease activity, and 50 patients did not reduce inhibitor dose (85%, 73% to 92%). At 18 months, four (3%) of 121 patients in the dose reduction group were switched to another drug, compared with four (7%) of 59 in the usual care group.

All characteristics in table 1 were tested for their predictive value. No clinical, laboratory, or cotreatment variables were significantly associated with successful dose reduction or discontinuation of TNF inhibitor treatment.

Intramusclar or intra-articular glucocorticoid injections were given to 43 patients (36%, 95% confidence interval 27% to 45%) in the dose reduction group (n=121) and 14 (24%, 14% to 37%) in the usual care group (n=59, P=0.26). Figure 5 shows the number of injections per patient for those receiving parenteral glucocorticoids on at least at one occasion. At 18 months, eight (7%, 3% to 13%) and six (10%, 4% to 22%) patients in the dose reduction and usual care groups, respectively, used oral glucocorticoids (P=0.56). DMARDs were reduced or discontinued more often in the usual care group than in the dose reduction group (16 (27%, 17% to 40%) *v* 12 (10%, 5% to 17%); P<0.01), while DMARD initiation or dose escalation occurred more often in the dose reduction group than in the usual care group (16 (13%, 8% to 21%) *v* 2 (3%, 6% to 13%); P<0.05). At 18 months, the percentage of patients using a DMARD remained lower in the dose reduction group (74 (61%, 52% to 70%)) than in the usual care group (41 (69%, 56% to 80%); P=0.61).

Radiological outcomes and safety

Radiographs were available for 175 patients (table 3). In neither group did any of the patients have a SvdH progression score exceeding the minimal clinical important change of eight points. The sensitivity analyses showed

Table 1 | Baseline patient characteristics

	Dose reduction (n=121)	Usual care (n=59)
General characteristics		
Age (years)*	59 (10.5)	58 (9.3)
Female sex	75 (62)	41 (69)
Current smoking	29 (24)	18 (31)
Body mass index*	27 (4.9)	26 (4.0)
Diagnosis according to 2010 or 1987 ACR criteria	114 (94)	58 (98)
Disease duration (years)†	10 (6–17)	10 (6–16)
Rheumatoid factor positive	94 (78)	49 (83)
Anti-citrullinated peptide antibodies positive	77 (64)	39 (68)
Erosive disease	99/116 (85)	54 (92)
SvdH score†	23 (6–50)	17.5 (8.5–46.5)
Employed	44 (36)	21 (36)
Travel distance (one way) to hospital (km)†	30.4 (13.5–47.2)	33.2 (17.3–50)
Disease activity		
No of swollen joints†	0 (0–0)	0 (0–1)
No of tender joints†	0 (0–1)	0 (0–0)
Erythrocyte sedimentation rate (mm/h)*	17 (14)	16 (10)
C reactive protein (mg/L)*	4 (4)	4 (4)
DAS28-CRP score*	2.2 (0.6)	2.1 (0.7)
DAS28-ESR score*	2.5 (0.7)	2.5 (0.8)
2011 ACR/EULAR Boolean based remission	31 (26)	21 (36)
Treatment		
Etanercept/adalimumab	79/42 (65/35)	39/20 (66/34)
Duration of current TNF inhibitor treatment (years)*	3.5 (2.5)	3.6 (2.3)
Previous dose reduction attempt with current TNFi	21 (17)	11 (19)
Previous DMARD treatment†	2 (1–3)	2 (1–3)
Previous conventional synthetic DMARD combination treatment‡	30/100 (30)	22/49 (45)
Previous TNF inhibitor treatment†	0 (0–1)	0 (0–1)
Concomitant treatment		
DMARD	73 (60)	47 (80)
Methotrexate	58 (48)	41 (69)
Methotrexate dose (mg)*	15.8 (5.7)	16.1 (5.5)
Glucocorticoids	6 (5)	3 (5)
Non-steroidal anti inflammatory drugs	65 (54)	35 (59)

Data are number (%) of patients unless stated otherwise. ACR/EULAR=American College of Rheumatology/European League Against Rheumatism.
*Mean (standard deviation).
†Median (interquartile range).
‡In the dose reduction and usual care groups, 21 and 10 patients had missing values, respectively.

no difference when using the smallest detectable change (4.1 points) as a cut-off value. More patients in the dose reduction arm exceeded the 0.5 units progression than in the usual care arm (fig 6). The difference in mean progression between groups was small but significant and was mainly due to difference in joint space narrowing, because progression in erosion scores was similar.

The occurrence of adverse events was similar between the groups (table 4). The, non-significant, higher incidence of overall serious adverse events was caused by more elective surgeries (mostly orthopaedic). Frequency of serious infections, cardiovascular events, and malignancies was similar between groups.

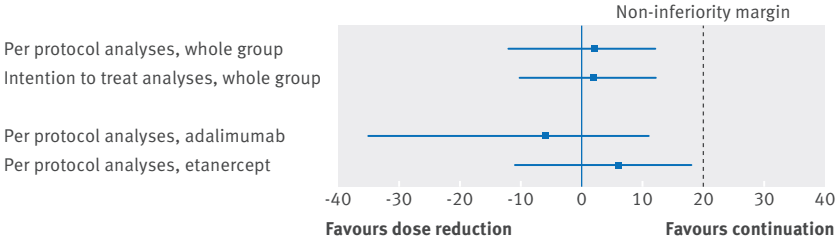

Fig 2 | Primary outcome analyses

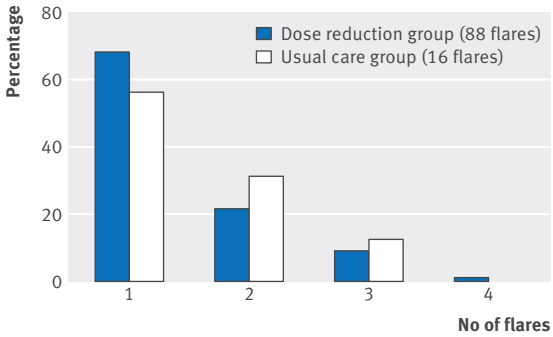

Fig 3 | Numbers of flares per patient during the study

Discussion

To our knowledge, this is the first study to show that a disease activity guided dose reduction strategy of adalimumab or etanercept in patients with rheumatoid

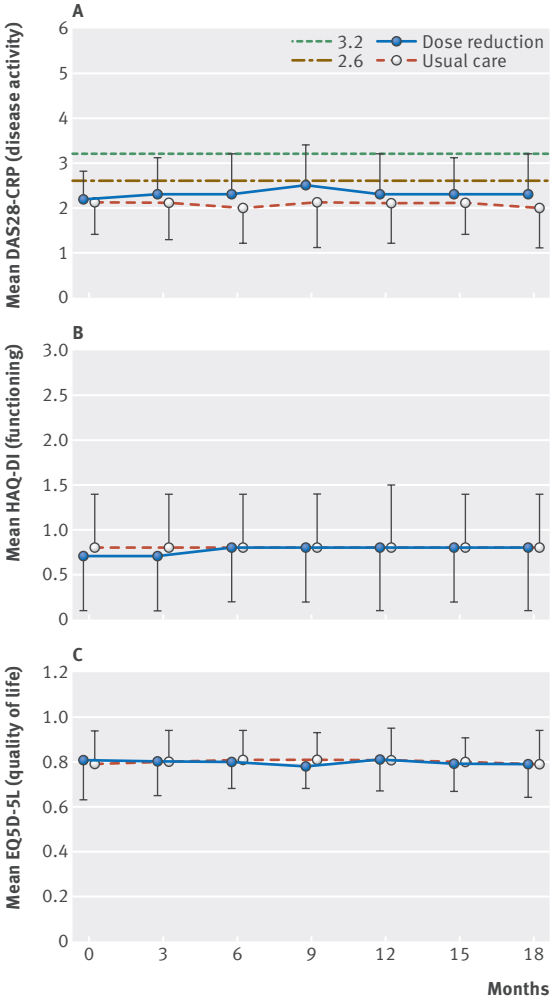

Fig 4 | Mean scores for (A) disease activity, (B) functioning, and (C) quality of life during planned study visits for the dose reduction and usual care groups

Table 2 | Disease activity levels at baseline and nine and 18 month follow-up

	Dose reduction (n=121)	Usual care (n=59)	P*
Baseline			
DAS28-CRP score <3.2	113 (93)	53 (90)	—
DAS28-CRP score <2.6	92 (76)	48 (81)	—
2011 ACR/EULAR Boolean based remission	31 (26)	21 (36)	—
9 month follow-up			
DAS28-CRP score <3.2	89 (74)	54 (92)	0.005
DAS28-CRP score <2.6	73 (60)	48 (81)	0.005
2011 ACR/EULAR Boolean based remission	22 (18)	17 (29)	0.104
18 month follow-up			
DAS28-CRP score <3.2	103 (85)	53 (90)	0.464
DAS28-CRP score <2.6	86 (71)	47 (80)	0.218
2011 ACR/EULAR Boolean based remission	29 (24)	24 (41)	0.021

Data are number (%) of patients. ACR/EULAR=American College of Rheumatology/European League Against Rheumatism.
*χ^2, crude estimates without adjustments.

arthritis and doing well is non-inferior to usual care for occurrence of major flare, while resulting in successful dose reduction or stopping in two third of the patients. In the majority of patients, TNF inhibitor intervals could be increased or TNF inhibitors 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. However, short lived flares and minimal radiographic progression were more frequent in the dose reduction group. No predictive factors for successful dose reduction or discontinuation could be found.

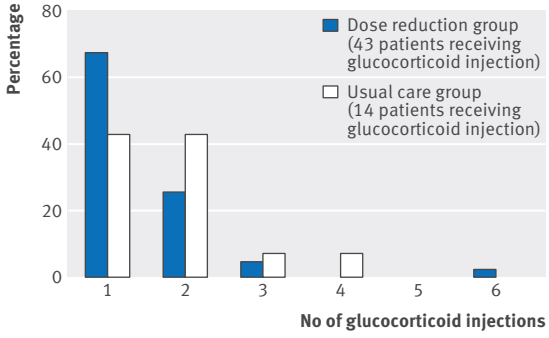

Fig 5 | Numbers of glucocorticoid injections received per patient in each study group

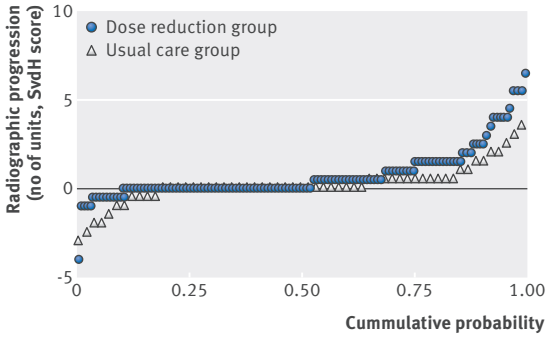

Fig 6 | Probability plot for radiological progression in dose reduction and usual care groups

Strengths and limitations of study

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 the 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.

Some methodological choices that our study was based on can be challenged. Firstly, the prespecified non-inferiority margin we chose was to some extent arbitrary, because only four non-inferiority studies so far have focused on the use of DMARD or biologicals in rheumatoid arthritis, and none was a strategy study or had used flare as a primary outcome. Our non-inferiority margin was considered clinically reasonable, because the resulting minimum number needed to harm of one in 10 (that is, a 10% difference between groups in major flare) seemed a fair trade-off when considering that the expected number needed to benefit was lower than one in two (that is, 50% difference between groups in successful dose reduction or stopping).

Furthermore, this study was not blinded. However, any potential expectation bias would lean towards the overestimation of short lived flares and the parallel underestimation of proportion of patients who can successfully taper in the intervention group, because both patients and doctors would expect a high risk of flare. This expectation is contrary to regular randomised controlled trials in which treatment is started, because 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 patients with successfully tapered treatment. This notion is supported by data from the PRESERVE study, which showed a higher percentage of patients who could reduce dose and stop treatment than in our study.[9]

Also, whether we chose the best flare criterion can be debated. Several non-validated flare criteria have been used in dose reduction and discontinuation research.[19] Our DAS28 based flare criterion has been validated, correlating well with patient and doctor judgment of disease worsening, and showing good construct validity. However, the optimal definition of flare is still under debate, with work currently in progress to develop patient reported flare criteria.[20]

Some differences in baseline characteristics and treatment during follow-up between the dose reduction and usual care groups could have resulted in bias. For example, lack of DMARD cotreatment and a higher level of radiological damage at baseline were more prevalent in the dose reduction group than the usual care group. However, these differences would have caused bias in the conservative direction, as they seem to favour the usual care group. This baseline imbalance in DMARD use 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. Furthermore,

Table 3 | Radiographic outcomes (n=175)

	Dose reduction (n=116)	Usual care (n=59)	Difference (95% CI)
Progression total SvdH score*	0.75 (1.5)	0.15 (1.1)	0.60 (0.17 to 1.0)
Progression erosion score*	0.29 (0.8)	0.12 (0.7)	0.17 (−0.07 to 0.41)
Progression joint space narrowing*	0.46 (1.2)	0.03 (0.9)	0.43 (0.08 to 0.78)
Progression >minimal clinical important change (8 units)†	0	0	0% (−8% to 4%)
Progression >smallest detectable change (4.1 units)†	5 (4%)	0	4% (−4% to 10%)
Progression >0.5 units†	37 (32%)	9 (15%)	17% (2% to 29%)

Progression=in units per 18 months.
*Mean (standard deviation).
†Number (%) of patients.

some patients in the usual care group wished to reduce the dose of other drugs, because TNF inhibitor treatment was aimed to remain stable. However, use of DMARDs and oral glucocorticoids at the end of the study 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 much lower TNF inhibitor use.

Although not statistically significant, the number of severe adverse events was higher in the dose reduction group than in the usual care group. This difference was, however, mostly caused by higher occurrence of elective surgery (joint replacement, arthrodesis, and joint prosthesis revision). A possible reason for this could be that surgeons are more likely to operate when patients are using a lower dose of TNF inhibitors or none at all. Also, as part of a substudy, whole body PET/CT scans were performed in the dose reduction group, revealing abnormal results in four patients, who then needed surgery. Because no PET/CT scans were performed in the usual care group, this result seems a case of information bias.

Comparison with other studies

How should our study results be interpreted in the light of existing evidence on tapering and stopping TNF inhibitor use? There are several studies on dose reduction and discontinuation of TNF inhibitors. However, most have been 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.[11]

When considering disease activity guided tapering in an individual patient, it is important to interpret and weigh the increased occurrence of short lived flares, their treatment, and the increased risk of minimal radiographic progression against reduced TNF inhibitor exposition and its advantages. In our view, the clinical effect of these short lived flares and their treatment is limited, and in general seems worth the trade-off with much lower TNF inhibitor exposition, including fewer injections and probably a lower risk for long term side effects. However, the perceived risk-benefit balance can differ between patients and also doctors, and shared decision making is therefore important in this context.

The difference in minimal radiological progression can be interpreted in several ways. It might have been caused by the one time, short lived flares that were more frequent in the dose reduction arm than in the usual care arm. In this case, it is to be expected that when treatment is not changed in future years, progression will be similar between both groups, and the difference remains clinically irrelevant. An alternative hypothesis is that the difference in progression is caused by lower TNF inhibitor exposition itself, and in this scenario, between group differences could become clinically relevant after, for example, a decade. A long term ongoing extension study is currently being performed to answer these questions.

Table 4 | Safety summary

	Dose reduction (n=121)	Usual care (n=59)	Difference (95%CI)
Flares			
All flares	88 (73)	16 (27)	46% (30% to 58%)
Major flares	15 (12)	6 (10)	2% (−9% to 11%)
Other adverse events			
Adverse events	95 (79)	45 (76)	2% (−9% to 16%)
Serious adverse events*	30 (25)	7 (12)	13% (−1% to 24%)
Planned surgery	11 (9)	1 (2)	7% (−1% to 14%)
PET/CT scan related†	4 (3)	—	—
Cardiovascular event	5 (4)	1 (2)	2% (−5% to 8%)
Infectious adverse event	3 (2)	3 (5)	−3% (−12% to 3%)
Malignancy	6 (5)	2 (3)	2% (−7% to 8%)
Allergic (injection) reaction	0	0	0
Death	0	0	0

Data are no (%) of patients. Cumulative incidence at 18 months: no of patients with at least one event in the study period. PET/CT=positron emission tomography/computed tomography.
*Four patients (all in the dose reduction group) had two serious adverse events each.
†Patients allocated to the dose reduction group were asked for a substudy, which included a whole body PET/CT scan. Four patients were diagnosed with extra-articular abnormalities that needed explorative surgery.

Conclusions and policy implications

We have shown the non-inferiority of a feasible dose reduction strategy of adalimumab or etanercept compared with usual care for occurrence of major flare in patients with rheumatoid arthritis and low disease activity. Implementation of this strategy would probably vastly improve the cost effectiveness of rheumatoid arthritis treatment, although formal cost effectiveness analyses should confirm this first. An important aspect of generalisability of our dose reduction strategy was its treat-to-target protocol (that is, aiming to maintain at least low disease activity). This aspect is important in the treatment of rheumatoid arthritis,[21 22] but especially so when disease activity guided dose reduction is attempted due to the increased risk of flare. In this study, implementation of the treat-to-target protocol was satisfactory, as witnessed by the low DAS28-CRP scores during the study in both groups. However, implementation of this strategy on a large scale and in other healthcare systems and countries could be challenging, for example, owing to potentially long travel distances for patients.[23 24]

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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Data sharing: The authors commit to making the relevant anonymised patient level data available on reasonable request.

Transparency: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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