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## CLINICAL SCIENCE

# Gradual tapering TNF inhibitors versus conventional synthetic DMARDs after achieving controlled disease in patients with rheumatoid arthritis: first-year results of the randomised controlled TARA study

Elise van Mulligen,<sup>1</sup> Pascal Hendrik Pieter de Jong,<sup>1</sup> Tjallingius Martijn Kuijper,<sup>2</sup> Myrthe van der Ven,<sup>1</sup> Cathelijne Appels,<sup>3</sup> Casper Bijkerk,<sup>4</sup> Joop B Harbers,<sup>5</sup> Yael de Man,<sup>6</sup> T H Esmeralda Molenaar,<sup>7</sup> Ilja Tchetverikov,<sup>8</sup> Yvonne P M Goekoop-Ruiterman,<sup>9</sup> Jende van Zeven,<sup>10</sup> Johanna M W Hazes,<sup>1</sup> Angelique E A M Weel,<sup>2</sup> Jolanda J Luime<sup>1</sup>

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For numbered affiliations see end of article.

## Correspondence to

Elise van Mulligen, Rheumatology, Erasmus MC, Rotterdam 3015, Netherlands; [elise.vanmulligen@erasmusmc.nl](mailto:elise.vanmulligen@erasmusmc.nl)

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## ABSTRACT

**Objectives** The aim of this study is to evaluate the effectiveness of two tapering strategies after achieving controlled disease in patients with rheumatoid arthritis (RA), during 1 year of follow-up.

**Methods** In this multicentre single-blinded (research nurses) randomised controlled trial, patients with RA were included who achieved controlled disease, defined as a Disease Activity Score (DAS)  $\leq 2.4$  and a Swollen Joint Count (SJC)  $\leq 1$ , treated with both a conventional synthetic disease-modifying antirheumatic drugs (csDMARD) and a TNF inhibitor. Eligible patients were randomised into gradual tapering csDMARDs or TNF inhibitors. Medication was tapered if the RA was still under control, by cutting the dosage into half, a quarter and thereafter it was stopped. Primary outcome was proportion of patients with a disease flare, defined as DAS  $> 2.4$  and/or SJC  $> 1$ . Secondary outcomes were DAS, European Quality of Life-5 Dimensions (EQ5D) and functional ability (Health Assessment Questionnaire Disability Index [HAQ-DI]) after 1 year and over time.

**Results** A total of 189 patients were randomly assigned to tapering csDMARDs (n = 94) or tapering anti-TNF (n = 95). The cumulative flare rates in the csDMARD and anti-TNF tapering group were, respectively, 33 % (95% CI, 24% to 43 %) and 43 % (95% CI, 33% to 53 %) (p = 0.17). Mean DAS, HAQ-DI and EQ-5D did not differ between tapering groups after 1 year and over time.

**Conclusion** Up to 9 months, flare rates of tapering csDMARDs or TNF inhibitors were similar. After 1 year, a non-significant difference was found of 10 % favouring csDMARD tapering. Tapering TNF inhibitors was, therefore, not superior to tapering csDMARDs. From a societal perspective, it would be sensible to taper the TNF inhibitor first, because of possible cost reductions and less long-term side effects.

**Trial registration number** NTR2754

## INTRODUCTION

Treatment outcomes of rheumatoid arthritis (RA) have improved enormously during the past decades due to earlier detection of the disease, a treat-to-target approach and intensified treatment, especially combination therapy with

## Key messages

### What is already known about this subject?

- With better treatment outcomes, it is nowadays common to taper medication in patients with rheumatoid arthritis who are in sustained remission. The optimal tapering approach still has to be unravelled.

### What does this study add?

- This study compares the effectiveness of gradual tapering the conventional synthetic disease-modifying antirheumatic drugs (csDMARD) or the TNF inhibitor in patients with rheumatoid arthritis with controlled disease treated with a combination of csDMARDs and a TNF inhibitor.
- The Tapering strategies in Rheumatoid Arthritis (TARA) trial is one of the first trials which assesses differences in tapering strategies, and elaborates on current viewpoints concerning tapering treatment, instead of only determining if tapering is feasible or not.

### How might this impact on clinical practice or future developments?

- Tapering TNF inhibitors was not superior to tapering csDMARDs. We, therefore, advise to taper the TNF inhibitor first. This supports current EULAR guidelines.

conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and biological DMARDs (bDMARDs). As a result, 50%–60% of patients with early RA are able to reach low disease activity or even sustained remission.<sup>1–4</sup> Because of these improved outcomes, it is nowadays more common to taper medication in patients with RA, who are in sustained remission. This is in accordance with current treatment guidelines.<sup>4</sup> However, an optimal tapering approach, including in which order, still has to be unravelled.

The benefits of tapering treatment are: (1) a decreased risk of long-term adverse events due to



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immunosuppression, that is, increased infection risk and possibility of malignancy development, (2) a reduction of healthcare costs, especially when biologicals are tapered and (3) a possibly improved compliance.<sup>5,6</sup> On the other hand, tapering treatment may lead to more transient or persistent disease flares with potential harmful consequences.<sup>1,7,8</sup>

Previous studies have shown that it is possible to taper DMARDs in various ways, which has been extensively reviewed by several research groups.<sup>7,9–15</sup> bDMARDs are most frequently completely withdrawn. However, with this tapering strategy, the risk of disease flares in the first year of follow-up is very high. Other bDMARD-tapering studies used a dose-reduction approach, which resulted in less disease flares. However, to our knowledge, no randomised trials have been performed that investigate which DMARD should be tapered first.

Therefore, the aim of this study is to compare the effectiveness of two tapering strategies, namely gradually tapering csDMARDs or tumor necrosis factor (TNF) inhibitors, in patients with RA with controlled disease under a combination of csDMARDs and a TNF inhibitor.

## PATIENTS AND METHODS

### Study design

Data were used from a clinical trial (NTR2754)—namely, Tapering strategies in Rheumatoid Arthritis (TARA). TARA, a multicentre, single-blinded (research nurses) randomised trial, was carried out in 12 rheumatology centres in the Southwestern part of the Netherlands. Inclusion started in September 2011 and ended July 2016.

### Patients

Adult patients with RA with controlled disease, defined as a Disease Activity Score (DAS)  $\leq 2.4$  and a Swollen Joint Count (SJC)  $\leq 1$  at two consecutive time points within a 3-month interval, with a combination of a csDMARD and TNF inhibitor, were included. Exclusion criteria were: (1) not being able to understand, speak and write in Dutch; (2) being diagnosed with a psychiatric or personality disorder and (3) tapering or stopping therapy due to other reasons.

### Randomisation and blinding

Patients were randomised using minimisation randomisation stratified for centre. Trained research nurses, blinded to the allocated treatment arm throughout the study, examined patients and calculated the DAS.

### Tapering schedule

Patients were randomised into gradual tapering their csDMARD or TNF inhibitor. csDMARD tapering was realised by cutting the dosage into half, a quarter and thereafter it was stopped. The TNF inhibitor was tapered by doubling the dose interval, followed by cutting the dosage into half, and thereafter it was stopped. The total tapering schedule took 6 months, with dose adjustments every 3 months as long as there was still a controlled disease. At the start of the study, patients were asked to refrain from glucocorticoids (GCs). There were no restrictions on the use of non-steroidal anti-inflammatory drugs (NSAIDs) or intra-articular GC injections.

If a disease flare occurred, defined as DAS  $> 2.4$  and/or SJC  $> 1$ , tapering was stopped and the last effective treatment, when RA was under control, was restarted. In case of a flare, one intramuscular GC injection was allowed as bridging therapy. After a

flare, no further attempts were taken to taper medication during the remainder of the first year of follow-up.

### Outcomes

The primary outcome was the proportion of patients with a disease flare within 1 year. Secondary endpoints were disease activity, functional ability, quality of life, medication usage and radiographic progression.

Disease activity was measured with the DAS. Functional ability was measured with the Health Assessment Questionnaire Disability Index (HAQ-DI).<sup>16</sup> Higher HAQ-DI scores indicate poorer function. Quality of life was measured with the European Quality of Life-5 Dimensions (EQ-5D) and Short Form-36 (SF-36).<sup>17–19</sup> A higher EQ-5D index or SF-36 score indicates a better quality of life. Radiographic progression was measured with the modified total Sharp score (mTSS).<sup>20</sup> Radiographs were scored chronologically by two out of three qualified assessors, who were blinded for study allocation and the identity of the patients.<sup>21</sup> Median mTSS are reported.<sup>22</sup> The weighted overall  $\kappa$  was 0.75 with  $> 99\%$  agreement. The percentage of patients with radiographic progression, defined as a change in mTSS  $> 0.5$  and  $> 0.9$  (the smallest detectable change), are given.<sup>22</sup>

### Follow-up and assessments

Treatment strategies were tightly controlled, with patients being examined at baseline and every 3 months thereafter. At each time point, the DAS, medication usage, development of complications and self-reported questionnaires were collected, except for hand and foot radiographs, which were obtained at baseline and after 1 year of follow-up.

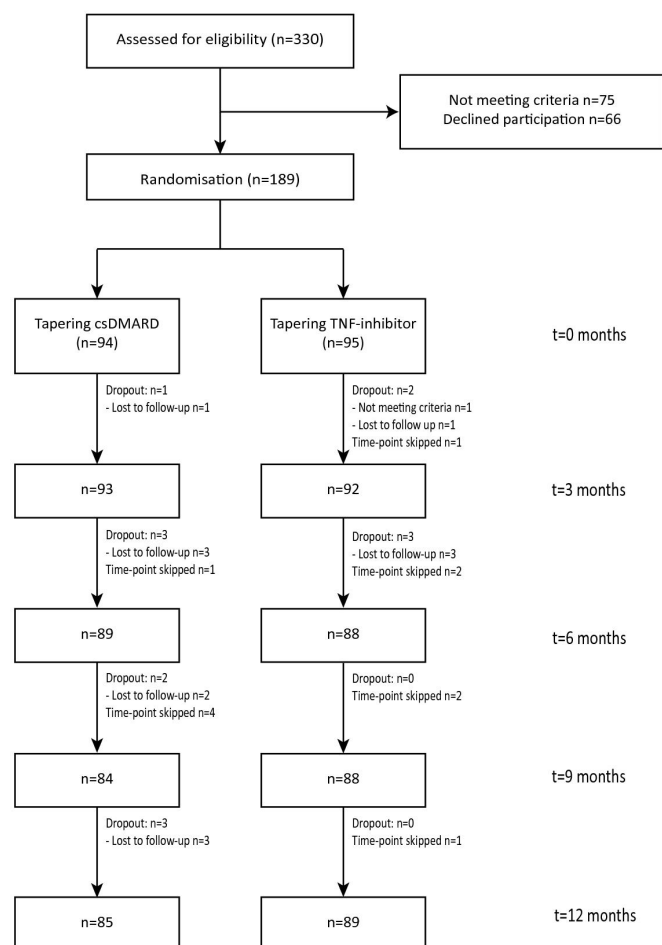
### Safety monitoring

Safety monitoring took place according to Dutch guidelines, and included laboratory tests every 3 months.<sup>23–25</sup> The medication was stopped or the dosage was lowered in case of adverse events related to medication use.

### Statistical analysis

The TARA study was a superiority trial, powered to detect a 20% difference in flare rates between both tapering strategies. Based on related prospective cohort studies from 2011 and before, following assumptions were made: (1) 40% of the patients tapering their TNF inhibitors to half will have controlled disease after 6 months and (2) 60% of the csDMARD tapering group will have controlled disease after 6 months.<sup>26–28</sup> Therefore, to detect this 20% difference using a significance level of  $\alpha = 0.05$  and a power of 80%, 107 patients were needed in each treatment arm, also taking a 10% drop-out ratio into account.

Outcomes were calculated in an intention-to-treat analysis, using all available data. Differences in cumulative flare rates between groups were analysed with a logistic regression model. To account for stratified randomisation by centre, intercepts for each centre were included. Flare-free survival was visualised with Kaplan-Meier curves. Descriptive statistics were used to assess the proportion of patients with a controlled disease after 12 months of follow-up. A linear mixed model with maximum likelihood optimisation was used to compare DAS, HAQ-DI and EQ-5D over time. Random intercepts were included for both hospital and individual patients. Residual correlation was modelled by inclusion of an autoregressive order correlation structure. In the final model, the differences in evolution over time for the outcome DAS, HAQ-DI and EQ-5D between the two groups were assessed.



**Figure 1** Trial profile and patient participation. Results are shown as number of patients. csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; TNF, tumor necrosis factor.

Statistical comparisons of the baseline characteristics and outcomes were made by Student's t-test,  $\chi^2$  test or Wilcoxon rank-sum test, when appropriate.

All data were analysed using STATA V.15. A  $p \leq 0.05$  was considered statistically significant.

## RESULTS

### Patients

A total of 330 patients were assessed for eligibility and 189 of those were randomly assigned to tapering their csDMARD ( $n=94$ ) or tapering their TNF inhibitor ( $n=95$ ). Most patients who were not eligible did not meet the inclusion criteria for remission or refused participation (figure 1). During the first year of follow-up, 14 patients withdrew from the study, mainly because of refraining from further participation (figure 1).

Table 1 shows the baseline characteristics for both tapering strategies. Patients had an average symptom duration of 6.8 years and were predominantly female (66.1%) with an average age of 56.6 years. Baseline mean (SD) HAQ-DI was 0.52 (0.47) and 0.47 (0.53) and EQ-5D was 0.86 (0.12) and 0.87 (0.11) for, respectively, the csDMARD and TNF inhibitor tapering group.

At baseline, 81% of the csDMARD tapering group and 88% of the TNF inhibitor tapering group were in remission (DAS <1.6) (table 1). The majority of patients in the csDMARD and TNF inhibitor tapering group used methotrexate (respectively, 97% and 86%) in combination with etanercept (respectively, 54% and

**Table 1** Baseline characteristics of the csDMARD tapering group and the TNF inhibitor tapering group

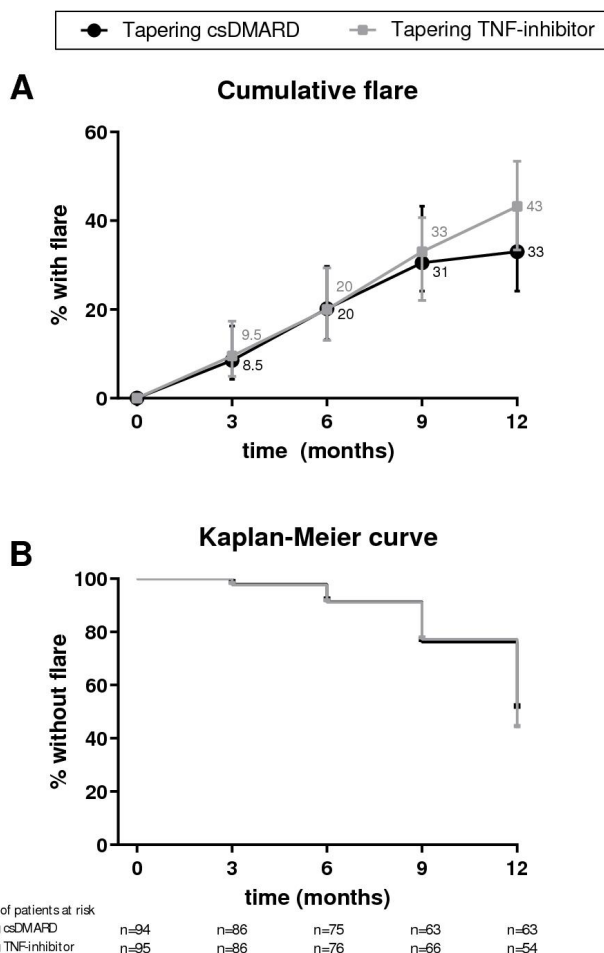
Characteristics	Tapering csDMARD (n=94)	Tapering TNF inhibitor (n=95)
<b>Demographic</b>		
Age (years), mean (95% CI)	55.9 (53.0 to 58.8)	57.2 (55.0 to 59.4)
Gender, female, n (%)	67 (71)	58 (61)
<b>Disease characteristics</b>		
Symptom duration (years), median (IQR)	6.0 (4.1–8.5)	6.4 (4.2–8.9)
RF positive, n (%)	50 (57)	59 (65)
ACPA positive, n (%)	62 (71)	67 (75)
<b>Disease activity</b>		
DAS44, mean (95% CI)	1.1 (0.9 to 1.2)	1.0 (0.9 to 1.1)
DAS clinical remission, DAS44 <1.6, n (%)	76 (81)	87 (88)
TJC44, median (IQR)	0 (0–2)	0 (0–1)
SJC44, median (IQR)	0 (0–0)	0 (0–0)
VAS disease activity (0–100 mm), median (IQR)	20 (4–32)	12 (4–23)
ESR in mm/hour, median (IQR)	8 (3–14)	8 (2–15)
CRP in mg/L, median (IQR)	2.2 (1–5)	2 (1–6)
<b>Use of csDMARDs*</b>		
MTX, n (%)	90 (96)	84 (88)
SASP, n (%)	10 (11)	12 (13)
HCQ, n (%)	24 (26)	37 (39)
Leflunomide, n (%)	2 (2)	4 (4)
<b>Use of TNF inhibitor</b>		
Etanercept, n (%)	51 (54)	52 (55)
Adalimumab, n (%)	37 (39)	40 (42)
Others, n (%)†	6 (6)	3 (3)
<b>Radiographs (hand/foot)</b>		
mTSS (0–488), median (IQR)	2 (0–6.5)	1 (0–3.5)
Erosion score (0–280), median (IQR)	0 (0–2.5)	0 (0–2)
JSN score (0–168), median (IQR)	0.5 (0–2.5)	0 (0–2.5)
Erosive disease, n(%)‡	37 (39)	26 (27)
<b>Patient-reported outcomes</b>		
HAQ-DI, mean (95% CI)	0.52 (0.42 to 0.62)	0.47 (0.35 to 0.58)
<b>SF-36, median (IQR)</b>		
PCS	43 (29–48)	47 (39–51)
MCS	60 (56–63)	57 (51–62)
EQ-5D index, mean (95% CI)	0.86 (0.83 to 0.88)	0.87 (0.85 to 0.89)

\*Some patients used a combination of csDMARDs.

†Certolizumab or golimumab.

‡Erosive disease is characterised as having >1 erosion in three separate joints. ACPA, anticitrullinated protein antibody; CRP, C reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS44, Disease Activity Score Measured in 44 joints; EQ5D, European Quality of Life-5 Dimensions; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire Disability Index; HCQ, hydroxychloroquine; JSN, joint space narrowing; MCS, mental component summary; mTSS, modified Sharp/Van der Heijde score. MTX, methotrexate; PCS, physical component summary; RF, rheumatoid factor; SASP, sulfasalazine; SF-36, Short Form-36; SJC, Swollen Joint Count; TJC, Tender Joint Count; VAS, Visual Analogue Scale;

55%) or adalimumab (respectively, 39% and 42%). Oral GCs were taken by 4 (4%) patients in the csDMARD tapering group and 2 (2%) patients in the TNF inhibitor tapering group, while NSAIDs were taken by 14 (15%) and 20 (21%) patients (table 1).



**Figure 2** Percentages flares and Kaplan-Meier curves for maintenance of controlled disease in the first 12 months. Percentages with flare indicates the cumulative number of patients with flares. Error bars indicate 95% CIs. Kaplan-Meier curves indicate loss of controlled disease (DAS >2.4 and/or SJC >1) over time. Numbers below the Kaplan-Meier curve indicate the number of patients at risk per time point. csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS, Disease Activity Score Measured; SJC, Swollen Joint Count; TNF, tumor necrosis factor.

At baseline, respectively, 39% and 27% of patients within the csDMARD or TNF inhibitor group had erosive disease.

## Outcomes

After 1 year of follow-up, the cumulative flare rate was 33% (95% CI, 24% to 43%) in the csDMARD and 43% (95% CI, 33% to 53%) in the TNF inhibitor tapering group (figure 2). This means that 63/94 (67%) in the csDMARD tapering group and 54/95 (57%) in the TNF inhibitor tapering group still had a well-controlled RA ( $p=0.17$ ). Of the patients who flared and restarted the last effective treatment strategy, 46% regained a DAS <2.4 within 3 months, which increased to 67% by 6 months. Two patients (1%) were unable to get back in remission within the first year.

No significant differences were seen in DAS ( $p=0.72$ ), HAQ-DI ( $p=0.63$ ) and EQ-5D ( $p=0.58$ ) after 1 year between both tapering strategies (table 2). Also over time, the DAS ( $p=0.49$ ) and EQ-5D ( $p=0.35$ ) were not significantly different between both tapering strategies (figure 3). Although the TNF inhibitor tapering group seems to have lower HAQ-DI scores over time, this was not significantly different ( $p=0.15$ ) (figure 3).

**Table 2** Clinical response after 12 months for both tapering groups, according to intention-to-treat

Clinical response after 12 months	Tapering csDMARD (n=85)	Tapering TNF inhibitor (n=89)
<b>Disease activity</b>		
DAS44, mean (95% CI)	1.31 (1.17 to 1.46)	1.35 (1.19 to 1.51)
TJC44, median (IQR)	0 (0–2)	0 (0–3)
SJC44, median (IQR)	0 (0–0)	0 (0–1)
VAS disease activity (0–100 mm), median (IQR)	17 (5–36)	19 (6–42)
ESR in mm/hour, median (IQR)	11 (5–21)	11 (4–19)
CRP in mg/L, median (IQR)	2.9 (1–6)	4 (1–9)
DAS clinical remission, DAS44 <1.6, n (%)	57 (69)	58 (66)
$\Delta$ DAS44 (T12–T0), mean (95% CI)	0.28 (0.16 to 0.40)	0.40 (0.22 to 0.57)
<b>Radiographic progression (hand/foot)</b>		
mTSS (0–488), median (IQR)	2 (0–6.5)	1 (0–4)
Erosion score (0–280), median (IQR)	0.5 (0–2)	0 (0–2)
JSN score (0–168), median (IQR)	0.5 (0–2.5)	0 (0–2.5)
$\Delta$ mTSS (T12–T0), median (IQR)	0 (0–0)	0 (0–0)
Patients with progression >0.5, n (%)	4 (5)	5 (6)
Patients with progression >0.9, n (%)	4 (5)	5 (6)
Erosive disease, n(%)*	37 (44)	30 (34)
<b>Patient-reported outcomes</b>		
HAQ-DI, mean (95% CI)	0.59 (0.46 to 0.73)	0.55 (0.43 to 0.66)
$\Delta$ HAQ-DI (T12–T0), mean (95% CI)	0.05 (–0.05 to 0.13)	0.07 (–0.01 to 0.16)
<b>SF-36, median (IQR)</b>		
PCS	43 (32–50)	44 (35–50)
MCS	58 (53–62)	59 (51–62)
EQ-5D index, mean (95% CI)	0.80 (0.76 to 0.84)	0.82 (0.79 to 0.85)
$\Delta$ EQ-5D index (T12–T0), mean (95% CI)	–0.06 (–0.09 to 0.02)	–0.05 (–0.08 to 0.02)

\*Erosive disease is characterised as having >1 erosion in three separate joints. JSN, Joint space narrowing; CRP, C reactive protein; DAS44, Disease Activity Score Measured in 44 joints; EQ-5D, European Quality of Life-5 Dimensions; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire Disability Index; MCS, mental component summary; PCS, physical component summary; SF-36, Short Form-36; SJC, Swollen Joint Count; TJC, Tender Joint Count; TNF, tumor necrosis factor; VAS, Visual Analogue Scale; csDMARD, conventional synthetic disease-modifying antirheumatic drug; mTSS, modified Sharp/Van der Heijde score.

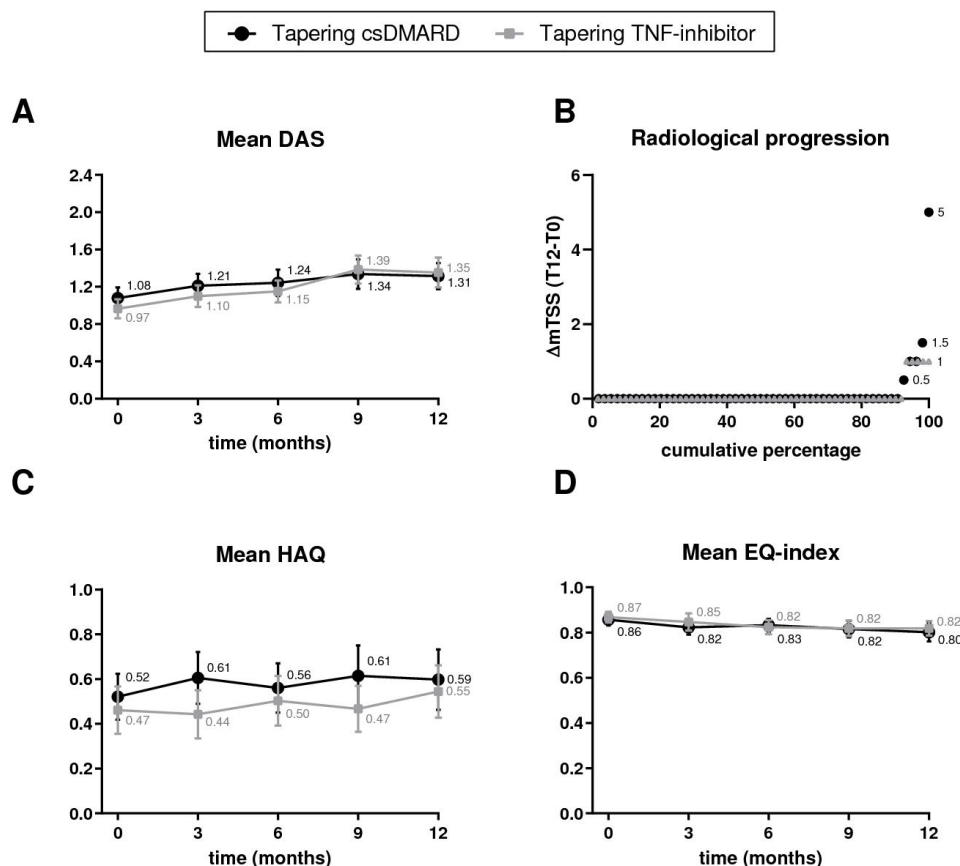
Over time, the patients with a disease flare increased and thus the proportion of patients with a DAS <2.4 decreased in both tapering strategies. A similar trend was seen for the HAQ-DI and EQ-5D over time (figure 3).

Median mTSS scores were 2 (IQR 0–6.5) in the csDMARD and 1 (IQR 0–4) in the TNF inhibitor tapering group after 1 year of follow-up (table 2). Radiographic progression was seen in 5% of the csDMARD-tapering group and 6% of the TNF inhibitor tapering group ( $p=0.82$ ). Also, the cumulative probability plots were overlapping (figure 3B).

## Treatment

After 12 months, 58 patients in the csDMARD-tapering group and 45 patients in the TNF inhibitor tapering group completely tapered their medication ( $p=0.09$ ). On the other hand, 8 and 16





**Figure 3** Disease activity, cumulative probability plot for radiological progression, functional ability and quality of life over time per tapering arm. (A, C, D) Error bars indicate 95% CIs. (B) Each point represents radiological progression (T12–T0) of an individual patient, measured with the mTSS score at 0 and 12 months. csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS: Disease Activity Score; EQ index, European Quality Index; HAQ-DI: Health Assessment Questionnaire disability index; mTSS, modified Sharp/Van Der Heijde score; TNF, tumor necrosis factor.

patients were using the same dosage as at start of the trial. The remaining patients were able to taper their medication partially (figure 4C). The course of the tapering schedule is visualised in figure 4A,B. There was an overall significant difference in tapering status after 12 months of follow-up between the two tapering strategies ( $p=0.02$ ). During the follow-up period, we found no significant differences in GC and NSAID usage between both tapering groups (figure 4D).

### Adverse events

In the csDMARD-tapering group, 82 adverse events were self-reported versus 98 in the TNF inhibitor tapering group (online supplemental table S1). Serious adverse events (SAEs) were seen in 10 (12%) patients tapering csDMARDs and 5 (6%) patients tapering TNF inhibitors ( $p=0.3$ , online supplemental table S1). Reported SAEs were hospitalisation, herpes zoster infection, basal cell carcinoma, large cell lung carcinoma and a bruised rib. None of the SAEs were considered to be related to the trial treatment.

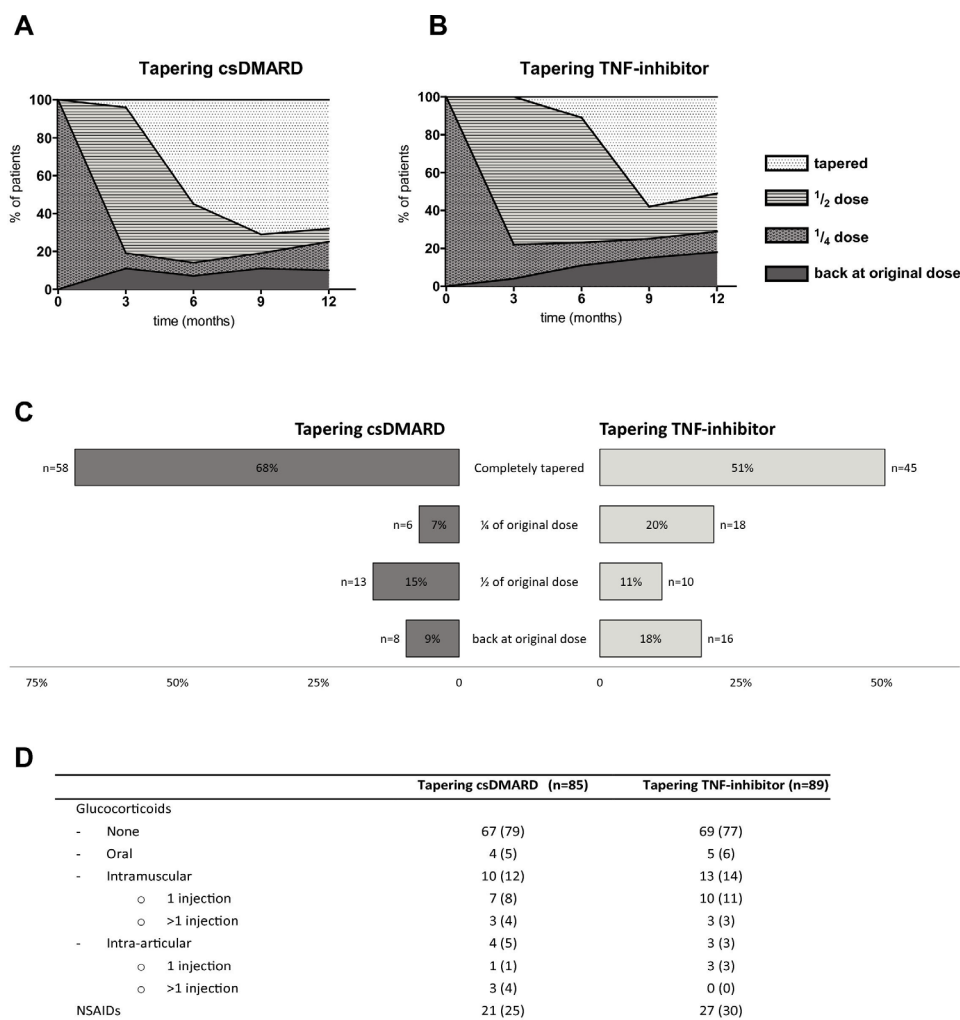
### DISCUSSION

Tapering csDMARDs resulted in a 33% (95% CI, 24% to 43%) flare rate ( $\text{DAS44} > 2.4$  and/or an  $\text{SJC} > 1$ ), while tapering TNF inhibitors gave a 43% (95% CI, 33% to 53%) flare rate over a 1-year period in the randomised controlled TARA trial. At 12 months, 103 (59%) patients were able to stop either their TNF inhibitor or csDMARD, while 47 (37%) patients were using a lower dosage. Clinical and patient-reported outcomes were

comparable in both tapering groups over time and after 1 year of follow-up. Also, no significant differences in adverse events or radiological progression were seen between both tapering strategies.

Nowadays, more patients with RA achieve a state of sustained remission, which makes them eligible for tapering treatment. This is reflected in current European league against rheumatism (EULAR) recommendations for the management for RA. The advice is to taper DMARD therapy in patients with RA who are in sustained remission in the following ordering: GCs, bDMARDs and csDMARDs.<sup>4</sup> Our results and the fact that TNF-blockers are more expensive than csDMARDs support aforementioned tapering order.

The majority of previous tapering trials focused on the withdrawal of TNF inhibitors alone. Flare rates for tapering TNF inhibitors varied between 51% and 77%. The Potential Optimisation of Expediency and Effectiveness of TNF-blockers (POET) study, for example, reported a 51.2% flare rate ( $\text{DAS28} > 3.2$  or  $\Delta\text{DAS28} > 0.6$ ) after stopping the TNF inhibitor.<sup>7</sup> The Spacing of TNF-blocker injections in Rheumatoid Arthritis Study (STRASS) showed a 76.6% flare rate ( $\text{DAS28} > 2.6$  or  $\Delta\text{DAS28} > 0.6$ ) when extending the dosage interval of the TNF inhibitor.<sup>14</sup> The Dose Reduction Strategy of Subcutaneous TNF inhibitors study (DRESS) reported a 55% flare rate ( $\Delta\text{DAS28-CRP} > 0.6$ ) after a dose reduction of the TNF inhibitor.<sup>13</sup> Finally, the PRESERVE trial (A Randomized, Double-Blind Study Comparing the Safety & Efficacy of Once-Weekly Etanercept 50 mg, Etanercept 25 mg, & Placebo in Combination With Methotrexate in Subjects



**Figure 4** Status of tapering in the first year of follow-up. (A, B) Overview of tapering status per time point. Results are shown as percentages of patients. According to protocol, the doses were halved every 3 months, starting at T0, and after 6 months, patients could stop their tapered medication when they were still in a controlled disease state. Detailed numbers per time point are given in online supplementary table S2. (C) Tapering status after 12 months. Columns indicate the percentage of patients that tapered medication until the indicated amount of the original dose. (D) Overview of glucocorticoids and NSAID use in the first year of follow-up. csDMARD, conventional synthetic disease-modifying antirheumatic drug; NSAIDs, non-steroidal anti-inflammatory drugs.

With Active Rheumatoid Arthritis) reported a 57.4% flare rate (DAS28 >3.2) when the TNF inhibitor was stopped, and a 20.9% flare rate (DAS28 >3.2) when the TNF inhibitor dose was cut into half.<sup>15</sup> Only few randomised controlled trials investigated tapering of csDMARDs, but the majority looked at the combined tapering of csDMARDs and biologicals. Flare rates within these studies varied between 35% and 56%.<sup>16 29–32</sup>

Although flare rates of aforementioned studies are similar to or higher than our findings, direct comparison is difficult, because of the differences in the study design. The most important study design differences are: (1) no common definition for relapse or flare, (2) no comparison between tapering of csDMARDs and TNF inhibitors, and (3) DMARD therapy could only be tapered or stopped once during follow-up. If we would use other criteria to define a flare in the TARA population, we would observe higher hypothetical flare rates. We would have encountered a 74.1% flare rate if using DAS28 >3.2 or  $\Delta$ DAS28 >0.6, an 80.5% flare rate if using DAS28 >2.6 or  $\Delta$ DAS28 >0.6, a 52.3% flare rate if we use  $\Delta$ DAS28-CRP >0.6, and a 39.1% flare rate if using DAS28 >3.2. Mostly, these flare rates are higher than our reported flare rates, but are similar to previous mentioned

trials. This indicates that our criteria were more strict than other studies, but that flare rates are comparable between the tapering studies.

Also, the flare duration was longer in the TARA trial compared with other trials, which could be due to the measurement intervals of 3 months. If patients did not have a controlled disease 3 months after flare, we assumed that the duration of flare was 6 months. That might be a reason that our results seem to have a long flare duration compared with the Dose Reduction or Discontinuation of Etanercept in Methotrexate-Treated Rheumatoid Arthritis Patients Who Have Achieved a Stable Low Disease Activity-State (DOSERA) study or DRESS study, in which they knew the exact duration of flare in weeks.<sup>12 13</sup>

In this study, there are several strengths and limitations. Strengths of the study are that we performed a randomised controlled trial to assess tapering in patients with RA with a controlled disease. The TARA trial is one of the first trials which assesses the differences in tapering strategies, and elaborates on current viewpoints concerning tapering treatment, instead of only determining if tapering is feasible or not.

Some limitations should be noted as well. First of all, inclusion was terminated earlier due to difficulties with recruiting. This was due to the initial inclusion criteria being too strict ( $DAS \leq 1.6$ ), and the start of another trial (POET study) which used the same pool of eligible patients.<sup>7</sup> The study sample size was based on a 20% difference between both tapering strategies resulting in 96 patients per arm. We found, however, a 10% difference with 85 patients in the csDMARD and 89 patients in the TNF inhibitor arm. This resulted in a power of 70% instead of 80%. For this reason, we performed a worst-case scenario analysis to see if our results were valid. We used the following assumptions: (1) all extra included patients in the csDMARD tapering group had no flares and (2) all extra included patients in the TNF inhibitor tapering group flared. This analysis showed an 18% difference in flares, which is still below the 20% difference on which our power calculation was based. Therefore, we think our current results and conclusions are valid.

Second, rheumatologist could have only referred patients who achieved low disease activity quickly and had less severe disease and, therefore, creating selection bias. However, we think that our target population is the same as the one we would apply our results to, because those are the patients who are suitable for tapering and are willing to taper their medication. Furthermore, only research nurses, who did the DAS assessment, were blinded. Rheumatologists, therefore, knew the tapering strategy of their patients. This design was chosen to mimic daily practise as much as possible. However, it could be a possible source of bias, since rheumatologist might prefer one of the two tapering strategies and would possibly treat patients differently depending on the tapering strategy.

Third, the time frame of follow-up was only 1 year. Although the differences in flare rates were not significantly different between both tapering strategies, the largest difference was seen at 12 months. Data of the second year are needed to investigate if this difference will increase.

Last, we encountered 19% protocol violations, which could underestimate the effect of one of the two tapering strategies. We analysed the type of violations and we can conclude that most protocol violations were randomly distributed over the two treatment arms and were made due to a treat-to-target approach.

To ensure optimal rheumatic care in the future, efficient use of biological treatment is needed.<sup>33</sup> By tapering medication, costs can be reduced, especially when tapering bDMARDs. On the other hand, 38% of the patients in the TARA study flared within the first year, which may have a direct impact on patients' lives (i.e. worker productivity and unemployment). Therefore, it is important to know which tapering strategy is most cost-effective, which will be addressed in a follow-up analysis.

In conclusion, the TARA study showed that up to 9 months, flare rates of tapering csDMARDs or TNF inhibitors were similar. After 1 year, a non-significant difference in flare rates was found of 10% in favour of csDMARD tapering. Tapering TNF inhibitors was, therefore, not superior to tapering csDMARDs. From a societal perspective, it would be sensible to taper the TNF inhibitor first, because of possible cost reductions and less long-term side effects.

#### Author affiliations

<sup>1</sup>Rheumatology, Erasmus Medical Centre, Rotterdam, The Netherlands

<sup>2</sup>Rheumatology, Maasstad Ziekenhuis, Rotterdam, The Netherlands

<sup>3</sup>Rheumatology, Amphia ziekenhuis, Breda, The Netherlands

<sup>4</sup>Rheumatology, Reinier de Graaf Gasthuis, Delft, The Netherlands

<sup>5</sup>Rheumatology, Franciscus ziekenhuis, Roosendaal, The Netherlands

<sup>6</sup>Rheumatology, Sint Antonius Ziekenhuis, Utrecht, The Netherlands

<sup>7</sup>Rheumatology, Groene Hart Ziekenhuis, Gouda, The Netherlands

<sup>8</sup>Rheumatology, Albert Schweitzer Ziekenhuis, Dordrecht, The Netherlands

<sup>9</sup>Rheumatology, Haga Ziekenhuis, The Hague, The Netherlands

<sup>10</sup>Rheumatology, Franciscus Gasthuis, Rotterdam, The Netherlands

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