Tapering and discontinuation of methotrexate in patients with RA treated with TNF inhibitors: data from the DREAM registry

Sofie H M Manders,1 Mart A F J van de Laar,2 Sanne A A Rongen-van Dartel,3 Reinhard Bos,4 Henk Visser,5 Herman L Brus,6 Tim Jansen,7 Harald E Vonkeman,2 Piet L C M van Riel,1 Wietske Kievit8

To cite: Manders SHM, van de Laar MAFJ, Rongen-van Dartel SAA, et al. Tapering and discontinuation of methotrexate in patients with RA treated with TNFi. RMD Open 2015;1:e000147. doi:10.1136/rmdopen-2015-000147

ABSTRACT

Objectives: To study the number of patients that taper or discontinue concomitant methotrexate (MTX) in daily practice in patients with rheumatoid arthritis (RA) treated with tumour necrosis factor inhibitor (TNFi) and to analyse the effects of that adaption on disease activity and drug survival.

Methods: Data were collected from the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry. Patients who started their first TNFi were included in the study. Treatment effectiveness after MTX tapering or discontinuation was analysed using Disease Activity Score of 28 joints (DAS28). Drug survival of the TNFi was analysed using the Cox proportional hazard model with a time-dependent covariate.

Results: In 458 patients (34%), MTX was tapered, 126 patients (10%) discontinued MTX and 747 patients (56%) continued MTX at the same dose. On average, DAS28 improved after tapering MTX (−0.40, −0.45) and after stopping MTX (−0.28, −0.12) at 6 and 12 months. In the taper group, 21% of the patients relapsed (DAS28 increase >0.6), and in the discontinuation group this was 21% and 24% at 6 and 12 months, respectively. Patients who taper and discontinue MTX have a similar DAS28 score over time as patients who continue MTX. Moreover, there was no influence of tapering or discontinuation of MTX on long-term drug survival of TNFi.

Conclusions: In daily practice, tapering or discontinuation of concomitant MTX in patients with RA treated with TNFi frequently occurs and it does not seem to influence the average DAS28 score over time or the long-term TNFi drug survival. It appears that in daily clinical practice the correct patients are selected to taper or discontinue MTX.

INTRODUCTION

Insufficient effect of methotrexate (MTX) is most often the reason to add a tumour necrosis factor inhibitor (TNFi) to the treatment strategy of patients with rheumatoid arthritis (RA). The combination of TNFi with MTX provides better results than TNFi monotherapy1–3 and is therefore recommended in clinical guidelines.4 However, MTX can cause mild adverse events like gastrointestinal problems in about 50% of the patients, with nausea as the main symptom. Also, headaches, dizziness and oral ulcers are often heard symptoms.5,6 This observation fits with the clinical experience that treatment with MTX is often a burden for patients. Owing to this burden, it might be the patient’s wish to taper or discontinue MTX when the combination with TNFi results in significant improvements rather than taper or discontinue TNFi. However, no data are available whether or not

Key messages

What is already known about this subject?

❖ Tumour necrosis factor inhibitor (TNFi) is more effective in combination with methotrexate (MTX), but 50% of patients with rheumatoid arthritis (RA) experience discomfort/inconvenience due to adverse events of the MTX.

What does this study add?

❖ MTX is tapered and discontinued in daily practice in patients with RA using TNFi with concomitant MTX. Tapering or discontinuation concomitant MTX has on average no negative effects on DAS28 scores or on long-term TNFi drug survival.

How might this impact on clinical practice?

❖ The correct patients were chosen to taper and discontinue concomitant MTX in daily practice. In these and perhaps also other patients, the discomfort/inconvenience of the adverse events of MTX can be reduced and therefore the quality of life can be increased.
concomitant MTX can be tapered or discontinued in daily clinical practice. Therefore, the objective of this study was to explore how frequently MTX is tapered or discontinued in daily clinical practice and the effects of that on disease activity in the short term, and on the TNFi drug survival in the long term.

PATIENTS AND METHODS

Design
This is a cohort study using data from the biologic register of the Dutch Rheumatoid Arthritis Monitoring (DREAM) project. Since February 2003, all patients with RA who started on one of the biological agents for the first time in one of 12 centres in the Netherlands have been included in the DREAM biologic register. Patients in this study were not randomised to a specific treatment and data collection continued even when patients stopped using biological agents. Since the study protocol is in line with the advice on safety and effectiveness monitoring of the Dutch guideline for diagnosis and treatment of patients with RA, this register does not need extended ethical approval. This was confirmed by the regional ethical committee Arnhem-Nijmegen. Patients signed informed consent on gathering their data in an electronic database and using their data for research purposes.

Inclusion/exclusion criteria
All patients had a diagnosis of RA according to the 1987 American College of Rheumatology classification criteria and a Disease Activity Score of 28 joints (DAS28) >3.2. Prior treatments with at least two other disease-modifying antirheumatic drugs (DMARDS) including MTX and absence of an absolute contraindication for a TNFi (eg, pregnancy, presence of a serious infection) were required. Inclusion criteria for the DREAM biologic registry were based on the Dutch regulations for reimbursement.

Assessments
Patients were assessed at the start of TNFi treatment (baseline) and every 3 months thereafter. The following baseline measurements were collected: age, gender, rheumatoid factor (RF), disease duration (since the time of diagnosis), presence of erosive disease, previous and/or current antirheumatic treatment, DAS28, Health Assessment Questionnaire Disability Index (HAQ-DI) and medication consumption. The clinical assessments used to determine DAS28 were performed by trained nurses, and the HAQ-DI was completed by the patients themselves. DAS28, HAQ-DI, medication history and the presence of comorbidities were reassessed at the scheduled clinical visits.

Statistical analyses
For this study, patients with RA and using their first TNFi with concomitant MTX were eligible for the analyses. First, the percentages of patients who tapered and discontinued MTX were analysed. Patients who tapered MTX during the TNFi treatment were included in the taper group. Patients who stopped MTX directly, without tapering first, were included in the discontinuation group. All other patients were analysed in the continuation group. Second, comparisons between these three groups were analysed. The intention-to-treat principal was used for these analyses.

To detect baseline differences in age, gender, RF positivity, presence of erosions, disease duration, type of TNFi treatment, amount of previous DMARDS, DAS28 at baseline, HAQ-DI at baseline and co-medication, univariate analyses of baseline variables were performed using analysis of variance, a Kruskal-Wallis test and a $\chi^2$ test, depending on the distribution and type of data.

Patient characteristics were compared between those who had a relapse (defined as an increase in disease activity $>0.6$ on DAS28) and those who did not have a relapse by using a t-test, a Mann-Whitney U test and a $\chi^2$ test, as appropriate. The change in DAS28 scores at 6 and 12 months after tapering and discontinuation of MTX was calculated. Patients with missing DAS28 data at baseline or the follow-up measurement could not be included. Linear mixed models with the interaction term between time and tapering MTX (yes/no) were used to analyse if the course of DAS28 over time is different in the MTX taper group compared to the patients who discontinued MTX and continued MTX. Using the linear mixed model approach for the repeated measures within the patients has the advantage that all available data could be used despite some missing values. The missing data are assumed to be missing at random. For the mixed model analyses, the first-order autoregressive (AR(1)) covariance structure was used. This structure was the best fit for these outcome measures ($-2$ restricted log likelihood). To analyse if there is a difference in long-term drug survival of TNFi between the groups, Cox proportional hazard modelling was used in which the time till tapering and discontinuation was defined as a time-dependent covariate. A hazard ratio significantly higher than one means that the patients who discontinue or taper have worse TNFi drug survival than those in the continuation group. In the mixed model and Cox regression analyses, a correction was made for all possible confounders. Patients using golimumab and certolizumab could not be taken into account because the number of patients in these groups were too small.

RESULTS

Between February 2003 and June 2012, a total of 1933 patients with RA started their first TNFi therapy. Sixty-nine per cent (1331/1933) of these patients used TNFi in combination with MTX. For the patients treated with infliximab, the percentage of MTX users was 71, for patients treated with adalimumab the percentage was 72, and for patients treated with etanercept this was 66%.

Table 1 shows the clinical characteristics of patients in whom MTX was tapered and discontinued during...
treatment with TNFi and of patients who continued MTX. The patients who tapered had a less number of previous DMARDs and higher MTX doses than patients who continued and discontinued MTX.

**Tapering of MTX**

There were 34.4% (458/1331) patients with concomitant MTX in whom MTX was tapered during follow-up. In half of the patients, the dose was tapered within 6 months (median=149 days (IQR 84–325)) after the start of their TNFi. MTX tapering occurred in 33% of the patients using infliximab, in 38% of patients using adalimumab, and in 35% of patients using etanercept. Most patients who tapered MTX had a dose of 25 mg MTX at the start: 50%. After this first MTX dose tapering, 41.3% (189) patients tapered their MTX dose further (median=180 days (IQR 91–354)) and 12.2% (56) increased their MTX dose again (median=99 days (IQR 77–240)).

**Table 2** presents the effects after tapering MTX at the group level. The average DAS28 score after MTX tapering decreased at 6 and 12 months.

**Relapse rates**

In 21% of the patients, DAS28 increased more than 0.6 at 6 and 12 months, table 2. Patients who relapsed at 6 months had significantly (p=0.004) more patients on <10 mg MTX after tapering (19.1%) than patients who did not relapse (7.4%). Moreover, DAS28 at the time of taper was lower (mean difference=1.20, p<0.001), the patients tapered later in time (mean difference=77 days, p=0.003), they used more previous DMARDs in the past (p=0.009) and had lower MTX doses before taper (p=0.016) in patients who relapsed compared to those who did not. At 12 months, patients who relapsed had lower DAS28 scores at the moment of taper (mean difference=1.25, p<0.001).

**Discontinuation of MTX**

In 9.5% (126/1331) of the patients, MTX was discontinued during follow-up. Half of those patients did so within 9 months (median=261 days (IQR 97–552)) after the start of their TNFi. MTX discontinuation occurred in 7.8% of the patients using infliximab, in 8.7% of patients using adalimumab, and in 10.3% of patients using etanercept. The largest group of patients used 15 mg of MTX before discontinuation (30.6%). Those patients discontinuing their MTX treatment had an average DAS28 at discontinuation of 3.6 (SD=1.4). The improvement in DAS28 at 6 and 12 months was 0.28 and 0.12, respectively.

**Table 1** Patients’ characteristics at start of the TNFi treatment

|                      | Discontinue (N=126) | Taper (N=458) | Continue (N=747) | p Value |
|----------------------|---------------------|---------------|------------------|---------|
| Mean age in years (SD) | 53 (13)             | 54 (12)       | 56 (13)          | 0.061   |
| Female gender in %    | 60                  | 69            | 67               | 0.017   |
| RF positive in %      | 65                  | 73            | 67               | 0.201   |
| Presence of erosions in % | 59              | 67            | 59               | 0.201   |
| Median disease duration in years (IQR) | 4 (1–12)          | 4 (2–11)      | 5 (2–11)         | 0.770   |
| Mean DAS28 (SD)       | 4.9 (1.2)           | 4.8 (1.4)     | 4.9 (1.3)        | 0.764   |
| Mean HAQ-DI (SD)      | 1.3 (0.6)           | 1.3 (0.7)     | 1.3 (0.6)        | 0.441   |
| Median MTX dose in mg (IQR) | 15 (15–25)        | 25 (20–25)    | 15 (10–25)       | **0.000** |
| <10                   | 18.2                | 1.3           | 8.3              |         |
| 10–17.5               | 46.3                | 21.4          | 31.6             |         |
| 20–30                 | 33.9                | 77.1          | 58.8             |         |
| >30                   | 1.7                 | 2.2           | 1.2              |         |
| Type of TNFi in % (n) |                      |               |                  | **0.079** |
| Adalimumab            | 38.1 (48)           | 44.3 (203)    | 40.3 (301)       |         |
| Etanercept            | 50.0 (63)           | 44.8 (205)    | 46.2 (345)       |         |
| Infliximab            | 9.5 (12)            | 10.9 (50)     | 12.3 (92)        |         |
| Certolizumab pegol    | 0 (0)               | 0 (0)         | 0.4 (3)          |         |
| Golimumab             | 2.4 (3)             | 0 (0)         | 0.8 (6)          |         |
| Median number of previous DMARDs (IQR) | 3 (2–4)          | 3 (2–3)       | 3 (2–4)          | **0.043** |
| Number of present DMARDs* in % (n) |               |               |                  | **0.107** |
| 1                     | 70.6 (89)           | 73.4 (336)    | 66.1 (494)       |         |
| 2                     | 27.0 (34)           | 24.0 (110)    | 30.0 (224)       |         |
| <2                    | 2.4 (3)             | 2.6 (12)      | 3.8 (28)         |         |

*These are without prednisone; prednisone was prescribed for 28% in the discontinuation group; for 25% in the taper group and for 31% in the continuation group.
Bold typeface indicates significance at p<0.05.
DAS28, Disease Activity Score of 28 joints; DMARDs, disease-modifying anti-rheumatic drugs; HAQ-DI, Health Assessment Questionnaire Disability Index; MTX, methotrexate; RF, rheumatoid factor; TNFi, tumour necrosis factor inhibitor.

Manders SHM, et al. RMD Open 2015;1:e000147. doi:10.1136/rmdopen-2015-000147

Rheumatoid arthritis

Rheumatoid arthritis on August 21, 2022 by guest. Protected by copyright. http://rmdopen.bmj.com/ RMD Open: first published as 10.1136/rmdopen-2015-000147 on 8 October 2015. Downloaded from http://rmdopen.bmj.com/ on August 21, 2022 by guest. Protected by copyright.
respectively, of the patients (see table 2). There were no significant differences in patient characteristics in patients who relapsed and those who did not.

DAS28 course over time
DAS28 over time from start of the TNFi treatment was evaluated with linear mixed models between discontinuation, tapering and continuation (figure 1). The results show that patients who taper have the lowest DAS28 over time. However, the three groups all have the same course over time after the initial improvement in DAS28. The interaction between taper (yes or no) and time (follow-up in months) is not significantly different ($\beta=0.006; CI -0.001$ to 0.013, $p=0.071$). The same accounts for the interaction between discontinuation and time ($\beta=0.002; CI -0.008$ to 0.013, $p=0.660$). (See figure 1).

TNFi drug survival
The long-term drug survival is significantly different between the patients tapering and the patients continuing with a hazard rate (Hr) of 0.744 (0.606 to 0.913; table 3). This means that patients’ risk of stopping TNFi decreased by 25.6% if patients tapered their MTX treatment. So, even with correction for the time-dependent variable of time of tapering MTX and other confounding factors, patients who taper MTX have a better drug survival of TNFi. The long-term drug survival of the TNFi is not significantly different between patients who discontinued MTX and patients who continued MTX (Hr=1.046; CI 0.760 to 1.440; $p=0.783$) (table 4).

DISCUSSION
The main objective of this observational study was to evaluate how many patients with RA treated with TNFi and concomitant MTX taper or discontinue their MTX.
In addition, we analysed the effect on disease activity and long-term TNFi drug survival of tapering or discontinuation of MTX. This study revealed that 34.4% of the patients starting with TNFi plus MTX taper their MTX treatment and 9.5% discontinue MTX. After tapering and discontinuation of MTX, the mean DAS28 score even decreased and the long-term drug survival of the TNFi was not worse from patients that continued. The TNFi drug survival of the taper group even tends to be better than that in the continuation group.

The number of patients who tapered or discontinued MTX in our cohort study was somewhat lower than in the study of Kremer et al. In the study by Kremer et al., 62% of the patients decreased or discontinued MTX in patients with RA that used etanercept with MTX. These patients were first included in a 12-month clinical trial where concomitant medication could not be adapted. In those patients who decreased or discontinued MTX, the response to etanercept was maintained. With respect to the effectiveness also, other studies showed more or less consistent results, although these studies had other outcomes and only studied infliximab in combination with MTX. In the clinical trial of Klarenbeek et al., MTX was tapered and discontinued in patients in remission (DAS <1.6) for more than 6 months. If the DAS level increased over 1.6, the MTX/DMARD was reintroduced. Thirty-six of 128 patients starting infliximab with MTX were DMARD drug free at one point in time and 21 patients were still DMARD drug free after 5 years. The study of Fleischmann et al. showed that 76% of the patients had 40% improvement in the combined tender and swollen joint count at week 22 after starting infliximab with MTX. In these patients, the MTX dose was decreased from 15 to 5 mg. In 79% of the responders, this tapering of MTX did not increase the disease activity. On the contrary, the Canadian randomised trial of Pope et al. showed an increase of DAS28 after discontinuation of MTX. These results are different from our non-controlled setting, and it is possible that in our daily practice the correct patients are selected to taper or discontinue MTX.

This study has some limitations that should be mentioned. The first limitation is the possible confounding by indication due to the study design. These were corrected for all measured confounders; however, in addition other, unmeasured factors might differ between the groups. Although it is good to see the differences between patients who taper, discontinue and continue MTX, the comparison between the groups should be carefully interpreted. Second, it was not possible to differentiate between TNFi treatments in the analyses in the patients who discontinued MTX. Here, the number of patients with complete data was too small to make valid conclusions. Moreover, the difference in patients characteristics in patients that relapsed compared to patients that did not relapse in the discontinuation group are performed on small amounts of patients. This could be a reason why no significant differences were found between those groups. Also, other analyses in subgroups, like different doses of MTX, will not result in valid conclusions due to the small number of patients.

By studying our observational data, some remarkable results were found that need some discussion. On the basis of the literature that TNFi in combination with MTX provides better drug survival, we hypothesised that if patients tapered their MTX, they would have a worse drug survival of the TNFi. This does not seem to be the case. Despite the correction for the time-dependent variable, the start of tapering MTX, the long-term drug survival is still better in the patients who taper MTX. Perhaps this is because the patients still use a low dose of MTX and only a small percentage <10 mg MTX. Burmester et al. show in a clinical trial that TNFi plus 20 mg MTX provides the same results as TNFi plus

Table 3 Cox proportional regression hazard model with a time-dependent covariate

| Covariate         | HR (95% CI)         | p Value |
|-------------------|---------------------|---------|
| Taper MTX         | 0.744 (0.606 to 0.913) | 0.005   |
| Female gender     | 1.048 (0.662 to 1.268) | 0.628   |
| RF positive       | 0.922 (0.748 to 1.137) | 0.448   |
| Erosions present  | 1.393 (1.144 to 1.697) | 0.001   |
| Age               | 0.996 (0.989 to 1.003) | 0.250   |
| Disease duration  | 1.001 (0.988 to 1.014) | 0.874   |
| Co-medication     | 1.028 (0.866 to 1.220) | 0.751   |
| Number of previous| 1.048 (0.965 to 1.138) | 0.265   |
| DMARDs            |                     |         |
| TNFi              |                     |         |
| Infliximab (ref)  |                     | 0.000   |
| Adalimumab        | 0.519 (0.406 to 0.662) | 0.000   |
| Etanercept        | 0.407 (0.317 to 0.522) | 0.000   |

DMARDs, disease-modifying antirheumatic drugs; MTX, methotrexate; ref, reference variable; RF, rheumatoid factor; TNFi, tumour necrosis factor inhibitor.

In the study by Kremer et al., 12% of the patients decreased or discontinued MTX. These patients were included in a 12-month study of Kremer et al. In the study of Kremer et al., the study of Kremer et al. MTX in our cohort study was somewhat lower than in better than that in the continuation group. In addition, we analysed the effect on disease activity and long-term TNFi drug survival of tapering or discontinuation of MTX. This study revealed that 34.4% of the patients starting with TNFi plus MTX taper their MTX treatment and 9.5% discontinue MTX. After tapering and discontinuation of MTX, the mean DAS28 score even decreased and the long-term drug survival of the TNFi was not worse from patients that continued. The TNFi drug survival of the taper group even tends to be better than that in the continuation group.

The number of patients who tapered or discontinued MTX in our cohort study was somewhat lower than in the study of Kremer et al. In the study by Kremer et al., 62% of the patients decreased or discontinued MTX in patients with RA that used etanercept with MTX. These patients were first included in a 12-month clinical trial where concomitant medication could not
continue their MTX dose. This does not seem to
interest in patients who experience inconvenience
continue MTX treatment. In these patients, the discom-
ance DAS28 over time or the long-term TNFi drug
survival, which might indicate that in daily practice the
physicians selected the correct patients to taper or dis-
continue MTX treatment. In these patients, the discom-
fort/inconvenience of the MTX use can be reduced.
However, it is difficult to generalise these findings to all
patients starting TNFi with MTX treatment, because the
reason to choose specially these patients is unknown. To
study in which patients MTX can be tapered and discon-
tinued, other and larger studies should be performed.

Now that we know that it is possible to taper and even
discontinue MTX when patients start with TNFi, the
question is: In which patients is this possible? Unfor-
fortunately, there were no clear patient characteristics
that have an association with patients who relapse or
not. Tapering later and lower MTX doses were asso-
ciated with relapse. Also, lower DAS28 scores at the
moment of tapering or discontinuation were associated
with relapse. This is in contrast with the TNFi stopping
and tapering studies. An explanation for this might be
the differences in patient populations: in the TNFi
studies, tapering or stopping is being done in patients
who reached a state of remission (DAS28 <2.6) or low
disease activity (DAS28 <3.2), while in our study no formal
criteria for disease activity were present; in addi-
tion also, for instance, intolerance was a reason for stop-
ning/tapering. As a result of this, the disease activity at
the moment of stopping/tapering was moderate: mean
DAS28 of 3.4. A future randomised clinical trial would
perhaps be able to investigate if tapering MTX is pos-
sible for all patients who have a good response to TNFi
treatment with concomitant MTX or in patients in
whom the MTX can be discontinued or tapered best.
The question if biological treatments can be tapered or
discontinued is nowadays also interesting because of the
possible reduction in costs. So how do we deal with this
in daily practice? A possibility would be to taper biolog-
ical treatment if patients are in remission and can tol-
erate their current MTX dose well. However, if patients
experience inconvenience from the MTX treatment, or
remission is not reached, MTX could be tapered. If
patients tapered their MTX dose to a tolerated dose and
they are still in remission, perhaps it is possible to taper
the TNFi after all. If we want to increase the quality of
the patients’ lives, tapering or discontinuing MTX can
be interesting in patients who experience inconvenience
from MTX treatment. In cost-effectiveness analysis, the
effects are usually expressed in quality of life years and
these are compared with the costs. The comparison of
cost-effectiveness between tapering TNFi and tapering
MTX in patients starting that combination would be an
interesting research question for future research.

In daily practice, patients with RA do taper and dis-
continue their MTX dose. This does not seem to influ-
ence DAS28 over time or the long-term TNFi drug

REFERENCES

1. Breedveld FC, Weisman MH, Kavanaugh AF, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum* 2006;54:26–37.

2. Klareskog L, Van Der Heijde D, De Jager JP, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet* 2004;363:675–81.

3. Van Der Heijde D, Klareskog L, Rodriguez-Valverde V, et al. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. *Arthritis Rheum* 2006;54:1063–74.

4. Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with
synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* 2014;73:492–509.

5. Harrison MJ, Lunt M, Verstappen SMM, *et al.* Exploring the validity of estimating EQ-5D and SF-6D utility values from the health assessment questionnaire in patients with inflammatory arthritis. *Health Qual Life Outcomes* 2010;8:21.

6. Verstappen SM, Bakker MF, Heurkens AHM, *et al.* Adverse events and factors associated with toxicity in patients with early rheumatoid arthritis treated with methotrexate tight control therapy: the CAMERA study. *Ann Rheum Dis* 2010;69:1044–8.

7. Arnett FC, Edworthy SM, Bloch DA, *et al.* The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315–24.

8. Prevoo ML, Van’t Hof MA, Kuper HH, *et al.* Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995;38:44–8.

9. Fries JF, Spitz P, Kraines RG, *et al.* Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980;23:137–45.

10. Van Der Maas A, Lie E, Christensen R, *et al.* Construct and criterion validity of several proposed DAS28-based rheumatoid arthritis flare criteria: an OMERACT cohort validation study. *Ann Rheum Dis* 2013;72:1800–5.

11. Seltman HJ. Mixed models: a flexible approach to correlated data. In Experimental Design for Behavioral and Social Sciences. 2014:357–379. http://www.stat.cmu.edu/~hseltman/309/Book/chapter15.pdf

12. Kremer JM, Weinblatt ME, Bankhurst AD, *et al.* Etanercept added to background methotrexate therapy in patients with rheumatoid arthritis: continued observations. *Arthritis Rheum* 2003;48:1493–9.

13. Klarenbeek NB, Van Der Kooij SM, Guler-Yuksel M, *et al.* Discontinuing treatment in patients with rheumatoid arthritis in sustained clinical remission: exploratory analyses from the BeSt study. *Ann Rheum Dis* 2011;70:315–19.

14. Fleischmann RM, Cohen SB, Moreland LW, *et al.* Methotrexate dosage reduction in patients with rheumatoid arthritis beginning therapy with infliximab: the Infliximab Rheumatoid Arthritis Methotrexate Tapering (iRAMT) trial. *Curr Med Res Opin* 2005;21:1181–90.

15. Pope JE, Harraoui B, Thorne JC, *et al.* The Canadian methotrexate and etanercept outcome study: a randomised trial of discontinuing versus continuing methotrexate after 6 months of etanercept and methotrexate therapy in rheumatoid arthritis. *Ann Rheum Dis* 2014;73:2144–51.

16. Kristensen LE, Saxne T, Nilsson JA, *et al.* Impact of concomitant DMARD therapy on adherence to treatment with etanercept and infliximab in rheumatoid arthritis. Results from a six-year observational study in southern Sweden. *Arthritis Res Ther* 2008;8:R174.

17. Selman MM, Ashcroft DM, Watson KD, *et al.* Impact of concomitant use of DMARDs on the persistence with anti-TNF therapies in patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. *Ann Rheum Dis* 2011;70:583–9.

18. Burmester GR, Kivitz AJ, Kupper H, *et al.* Efficacy and safety of ascending methotrexate dose in combination with adalimumab: the randomised CONCERTO trial. *Ann Rheum Dis* 2015;74:1037–44.

19. Manders SH, Kievit W, Adang E, *et al.* Effectiveness of TNF inhibitor treatment with various methotrexate doses in patients with rheumatoid arthritis: results from clinical practice. *Ann Rheum Dis* 2015;74:e24.