Treat-to-target dose reduction and withdrawal strategy of TNF inhibitors in psoriatic arthritis and axial spondyloarthritis: a randomised controlled non-inferiority trial

Michielsens, C.A.J.; Broeder, N. den; Hoogen, F.H.J. van den; Mahler, E.A.M.; Teerenstra, S.; Heijde, D. van der; ... ; Broeder, A.A. den

CLINICAL SCIENCE

Treat-to-target dose reduction and withdrawal strategy of TNF inhibitors in psoriatic arthritis and axial spondyloarthritis: a randomised controlled non-inferiority trial

Celia AJ Michielsens ,[1,2] Nathan den Broeder ,[1,2] Frank HJ van den Hoogen,[1] Elien AM Mahler ,[1] Steven Teerenstra,[3] Désirée van der Heijde ,[4] Lise M Verhoef,[1] Alfons A den Broeder[1,2]

Handling editor Josef S Smolen

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2022-222260).

[1]Rheumatology, Sint Maartenskliniek, Nijmegen, Gelderland, The Netherlands
[2]Department of Rheumatic Diseases, Radboudumc Radboud Institute for Health Sciences, Nijmegen, Gelderland, The Netherlands
[3]Radboud Institute for Health Sciences, Department for Health Evidence, group Biostatistics, Radboudumc, Nijmegen, Gelderland, The Netherlands
[4]Rheumatology, Leiden University Medical Center, Leiden, Zuid-Holland, The Netherlands

Correspondence to
Celia AJ Michielsens, Rheumatology, Sint Maartenskliniek, 6500 GM Nijmegen, Gelderland, The Netherlands; celiamichielsens@gmail.com

Received 31 January 2022
Accepted 30 May 2022
Published Online First 14 June 2022

To cite: Michielsens CAJ, den Broeder N, van den Hoogen FHJ, *et al*. *Ann Rheum Dis* 2022;**81**:1392–1399.

ABSTRACT

Objectives Tumour necrosis factor inhibitors (TNFi) are effective in psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA), but are associated with a small (0.6%) increase in serious infection risk, patient burden due to need for self-injection and high costs. Treat-to-target (T2T) tapering might ameliorate these drawbacks, but high-quality evidence on T2T tapering strategies is lacking in PsA and axSpA.

Methods We performed a pragmatic open-label, monocentre, randomised controlled non-inferiority (NI) trial on T2T tapering of TNFi. Patients with PsA and axSpA using a TNFi with ≥6 months stable low disease activity (LDA) were included. Patients were randomised 2:1 to disease activity-guided T2T with or without tapering until withdrawal and followed-up to 12 months. Primary endpoint was the difference in proportion of patients having LDA at 12 months between groups, compared with a prespecified NI margin of 20%, estimated using a Bayesian prior.

Results 122 patients (64 PsA and 58 axSpA) were randomised to a T2T strategy with (N=81) or without tapering (N=41). The proportion of patients in LDA at 12 months was 69% for the tapering and 73% for the no-tapering group: adjusted difference 5% (Bayesian 95% credible interval: −10% to 19%) which confirms NI considering the NI margin of 20%. The mean percentage of daily defined dose was 53% for the tapering and 91% for the no-tapering group at month 12.

Conclusions A T2T TNFi strategy with tapering attempt is non-inferior to a T2T strategy without tapering with regard to the proportion of patients still in LDA at 12 months, and results in a substantial reduction of TNFi use.

Trial registration number NL 6771.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT?

⇒ Fixed tumour necrosis factor inhibitor (TNFi) dose reduction strategies seem feasible in psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA), whereas discontinuation warrants caution due to risk of flares.

⇒ Current evidence on (stepwise) treat-to-target (T2T) tapering strategies is limited and inconsistent in PsA and axSpA.

WHAT DOES THIS STUDY ADD?

⇒ This first randomised controlled trial on disease activity-guided stepwise T2T tapering strategies demonstrates non-inferiority with regard to the proportion of patients in low disease activity accompanied by a substantial reduction in TNFi use in both PsA and axSpA.

HOW MIGHT THIS IMPACT ON CLINICAL PRACTICE OR FUTURE DEVELOPMENTS?

⇒ Implementing T2T tapering strategies into practice will reduce TNFi use, and thereby patient burden, risk for adverse events and costs, while maintaining disease control.

INTRODUCTION

Psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA) are pathophysiologically and clinically related inflammatory rheumatic diseases. PsA is characterised by asymmetrical peripheral arthritis associated with psoriasis. AxSpA is predominantly identified by axial inflammation resulting in inflammatory back pain. Biological disease-modifying antirheumatic drug (bDMARDs), especially tumour necrosis factor inhibitors (TNFi), are widely used in both PsA and axSpA, and have proven to be safe and effective.[1 2] However, these drugs have drawbacks such as a small increased risk of infection, injection site reactions and relatively high costs,[3–7] which adds to the financial burden of healthcare. Treat-to-target (T2T) tapering until complete withdrawal or flare might reduce these disadvantages,[4] and has shown to be safe and (cost-)effective in rheumatoid arthritis (RA) trials.[8 9] However, although this strategy is already being recommended for PsA and axSpA, high quality evidence for this recommendation is lacking.

Current recommendations on dose tapering are based on fixed dose reduction or discontinuation studies, and data on stepwise T2T tapering strategies for PsA and axSpA is lacking. In PsA, one randomised controlled trial (RCT) showed that continuation of ixekizumab was superior to

discontinuation, but the majority of patients with loss of efficacy after discontinuation regained low disease activity (LDA) after reinstatement.[10] In axSpA, six RCTs studied fixed dose reduction or discontinuation using different TNFi.[11–16] The majority of tapered patients in these studies maintained clinical remission or LDA; or regained it quickly after therapy reinstatement, whereas discontinuation was discouraged due to the risk of flares.

We therefore performed an RCT to investigate whether a T2T strategy with tapering is non-inferior to a T2T strategy without tapering.

METHODS

Trial design and patients

We performed a pragmatic, open-label, monocentre, randomised controlled, non-inferiority (NI) trial, to compare the effect of a stepwise T2T tapering strategy (intervention) with a T2T strategy without tapering (control) regarding disease activity, (concomitant) medication use, physical function, quality of life and joint damage (for PsA).

Patients, ≥16 years of age, had to have stable LDA at least 6 months prior to inclusion. For PsA, LDA was defined as Psoriatic Arthritis Disease Activity Score (PASDAS) ≤3.2 and modified body surface area (mBSA) involvement ≤3% (as used in the minimal disease activity (MDA) status for PsA). For axSpA, LDA was defined as Ankylosing Spondylitis Disease Activity Score (ASDAS) <2.1 for axSpA and/or according to the treating rheumatologist and patient). The study rationale and design were extensively described before[17] and are further explained in online supplemental appendix 1.

The study has been registered in the Dutch Trial Register. The trial was conducted according to the principles of the Declaration of Helsinki and the International Conference on Harmonisation guideline on Good Clinical Practice. Written informed consent of all eligible patients was received at trial procedure commencement. Patients were enrolled between 9 January 2019 and 16 July 2020 at the rheumatology departments of the Sint Maartenskliniek, located in Nijmegen and Woerden, the Netherlands. A data safety monitoring board with members independent of the study met every 4 months and looked at recruitment, efficacy (mean PASDAS for PsA and ASDAS for axSpA), number of flares and (serious) adverse events per group.

Randomisation

Patients were allocated to a T2T strategy using TNFi with or without tapering attempt in a ratio of 2:1 using varying block sizes of three or six, stratified for diagnosis (PsA or axSpA) and concomitant conventional synthetic DMARD (csDMARD) use (yes or no). In total, there are four strata (2×2), with every stratum having its own randomisation list. Randomisation sequences for each of the four strata were generated online by an independent researcher at the Sint Maartenskliniek (LMV) and were concealed during the study period, with the researcher (LMV) sealing them into sequentially numbered opaque envelopes. The allocation in these envelopes were revealed to the patients and physician after inclusion. Patients visited the outpatient clinic every 3 months and were followed for 12 months.

T2T strategy with and without tapering

Patients in both groups were treated according to the prespecified protocol regarding dose tapering, co-medication and treatment of flares, from which the rheumatologist could deviate in shared decision-making with the patient. Patients randomised to the tapering group were tapered stepwise starting at baseline, from 100% to 66% and 50% until discontinuation (table 1) during each visit where low disease activity was maintained. Patients who were using <100% of the authorised TNFi dose stepped in at the nearest dosing interval, for example, patients using adalimumab one time every 3 weeks (66%), stepped in at an every 4-week interval (50%). Patients randomised to the no-tapering group continued their original TNFi dose or interval. Concomitant csDMARDs were not tapered during the study. At each visit, the treating rheumatologist was advised by the researcher, guided by the PASDAS and mBSA for PsA and the ASDAS for axSpA. Patients visited the outpatient clinic every 3 months and in case of flares. At every visit, disease activity state, (concomitant) medication use, (serious) adverse events, function and quality of life was determined. In case of a (suspected) flare patients were assessed at the outpatient clinic, where concomitant treatment as non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids could be added to the current treatment. After this, patients were re-evaluated 4 weeks later: in case of a persistent flare (>4 weeks), treatment was intensified, in case the flare was adequately addressed by glucorticoid or NSAID bridging, no further treatment changes were made. The dose was adjusted to the last effective interval or dosage which was maintained throughout the study period. When already using full TNFi dose or if dose adjustment did not suffice, patients were switched to another b/targeted synthetic (ts)DMARD. Since treatment changes were based on shared decision-making between patient and physician, treatment could also be intensified if the proposed flare criteria were not met.

Table 1 Stepwise tapering protocol for patients with PsA and axSpA in the T2T strategy group with tapering steps at baseline, 3 months and 6 months. Introduction of first tapering step at baseline visit, assuming the use of the authorised TNFi dose

TNFi	100%*	66%	50%	0%
Adalimumab/ certolizumab pegol	40 mg 2-week interval	40 mg 3-week interval	40 mg 4-week interval	Stop TNFi
Etanercept	50 mg 1-week interval	50 mg 10-day interval	50 mg 2-week interval	Stop TNFi
Golimumab	50 mg 1-month interval	50 mg 1.5-month interval	50 mg 2-month interval	Stop TNFi
Infliximab†	3 mg/kg 8-week interval	2.25 mg/kg 8-week interval	1.5 mg/kg 8-week interval	Stop TNFi

*Full authorised TNFi dose, used before baseline: adalimumab/certolizumab pegol 40 mg/200 mg every other week; etanercept 50 mg every week; golimumab 50 mg every month; infliximab 3 mg/kg every 8 weeks.
†In our local protocol, in line with rheumatoid arthritis, standard infliximab dose is started at 3 mg/kg every 8 weeks for PsA and axSpA, instead of the registered 5 mg/kg every 6 weeks (for axSpA).
axSpA, axial spondyloarthritis; PsA, psoriatic arthritis; TNFi, tumour necrosis factor inhibitors; T2T, treat-to-target.

Flare definition

Flare was defined for PsA by a current PASDAS >3.2 or increase of ≥0.8[17], and for axSpA as a current ASDAS≥2.1 or increase of ≥0.9 points.[18] For both diseases, a flare was also noted when an important worsening of mBSA or active extra-musculoskeletal symptoms (as judged by the treating rheumatologist) occurred. Clear cut-off values for important worsening are lacking for mBSA and treatment was adjusted as judged by the treating rheumatologist and patient in clinical practice.

Assessments

Disease activity was measured at every visit by PASDAS (0 to ≈10) for PsA and ASDAS (0.6–6.3) for axSpA. Adverse events

(AEs) and serious AEs (SAEs) were recorded and graded according to the Common Terminology Criteria for Adverse Events V.5.0. For function the health assessment questionnaire disability index (0–3) and for axSpA the Bath Ankylosing Spondylitis Functional Index (0–10) was used, with higher scores indicating greater disability. Quality of life was measured by using the EuroQol five-dimension scale with three levels (0–1) and the Short Form Health Survey 12 (SF-12) (0–100 for each component score) which consist of a physical and mental component score (0–100), with higher scores indicating better quality of life. For axSpA specifically, quality of life was also scored by the Assessment of SpondyloArthritis international Society Health Index (ASAS-HI) (0–17). For PsA, radiographs of hands and feet were taken at baseline and 12 months. Progression of joint damage was assessed by using the Short Erosion Narrowing Score (SENS) (0–86), with a higher score indicating more joint damage. Sets of radiographs were scored independently and without blinding for allocation by two out of three readers each, with known sequence. For axSpA, sacroiliitis was assessed by radiography of sacroiliac (SI) joints at baseline and scored by using the modified New York criteria (0–4 for each joint), with a higher score depicting more damage. Radiographs of the SI-joints were graded in known sequence by two rheumatologists and dependent on this grading sacroiliitis was diagnosed (yes or no). Any disagreements were resolved by consensus. In axSpA it is predominantly of importance to assess sacroiliitis for the fulfilment of the supporting ASAS classification criteria. We decided not to assess radiographic progression as a secondary outcome because of limited effect of TNFi on this outcome in axSpA especially within our follow-up period, since an extensive review demonstrated that radiographic changes only occur after 2 years of follow-up.[19]

Outcomes

The primary outcome of this study was the difference in proportion of patients in LDA (PASDAS ≤3.2 and BSA ≤3% of the skin (PsA), ASDAS <2.1 (axSpA) and an absence of active extra-musculoskeletal symptoms) between the tapering and no-tapering group at 12 months follow-up, compared with the prespecified NI margin of 0.2 (20%). Secondary outcomes at 3, 6, 9 and 12 months were differences in the TNFi use between both groups, by calculating the mean percentage of daily defined dose (%DDD); efficacy measured by change in the mean PASDAS for PsA and ASDAS for axSpA between both groups; start or escalation of concomitant csDMARDs, oral or intra-articular/intramuscular glucocorticoids and NSAIDs; flares and infections; functioning; and quality of life. At 12 months, differences were assessed in bDMARD drug retention between both groups; the percentage of patients in the tapering group still on a tapered dose and the percentage who had discontinued their TNFi altogether. Additionally, progression of joint damage was assessed at 12 months between both groups (PsA only).

Statistical analyses

The sample size and choice for NI margin have been extensively discussed in a previous article.[17] The sample size was based on a Bayesian analysis where NI would be claimed if the lower limit of the Bayesian 95% credibility interval of the difference lies above 20%. A minimum of 95 patients was needed to have 80% power to claim NI, taking dropout into account, for further details see online supplemental appendix 2. Our primary Bayesian analyses were done per-protocol (PP) and in addition on an intention-to-treat (ITT) basis. For PP analyses, we included all patients in the tapering group that attempted at least one dose optimisation step and all patients in the no-tapering group who did not attempt dose optimisation, unless when medically required such as in the case of adverse events or contraindications. Descriptive statistics included mean and SD, median (p25–p75) or frequencies/percentages depending on the type of distribution of the data. Continuous data and categorical data were compared between arms using an unpaired t-test or Mann-Whitney U test and χ^2 test (cumulative incidences). Differences in (serious) AEs were presented by 95% CIs and Poisson regression (incidence densities) was used. Analysis of variance was used for representation of radiographic results such as the smallest detectable difference and smallest detectable change (SDC).[20] For exclusion and dropout, numbers and reasons were reported to ensure internal validity. All data were registered in patients' electronic health record and entered anonymously in an electronic database (Castor EDC) and subsequently exported to Stata (V.13.1) for statistical analyses.

RESULTS

Patients

We enrolled 122 patients, who were allocated to the tapering (N=81 (PsA, N=42; axSpA, N=39)) or no-tapering group (N=41 (PsA, N=22; axSpA, N=19)). Baseline characteristics were similar between both groups (table 2), except for csDMARD use, sex and extend of joint involvement in PsA (see online supplemental table 3). Medication use was similar between both groups with adalimumab being the most frequently used TNFi. One visit at 9 months was missing, with no missing values influencing the primary outcome and missings for other outcomes <5%, therefore all analyses were performed on a complete-case basis.

Disease activity and medication use (efficacy)

All patients adhered to the prespecified treatment protocol and according to our definitions, the PP population was therefore the same as the ITT population (figure 1). Our primary Bayesian analysis showed that the proportion of patients in LDA at 12 months was 69% for the tapering and 73% for the no-tapering group: adjusted difference 5% (Bayesian 95% credible interval (CI): −10% to 19%) confirming NI (figure 2). See online supplemental tables 2 and 3 for the Bayesian sensitivity analyses of proportion of LDA for diseases separately and for baseline imbalances. The mean %DDD was 53% (95% CI (44% to 63%)) for the tapering and 91% (95% CI (85% to 97%)) for the no-tapering group at month 12. Mean disease activity and mean percentage of the TNFi dose during each timepoint (3, 6, 9 and 12 months) are shown in figure 3 and online supplemental tables 4-6. The percentage of patients with PsA meeting MDA during each time point is shown in online supplemental table 7. The cumulative incidence of start or escalation of concomitant medication was higher in the tapering group, and significantly so for NSAID use: csDMARDs (only for PsA): 1 (2%) versus 1 (5%) (p=0.64); NSAIDs: 44 (54%) versus 10 (24%) (p=0.002); glucocorticoids intramuscular: 24 (30%) versus 7 (17%) (p=0.15); glucocorticoids intra-articular: 12 (15%) versus 3 (7%) (p=0.66); glucocorticoids oral: 3 (4%) versus 2 (5%) (p=0.29) (see online supplemental table 8 for additional information). Additional sensitivity analyses per diagnosis showed slightly more NSAIDs use in the tapering group compared with the no-tapering group: 21 (50%) versus 5 (23%) (p=0.035) for PsA and 23 (59%) versus 5 (26%) (p=0.019) for axSpA. For glucocorticoid use was this respectively: 12 (29%) versus

Table 2 Baseline characteristics of T2T strategy treated patients with PsA and axSpA with or without tapering

Characteristic	T2T with tapering (N=81)	T2T without tapering (N=41)
Diagnosis, n (%)		
PsA	42 (52)	22 (54)
axSpA	39 (48)	19 (46)
Female, n (%)	28 (35)	20 (49)
Age in years at inclusion, mean (SD)	50 (14)	52 (15)
Disease duration at inclusion, years, median (IQR)	11 (5–21)	12 (5–21)
Rheumatoid factor positivity, n (%) - (64/64 PsA)	3 (7)	1 (5)
Anti-CCP positivity, n (%) - (64/64 PsA)	0 (0)	1 (5)
HLA-B27 positivity, n (%) - (58/58 axSpA)	34 (87)	18 (95)
CASPAR criteria, n (%)	34 (81)	17 (77)
ASAS criteria, n (%)	35 (90)	17 (89)
Concomitant psoriasis, n (%)	39 (48)	18 (44)
Concomitant IBD, n (%)	4 (5)	2 (5)
BMI (kg/m^2), mean (SD) - (121/122)	27 (4)	26 (4)
Monoarticular/oligoarticular as PsA type, n (%) - (64/64 PsA)	27 (64)	7 (32)
Erosive disease, n (%) - (64/64 PsA)	13 (31)	8 (36)
Sacroiliitis on radiographic imaging, n (%) - (58/58 axSpA)	25 (64)	11 (58)
Disease activity, mean (SD)		
PASDAS - (64/64 PsA)	1.60 (1.26)	1.63 (0.98)
ASDAS - (57/58 axSpA)	1.34 (0.87)	1.21 (0.61)
Number of previous bDMARD, n (%)		
0	61 (75)	26 (63)
1	14 (17)	13 (32)
≥2	6 (7)	2 (5)
Duration of current bDMARD use, years, median (IQR)	2 (1–6)	2 (2–7)
Current bDMARD use, n (%)		
Adalimumab	62 (77)	28 (68)
Etanercept	10 (12)	6 (15)
Certolizumab pegol	2 (2)	1 (2)
Golimumab	2 (2)	1 (2)
Infliximab	5 (6)	5 (12)
Current csDMARD use, n (%)		
None	63 (78)	31 (76)
Methotrexate	9 (11)	6 (15)
Hydroxychloroquine	0 (0)	1 (2)
Leflunomide	6 (7)	3 (7)
Sulfasalazine	2 (2)	0 (0)
Azathioprine	1 (1)	0 (0)
Current NSAID use, n (%)	26 (32)	14 (34)

Anti-CCP, anti–cyclic citrullinated peptide; ASAS, Assessment of SpondyloArthritis international Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; axSpA, axial spondyloarthritis; bDMARD, biological disease modifying anti-rheumatic drug; BMI, body mass index; CASPAR, Classification Criteria for Psoriatic Arthritis; csDMARD, conventional synthetic DMARD; HLA-B27, human leukocyte antigen B27 ; IBD, inflammatory bowel disease; NSAID, non-steroidal anti-inflammatory drug; PASDAS, Psoriatic Arthritis Disease Activity Score; PsA, psoriatic arthritis; T2T, treat-to-target.

4 (18%) (p=0.13) (intramuscular); 10 (24%) versus 2 (9%) (p=0.28) (intra-articular); 2 (5%) versus 2 (9%) (p=0.38) (oral) for PsA and 12 (31%) versus 3 (16%) (p=0.34) (intramuscular); 2 (5%) versus 1 (5%) (p=0.69) (intra-articular); 1 (3%) versus

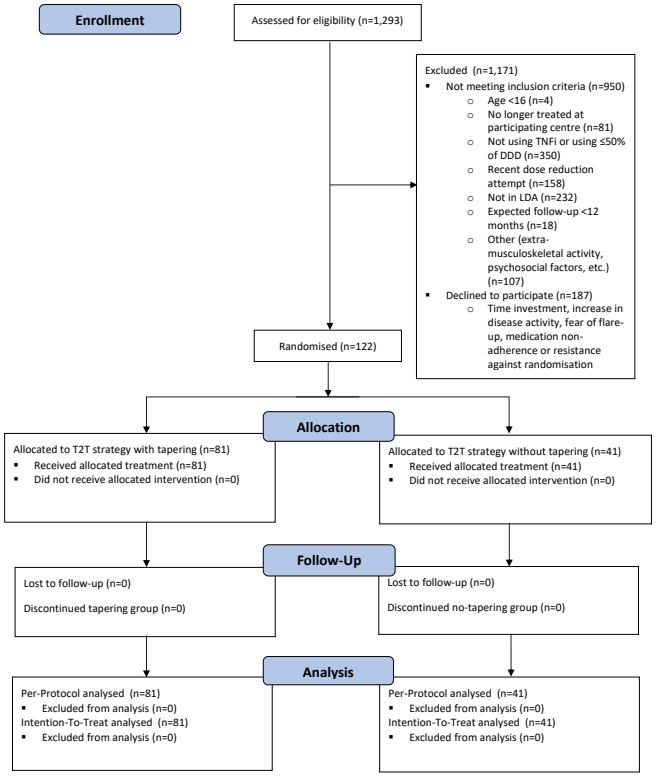

Figure 1 Flow diagram regarding enrolment, randomisation to a T2T strategy with or without tapering, follow-up and per-protocol and intention-to-treat analyses of patients with PsA and axSpA in the DRESS-PS study. axSpA, axial spondyloarthritis; DDD, daily defined dose; DRESS-PS, Dose REduction Strategy Study in Psoriatic arthritis and axial Spondylartritis; LDA, low disease activity; PsA, psoriatic arthritis; TNFi, tumour necrosis factor inhibitors; T2T, treat-to-target.

0 (0%) (p=0.48) (oral) for axSpA. The cumulative incidence of flare was 85% in the tapering and 78% in the no-tapering group (p=0.32). At 12 months, of the patients in the tapering group, 58/81 (72%) patients remained tapered, of whom 23/58 (28%

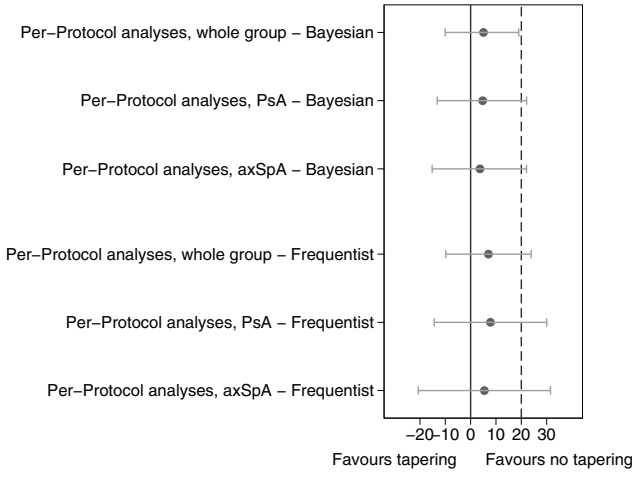

Figure 2 Difference in proportion of LDA according to Bayesian and frequentist per-protocol analyses with a non-inferiority margin of 20%. Differences in proportion of LDA are reported with point estimates and the corresponding 95% CIs. The dotted line represents the non-inferiority margin of 20% (see online supplemental table 1). axSpA, axial spondyloarthritis; LDA, low disease activity; PsA, psoriatic arthritis.

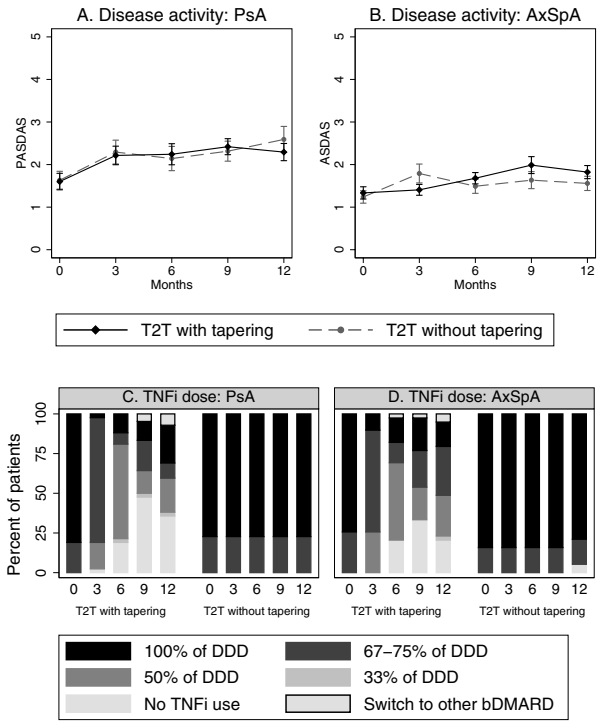

Figure 3 Mean disease activity and %DDD of T2T strategy treated patients with PsA (A and C) and axSpA (B and D) with or without tapering at baseline, 3, 6, 9 and 12 months (per-protocol/intention-to-treat population). Disease activity was measured by the PASDAS for PsA and ASDAS for axSpA. The disease activity is displayed as a mean with their corresponding 95% CI. Both the disease activity and percent of patients with their corresponding %DDD are displayed at each time point. ASDAS, Ankylosing Spondylitis Disease Activity Score; axSpA, axial spondyloarthritis; bDMARD, biological disease modifying anti-rheumatic drug; %DDD, percentage of daily defined dose; PASDAS, Psoriatic Arthritis Disease Activity Score; PsA, psoriatic arthritis; TNFi, tumour necrosis factor inhibitors; T2T, treat-to-target.

of the total group) were able to discontinue their TNFi. Another 23/81 (28%) of the patients could not taper of whom 18/23 (22% of the total group) were reinstalled on 100% of their TNFi dose and 5/23 (6% of the total group) patients switched their TNFi to another bDMARD due to AEs (N=1) or loss of LDA (N=4). In the no-tapering group, one patient discontinued TNFi therapy due to adverse events and did not switch to another bDMARD.

Safety

For SAEs similar results were seen between both groups, with the occurrence of nine SAEs in total (table 3 and online supplemental tables 9 and 10) and no deaths.

Function, quality of life and radiographic outcomes

Mean function and quality of life did not differ significantly between both groups at any time point (table 4 and online supplemental table 11 for diseases separately). In PsA, for the tapering group the median SENS was 4 (IQR, 0.75–11) at baseline and 4.25 (IQR, 1.25–13) at follow-up. For the no-tapering group this was respectively, 7.25 (IQR, 2.25–16.25) and 8 (IQR, 2.25–16.75). For the median erosion score and joint narrowing between both groups, see table 5. The SDC was 1.5. The distribution of progression was similar in both groups apart from a few very slightly higher progressors in the tapering group (table 5 and online supplemental figure 1).

DISCUSSION

Our results indicate that a T2T tapering strategy is an effective and safe alternative to a T2T full dose continuation strategy in patients with PsA and axSpA with stable LDA using TNFi. The strategy resulted in non-inferior disease control, and a sizeable reduction in TNFi use.

Our findings seem to be in line with other studies on T2T tapering strategies with biologicals in different diseases, although outcomes vary, depending on the level of T2T execution and the primary outcome. In the DRESS study in RA, NI was shown for occurrence of major flare and disease activity in patients with RA,[9] although in the smallerSTRASS study tapering showed to be somewhat inferior, possibly due to suboptimal T2T execution.[21] In the psoriasis CONDOR study, NI was demonstrated numerically for the secondary outcome Dermatology Life Quality Index score, but not for the primary outcome Psoriasis Area and Severity Index score.[22] The NI margin for the latter outcomes might well have been too stringent, emphasising the importance for the correct choice of NI margin.

Although the treatments for several inflammatory diseases are similar, differences in ease of monitoring or consequences of flaring influence the feasibility of the T2T strategies. A T2T tapering strategy in psoriasis is conceptually easiest to monitor, assess and treat with visible improvement after treatment adaptation and without risk of damage from this non-scarring disease. T2T tapering strategies in PsA and axSpA seems likewise relatively safe and easy to monitor. In comparison, in IBD these strategies may be much more challenging as monitoring disease activity is harder and consequences of flare may be more severe, potentially causing complications such as fistulas and even bowel surgery.[23]

Strengths of our study include the high internal validity due to our randomised design, inclusion of the intended number of participants with nearly 40% of eligible patients participating in our trial, and good data integrity with no missing data for our primary outcome. Protocol adherence was high, shown by all patients in the tapering group and no patients in the no-tapering group initiating tapering. This also illustrates the acceptability of the treatment strategy for patients and their care providers. The choice for a Bayesian instead of a frequentist approach has had the advantage that adequate precision could be attained with less patients in a smaller time frame, because priors could be based on knowledge from earlier studies in a comparable disease. Frequentist sensitivity analyses showed that the prior did not impact the point-estimate. Lastly, generalisability seems good, as we used broad inclusion criteria, and implemented T2T using readily available measures.[24]

Potential limitations of our study are; first, the open-label nature, potentially causing nocebo effects and incorrect attribution resulting in a perception of a higher disease activity status and flares because of tapering. We expect this should have led to a bias in the conservative direction (towards inferiority), but cannot exclude a bias towards the desired outcome (towards non-inferiority). However, the open nature of our trial is more generalisable, as the communication to patients is more akin to tapering in clinical care. Furthermore, we combined both subtypes of spondyloarthritis, with the risk that the effect of tapering may differ between patients with PsA and axSpA, but sensitivity analyses showed that the effect did not differ between both diseases. Of note, the outcome of NI of the T2T tapering

Table 3 Occurence of (serious) adverse events with adjusted difference in T2T strategy treated patients with PsA and axSpA with or without tapering

	T2T strategy with tapering (N=81)	T2T strategy without tapering (N=41)	Incidence rate ratio (IRR) or relative risk (RR)
Any adverse event			
Number of events:	176	86	
Incidence rate (events/patient-year) (95% CI), IRR	2.18 (1.88 to 2.53)	2.09 (1.69 to 2.58)	1.04 (0.80 to 1.35)
Cumulative incidence of adverse events:	75	31	
Number of patients Proportion (95% CI), RR	0.93 (0.84 to 0.97)	0.76 (0.60 to 0.87)	1.22 (1.01 to 1.48)
Serious adverse events			
Any serious adverse event			
Number of events:	6	3	
Incidence rate (events/patient-year) (95% CI), IRR	0.07 (0.03 to 0.17)	0.07 (0.02 to 0.23)	1.02 (0.26 to 4.09)
Cumulative incidence of serious adverse events:	6	3	
Number of patients Proportion (95% CI), RR	0.07 (0.03 to 0.16)	0.07 (0.02 to 0.21)	1.02 (0.27 to 3.90)
Adverse events of interest			
Any infection			
Number of events:	85	38	
Incidence rate of any infection (events/patient-year) (95% CI), IRR	1.05 (0.85 to 1.30)	0.92 (0.67 to 1.27)	1.14 (0.78 to 1.67)
Cumulative incidence of infections:	49	24	
Number of patients Proportion (95% CI), RR	0.60 (0.49 to 0.71)	0.59 (0.42 to 0.73)	1.04 (0.77 to 1.41)
Cumulative incidence of infections (grade ≥2):	26	14	
Number of patients Proportion (95% CI), RR	0.32 (0.23 to 0.43)	0.34 (0.21 to 0.50)	0.93 (0.55 to 1.58)
Cumulative incidence of infections (grade 3/4):	1	1	
Number of patients Proportion (95% CI), RR	0.01 (0.00 to 0.09)	0.02 (0.00 to 0.17)	0.54 (0.04 to 7.96)
Any injection reaction			
Number of events:	9	6	
Incidence rate of any injection reaction (events/patient-year) (95% CI), IRR	0.11 (0.06 to 0.21)	0.15 (0.07 to 0.32)	0.77 (0.27 to 2.16)
Cumulative incidence of injection reactions:	9	6	
Number of patients Proportion (95% CI), RR	0.11 (0.06 to 0.20)	0.15 (0.06 to 0.30)	0.77 (0.30 to 2.00)

Comparison of intervention group to control group. Of the total 122 patients, 16 patients did not experience an adverse event from any cause during the study period (intervention: 6 and control: 10). No grade 4 or 5 adverse events or deaths unrelated to adverse events occurred during the study period.
axSpA, axial spondyloarthritis; PsA, psoriatic arthritis; T2T, treat-to-target.

strategy is not only dependent on the percentage of patients that can taper or stop, but mostly on the implementation of the T2T strategy and the effectiveness of increased or restarted dosing on disease activity. We did not anticipate effect modification between the two closely related diseases and this was confirmed in the analyses stratified by disease. The use of SENS, which is intended for RA instead of PsA, also limits the strength of our conclusions of radiographic progression. Another potential limitation is the fact that we based our T2T on a flare definition that has not been formally validated, as validated flare criteria are absent for PsA and axSpA. However, we did use validated disease activity measures to base the flare criteria on. Also, for axSpA we used the previously determined minimally clinically important worsening[18] and interestingly, our 'guesstimated' minimally clinically important worsening for the PASDAS in PsA of 0.9 turned out to be not that far from the recently determined formally minimal important worsening of 0.7.[25]

A final potential limitation would be suboptimal execution of the T2T tapering or continuation strategy which could jeopardise the study conceptually in three ways. First of all, tapering could have been executed too reluctantly, resulting in a NI outcome, but no to low bDMARD dose reduction. The study would then in fact infer true and valid NI, but the tapering strategy would not provide any other benefits, so this NI would be a moot point. In light of the approximately 40% DDD reduction difference between the strategies this is clearly not the case. It remains possible that a more protocolised T2T tapering strategy would have achieved an even higher reduction of TNFi, although then it also might not have reached NI regarding disease activity. Second, tapering could have been executed well, but T2T could have been done suboptimally. This would have resulted in differences in proportion of patients in LDA between the groups, and the strategy would then not be non-inferior. This was however not seen in our data. Third, tapering and T2T could have been done optimally, but result in the exchange of bDMARDs for other medication such as NSAIDs, glucocorticoids or other DMARDs. This would result in a correct claim of NI, but without the associated benefits in medication use. No relevant increase in use of other DMARDS and glucocorticoids were seen in our data. In

Table 4 Questionnaires of function and health status at baseline, 3, 6, 9 and 12 months in T2T strategy treated patients with PsA and axSpA with (intervention) or without (control) tapering (per-protocol/intention-to-treat population)

	Baseline		3 months			6 months			9 months			12 months		
Function	Intervention	Control	Intervention	Control	95% CI difference	Intervention	Control	95% CI difference	Intervention	Control	95% CI difference	Intervention	Control	95% CI difference
HAQ-DI	0.35 (0.47)	0.39 (0.51)	0.38 (0.47)	0.45 (0.54)	(−0.11 to 0.26)	0.32 (0.44)	0.47 (0.53)	(−0.03 to 0.33)	0.42 (0.55)	0.46 (0.52)	(−0.17 to 0.25)	0.39 (0.51)	0.53 (0.58)	(−0.07 to 0.34)
BASFI	2.59 (2.32)	2.03 (1.86)	2.61 (2.31)	2.48 (1.93)	(−1.37 to 1.11)	2.76 (2.29)	2.50 (2.05)	(−1.50 to 0.98)	3.15 (2.58)	2.58 (2.08)	(−1.93 to 0.79)	3.01 (2.38)	2.17 (2.04)	(−2.11 to 0.44)
Health status	**Intervention**	**Control**	**Intervention**	**Control**	**95% CI difference**	**Intervention**	**Control**	**95% CI difference**	**Intervention**	**Control**	**95% CI difference**	**Intervention**	**Control**	**95% CI difference**
EQ-5D-3L	0.81 (0.13)	0.81 (0.15)	0.80 (0.17)	0.80 (0.16)	(−0.07 to 0.06)	0.81 (0.14)	0.80 (0.18)	(−0.07 to 0.05)	0.81 (0.17)	0.78 (0.22)	(−0.10 to 0.04)	0.79 (0.19)	0.78 (0.19)	(−0.08 to 0.06)
SF-12 PCS	44 (7.5)	44 (6.6)	43 (7.1)	43 (6.7)	(−2.90 to 2.41)	44 (6.8)	42 (7.2)	(−4.61 to 0.66)	44 (7.4)	42 (6.6)	(−4.03 to 1.47)	44 (7.0)	43 (7.0)	(−3.82 to 1.49)
SF-12 MCS	53 (10)	55 (7.8)	52 (10)	52 (9.8)	(−4.15 to 3.39)	52 (11)	54 (9.4)	(−2.47 to 5.42)	53 (9.7)	53 (8.8)	(−3.74 to 3.46)	52 (11)	53 (8.8)	(−3.68 to 4.06)
ASAS-HI	4.70 (3.27)	3.50 (2.79)	3.82 (3.02)	4.56 (2.86)	(−0.96 to 2.46)	4.72 (3.81)	5.12 (3.71)	(−1.80 to 2.60)	4.57 (3.20)	4.67 (4.19)	(−1.95 to 2.14)	4.35 (3.47)	4.83 (3.71)	(−1.54 to 2.51)

All values are expressed as a mean (SD); Health Assessment Questionnaire-Disability Index (HAQ-DI), ranges from 0 to 3, with higher scores indicating lower functioning. Not all patients fulfilled the HAQ-DI score (T0:1, T9:1, T12:1 missing); Bath Ankylosing Spondylitis Functional Index (BASFI), range 0–10 with a higher score indicating a higher degree of functional limitations. The BASFI was only assessed for patients with axSpA (intervention: 39 and control: 19), not all patients fulfilled the BASFI (T0:1, T3:2 missing); EuroQol five-dimension scale with three levels (EQ-5D-3L) ranges from 0 to 1, with a with higher scores indicating a better health status. Of the EQ-5D-3L score, not all patients fulfilled the EQ-5D-3L score (T0:1, T9:1 missing); Short Form Health Survey 12 (SF-12) consist of a physical and mental component score (PCS and MCS), range 0–100 for each component score with a higher score indicating better health status. Not all patients completed the SF-12 (T0:2, T9:1 missing); Assessment of SpondyloArthritis International Society-Health Index (ASAS-HI) ranges from 0 to 17, with a higher score indicating lower health status. The ASAS-HI was only assessed for patients with axSpA (intervention: 39 and control: 19), of the in total 58 patients with axSpA, not all patients fulfilled the ASAS-HI (T0:2, T3:3, T6:2, T9:3, T12: 1 missing).
axSpA, axial SpondyloArthritis; PsA, Psoriatic Arthritis; T2T, Treat-to-Target.

Table 5 Radiographic outcomes in T2T strategy treated patients with PsA with or without tapering

	T2T with tapering (N=42)	T2T without tapering (N=22)	P value
Progression >SDC (1.54), n (%)	5 (13)	2 (10)	0.78
Progression >0.5, n (%)	17 (43)	7 (35)	0.58
Mean progression, mean (SD)	0.8 (1.4)	0.52 (0.82)	0.33*
Median progression, median (IQR)	0.5 (0–1)	0.5 (0–1)	0.77†

Not all patients had complete radiographs (intervention: 2 and control: 2 missing at 12 months).
*Welch T-test.
†Wilcoxon rank-sum test.
PsA, psoriatic arthritis; SDC, smallest detectable change; T2T, treat-to-target.

addition, NSAID increase was much lower than the bDMARD decrease and often temporary.

We chose the PASDAS as our disease activity measurement tool for PsA because first it is a continuous composite disease index with parametric distribution that best fitted our study design. Also, it contains almost all domains necessary, and has sufficiently been validated. It has the advantage over, for example, MDA criteria that it is a continuous outcome, and that different thresholds can be used. However, this measure has some drawbacks such as the inclusion of the functional (dis)ability domain (SF-12) which is different from the construct of actual disease activity.[26] This makes it prone to overestimating disease activity, since functional ability can also be affected by many other factors. In addition, the SF-12 requires an annual license fee, which makes it less suited to use in clinical practice. Finally, the calculation of the PASDAS is quite cumbersome, which could be more problematic for usage in clinical practice where parametric distribution is less important. Indeed, other composite indices than the PASDAS are available, such as the Disease Activity in Psoriatic Arthritis, MDA criteria, the Composite Psoriatic Disease Activity Index, the Arithmetic Mean of the Desirability Function and the GRAppa Composite scorE project, but they have their specific drawbacks also. However, all things considered, the required variables for all composite disease indices are largely comparable, therefore no major difference in workload is to be expected and so far no other studies compared the validity of T2T for any proposed composite disease indices in PsA, in an RCT or clinical care. The PASDAS has proven to be feasible both as T2T instrument as well as primary trial outcome. A final study limitation could be the limited follow-up period. We do think 12 months follow-up is sufficient to capture (primary and second order) effects of tapering, however, we anticipate an observational extension study to provide more insights in the long-term effects of this T2T strategy.

CONCLUSION

In conclusion, our study shows that a stepwise T2T strategy with tapering is non-inferior to a T2T strategy without tapering with regard to maintenance of LDA at 12 months in PsA and axSpA. Furthermore, TNFi use was strongly reduced, as the majority of patients were able to maintain LDA with a lower dose, and about a quarter were able to discontinue their TNFi. Implementing T2T tapering strategies into practice will reduce TNFi use, and thereby potentially AEs, patient burden, and costs.

Acknowledgements We thank all the patients who were willing to participate in this study and the rheumatologists in the Sint Maartenskliniek Nijmegen and

Woerden for participation in patient recruitment and data collection; SR van de Plassche, AH Verkerk and M den Broeder for data collection and entering; M Roelofs, I Cillessen, C Kleinveld and I van Neste for aiding with study coordination; D van Aggelen, D Rotteveel and L Schiersbergen for aiding with laboratory implementation and procedures; BJF van de Bemt and M Flendrie for being part of the data safety monitoring board.

Contributors CM, NdB, FHJvdH, EAMM, ST, DvdH, LMV and AAdB contributed to study design. CM was responsible for data collection. CM, NdB and ST contributed to data analyses. All authors contributed to data interpretation and writing of the report. CM accepts full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish.

Funding This study received funding from ReumaNederland, a health fund covering different topics on rheumatism, the Netherlands.

Competing interests DvdH has received consulting fees from AbbVie, Bayer, BMS, Cyxone, Eisai, Galapagos, Gilead, GlaxoSmithKline, Janssen, Lilly, Novartis, Pfizer and UCB Pharma and is director of Imaging Rheumatology. AAdB has received research grants (to the institution) from AbbVie, Lilly, Novartis, Sanofi, Galapagos and Gilead. The remaining authors have declared no conflicts of interest.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Commissie Mensgebonden Onderzoek Regio Arnhem-Nijmegen. File number: 2018-4538. NL-number: NL66181.091.18. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The data underlying this article will be shared on reasonable request to the corresponding author.

ORCID iDs
Celia AJ Michielsens http://orcid.org/0000-0001-8625-034X
Nathan den Broeder http://orcid.org/0000-0001-7126-2209
Elien AM Mahler http://orcid.org/0000-0002-6833-3157
Désirée van der Heijde http://orcid.org/0000-0002-5781-158X

REFERENCES

1 Gossec L, Smolen JS, Ramiro S, *et al*. European League against rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. *Ann Rheum Dis* 2016;75:499–510.
2 Ward MM, Deodhar A, Akl EA, *et al*. American College of Rheumatology/Spondylitis association of America/Spondyloarthritis research and treatment network 2015 recommendations for the treatment of ankylosing spondylitis and Nonradiographic axial spondyloarthritis. *Arthritis Rheumatol* 2016;68:282–98.
3 Hewlett S, Haig-Ferguson A, Rose-Parfitt E, *et al*. Dose reduction of biologic therapy in inflammatory arthritis: a qualitative study of patients' perceptions and needs. *Musculoskeletal Care* 2019;17:63–71.
4 Singh JA, Cameron C, Noorbaloochi S, *et al*. Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis. *Lancet* 2015;386:258–65.
5 Vinson D, Molet-Benhamou L, Degboé Y, *et al*. Impact of tapering targeted therapies (bDMARDs or JAKis) on the risk of serious infections and adverse events of special interest in patients with rheumatoid arthritis or spondyloarthritis: a systematic analysis of the literature and meta-analysis. *Arthritis Res Ther* 2020;22:97.
6 Minozzi S, Bonovas S, Lytras T, *et al*. Risk of infections using anti-TNF agents in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: a systematic review and meta-analysis. *Expert Opin Drug Saf* 2016;15:11–34.
7 van Heuckelum M, Mathijssen EG, Vervloet M, *et al*. Preferences of patients with rheumatoid arthritis regarding disease-modifying antirheumatic drugs: a discrete choice experiment. *Patient Prefer Adherence* 2019;13:1199–211.
8 Verhoef LM, Tweehuysen L, Hulscher ME, *et al*. bDMARD dose reduction in rheumatoid arthritis: a narrative review with systematic literature search. *Rheumatol Ther* 2017;4:1–24.
9 van Herwaarden N, van der Maas A, Minten MJM, *et al*. 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. *BMJ* 2015;350:h1389.
10 Coates LC, Pillai SG, Tahir H, *et al*. Withdrawing ixekizumab in patients with psoriatic arthritis who achieved minimal disease activity: results from a randomized, double-blind withdrawal study. *Arthritis Rheumatol* 2021;73:1663–72.
11 Cantini F, Niccoli L, Cassarà E, *et al*. Duration of remission after halving of the etanercept dose in patients with ankylosing spondylitis: a randomized, prospective, long-term, follow-up study. *Biologics* 2013;7:1–6.
12 Yates M, Hamilton LE, Elender F, *et al*. Is etanercept 25 Mg once Weekly as effective as 50 Mg at maintaining response in patients with ankylosing spondylitis? A randomized control trial. *J Rheumatol* 2015;42:1177–85.
13 Chen X, Zhang T, Wang W, *et al*. Analysis of relapse rates and risk factors of tapering or stopping pharmacologic therapies in axial spondyloarthritis patients with sustained remission. *Clin Rheumatol* 2018;37:1625–32.
14 Landewé RB, van der Heijde D, Dougados M, *et al*. Maintenance of clinical remission in early axial spondyloarthritis following certolizumab pegol dose reduction. *Ann Rheum Dis* 2020;79:920–8.
15 Landewé R, Sieper J, Mease P, *et al*. Efficacy and safety of continuing versus withdrawing adalimumab therapy in maintaining remission in patients with non-radiographic axial spondyloarthritis (ABILITY-3): a multicentre, randomised, double-blind study. *Lancet* 2018;392:134–44.
16 Gratacós J, Pontes C, Juanola X, *et al*. Non-Inferiority of dose reduction versus standard dosing of TNF-inhibitors in axial spondyloarthritis. *Arthritis Res Ther* 2019;21:11.
17 Michielsens CAJ, Boers N, den Broeder N, *et al*. Dose reduction and withdrawal strategy for TNF-inhibitors in psoriatic arthritis and axial spondyloarthritis: design of a pragmatic open-label, randomised, non-inferiority trial. *Trials* 2020;21:90.
18 Molto A, Gossec L, Meghnathi B, *et al*. An Assessment in SpondyloArthritis International Society (ASAS)-endorsed definition of clinically important worsening in axial spondyloarthritis based on ASDAS. *Ann Rheum Dis* 2018;77:124–7.
19 Boers N, Michielsens CAJ, van der Heijde D, *et al*. The effect of tumour necrosis factor inhibitors on radiographic progression in axial spondyloarthritis: a systematic literature review. *Rheumatology* 2019;58:1907–22.
20 Bruynesteyn K, Boers M, Kostense P, *et al*. Deciding on progression of joint damage in paired films of individual patients: smallest detectable difference or change. *Ann Rheum Dis* 2005;64:179–82.
21 Fautrel B, Pham T, Alfaiate T, *et al*. Step-Down strategy of spacing TNF-blocker injections for established rheumatoid arthritis in remission: results of the multicentre non-inferiority randomised open-label controlled trial (STRASS: spacing of TNF-blocker injections in rheumatoid arthritis study). *Ann Rheum Dis* 2016;75:59–67.
22 Atalay S, van den Reek JMPA, den Broeder AA, *et al*. Comparison of tightly controlled dose reduction of biologics with usual care for patients with psoriasis: a randomized clinical trial. *JAMA Dermatol* 2020;156:393–400.
23 Smits LJT, Pauwels RWM, Kievit W, *et al*. Lengthening adalimumab dosing interval in quiescent Crohn's disease patients: protocol for the pragmatic randomised non-inferiority LADI study. *BMJ Open* 2020;10:e035326.
24 Mulder MLM, den Broeder AA, van Ginneken BTJ, *et al*. Implementing Psoriatic Arthritis Disease Activity Score-guided treat-to-target in psoriatic arthritis routine clinical practice: (im)possible? *Rheumatology* 2019;58:2330–1.
25 Mulder MLM, Bertram AM, Wenink MH, *et al*. Defining the minimal important change (MIC) and meaningful change value (MCV) for the psoriatic arthritis disease activity score (PASDAS) in a routine practice cohort of patients with psoriatic arthritis. *Rheumatology* 2022;33.
26 Landewé RBM, van der Heijde D. Use of multidimensional composite scores in rheumatology: parsimony versus subtlety. *Ann Rheum Dis* 2021;80:280–5.