Disease activity-guided tapering of biologics in patients with inflammatory arthritis: *A pragmatic, randomised, open-label, equivalence trial*

Short running title: The BIODOPT trial

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ABSTRACT

Objectives

To evaluate if disease activity-guided tapering of biologics compared to continuation as usual care enables a substantial dose reduction while disease activity remains equivalent.

Methods

In this pragmatic, randomised, open-label, equivalence trial, adults with rheumatoid arthritis, psoriatic arthritis, or axial spondyloarthritis in low disease activity on stable dose biologics ≥12 months were randomised 2:1. The tapering group prolonged the biologic dosing interval by a disease activity-guided algorithm until flare or withdrawal. The control group maintained baseline biologics but, at the patient's request, a small interval increase was allowed. The co-primary outcome in the intention-to-treat population was met if superiority in ≥50% biologic reduction at 18 months was demonstrated and disease activity was equivalent (equivalence margins ±0.5).

Results

Ninety-five patients were randomised to tapering and 47 to control of which 37% (35/95) vs 2% (1/47) achieved ≥50% biologic reduction at 18 months. The risk difference was statistically significant: 35% (95%CI: 24% to 45%) while disease activity remained equivalent: mean difference 0.05 (95%CI: -0.12 to 0.29). Among other important outcomes was a statistically significant flare risk: tapering group 41% (39/95) vs control group 21% (10/47), risk difference: 20% (95%CI: 4% to 35%). Reassuringly, only 1% (1/95) and 6% (3/47) had persistent flare and needed switch to another biological drug.

Conclusions

Disease activity-guided tapering of biologics in patients with inflammatory arthritis enabled one-third to achieve ≥50% biologic reduction while disease activity between groups remained equivalent. Flares were more frequent in the tapering group but managed with rescue therapy.

Trial registration

EudraCT: 2017-001970-41.

KEY WORDS

Rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis, ankylosing spondylitis, biologic agents, tumour necrosis factor inhibitor, disease activity-guided tapering.

INTRODUCTION

Biological therapies and disease activity-guided monitoring have improved the management of patients with inflammatory arthritis (IA), i.e. rheumatoid arthritis (RA), psoriatic arthritis (PsA), and axial spondyloarthritis (axSpA), as large proportions of patients reach low disease activity (LDA) (1–3). But what is the most appropriate maintenance treatment: continuation of standard dose biologics lifelong or tapering to the lowest possible dose?

In clinical trials, biologic tapering is done as either fixed dose reduction, often in one step e.g., 50% interval prolongation/dose reduction, or disease activity-guided tapering after an algorithm until flare or withdrawal. Fixed dose reduction is more frequently evaluated; the majority of studies have an RA population (4–8), fewer an axSpA population (6,7,9) and limited studies a PsA population (7,10). Disease activity-guided tapering of biologics is generally the more aggressive approach as it allows maximal tapering. Evidence is limited to few randomised, controlled trials (11–13) and some observational study (14–18). Both fixed dose reduction and disease activity-guided tapering seem to allow a considerable biologic dose reduction without persistent disease activity deterioration (5,6,16,18,7–12,14,15). However, the STRASS trial did not observe equivalent disease activity at 18 months (13).

International treatment guidelines recommend to taper biologics in patients with IA in sustained remission (19–21) but not how this should be implemented. The BIOlogical Dose OPTimisation (BIODOPT) trial compares a disease activity-guided tapering algorithm to continuation of biologics as usual care among patients with IA in sustained LDA. The primary aim was to evaluate if the algorithm enabled a ≥50% biologic dose reduction at 18 months while disease activity remained equivalent.

METHODS

Patient and public involvement

Two patient research partners were involved in the initial trial protocol development; one provided additional advice on the intervention burden and approved the trial protocol and participant information.

Study design and participants

This investigator-initiated, pragmatic, multicentre, randomised, open-label, equivalence trial was conducted at four rheumatology outpatient clinics in Denmark. The study complied with the Declaration of Helsinki; approval was obtained from the North Denmark Region Committee on Health Research Ethics (N-20170073), the Danish Medicine Agency (2017091722) and the Danish

Data Protection Agency (2017-194). The trial was registered at EudraCT (2017-001970-41) on December 21, 2017.

The study setting has been described in detail elsewhere (22). Eligible patients were adults diagnosed with RA, PsA (peripheral) or axSpA (including axial PsA) treated with abatacept, adalimumab, certolizumab-pegol, etanercept, golimumab, infliximab, or tocilizumab incl. biosimilars in stable dosage ≥12 months. Other biologic modes of action were not included due to limited use or availability (approval) when the protocol was drafted. Patients treated with oral, intra-articular, or subcutaneous glucocorticoids within the last 12 months were excluded. A revision to allow for inclusion of patients in LDA and not solely remission was approved March 12, 2019. LDA at enrolment was defined as: no swollen joints and 1) RA: Disease Activity Score28-C-Reactive Protein (DAS28-CRP) ≤3.2 (23), 2) PsA: Disease Activity in PSoriatic Arthritis (DAPSA) ≤14 (24), and 3) axSpA: Ankylosing Spondylitis Disease Activity Score (ASDAS) <2.1 (25). Written informed consent was obtained before inclusion. The trial protocol (version 7, December 16, 2017) is available as a supplementary. Supplementary Data S1 provides an overview of important protocol modifications.

Procedures

Patients were randomised 2:1 (tapering:control) stratified by trial site, diagnosis, and biologic failure history (on biologic number ≤2, or ≥3) by a computer-generated allocation sequence in a dedicated electronic case report form in Research Electronic Data Capture (REDCap) (26,27), Supplementary Data S2. A disease activity-guided tapering strategy for biologics was applied to the tapering group; the dosing interval was prolonged approximately 25% every four months (Supplementary Figure S1) until flare or discontinuation except for infliximab which was spaced with two weeks at each infusion as previously described (22). A pragmatic usual care practise was applied to the control group i.e., unchanged biologic dosing interval but, if requested by the patient, a small increase was allowed. Disease activity was monitored every four months during the first year and at 18 months by DAS28-CRP (28) (RA and PsA), or ASDAS (29) (axSpA). Furthermore, enthesitis, dactylitis, skin- and nail psoriasis, uveitis, and symptoms of inflammatory bowel disease (IBD) were assessed for patients with PsA or axSpA.

Flare was defined as: ΔDAS28-CRP >1.2, or ΔDAS28-CRP >0.6 AND current DAS28-CRP ≥3.2 (30) (RA and PsA), or inflammatory back pain AND ΔASDAS ≥0.9 (31) and/or ≥1 swollen joint (axSpA). Patients with symptoms of flare (e.g., increasing arthralgia/inflammatory backpain or swollen joints) who did not fulfil the flare criteria were noted. Patients with flare due to tapering went back to the last effective biologic dosing interval, or if necessary, to standard dose, and could

receive glucocorticoids and/or Non-Steroidal Anti-Inflammatory Drugs. Patients with persistent flare despite step back to standard dose biologic were switched to another biological therapy. Patients with symptoms of flare, who the physician judged to be in LDA, were advised to continue tapering but could remain on the current dosing interval or even go one algorithm step back.

Outcomes

The co-primary outcome was met if superiority in the proportion of patients achieving ≥50% biologic reduction at 18 months was demonstrated and mean disease activity was equivalent (hierarchical order). Thus, the co-primary endpoint reflects the importance of not only achieving a considerable biologic dose reduction with tapering but also maintaining equivalent disease activity. Key secondary outcomes were rates of remission and LDA at 18 months. Other secondary outcomes included changes from baseline to month 18: Health Assessment Questionnaire Disability Index (HAQ-DI), Pain Visual Analogue Scale (VAS), Fatigue VAS, Patient Global Health VAS, Short Form Health Survey 36 (SF-36) version 1.0 physical component summary (PCS) and mental component summary (MCS), Physician Global Health VAS, tender joint count, swollen joint count, and CRP. Harm and safety outcomes were serious adverse events (SAE), serious infections, non-serious infections, cardiovascular events, malignancy, death, uveitis, skin or nail psoriasis flare, IBD flare, and biologic discontinuation due to any adverse event (AE). Furthermore, arthritis flare as well as need for rescue therapy were summarised.

Statistical analyses

The sample size calculation was performed in accordance with the DELTA^2 guideline (32) and based on the primary efficacy endpoint 'disease activity' with an equivalence margin of ±0.5 disease activity points and a requirement of minimum 85% power, Supplementary Data S3.

All analyses were performed and reported in accordance with the pre-specified statistical analysis plan (available as a supplementary) and the 'Consolidated Standards of Reporting Trials' (CONSORT) statements (33,34). The primary analyses were based on Intention to Treat (ITT); i.e., all randomised patients independent of protocol deviations (35). Repeated-measures, linear mixed-effects models were applied to evaluate contrast between groups for continuous outcomes. The fixed factors were: group, diagnosis, biologics failure history, centre, and time point as well as the interaction between group and time. To reduce random variation, the baseline value of the relevant variable was included as a covariate. Missing data was handled indirectly via the mixed-effects model framework (36). Categorical outcomes were analysed using generalised linear models for binomial data; missing data was handled as trial failures. Sensitivity analyses on the primary and

secondary outcomes, which included a per protocol analysis, were performed to explore the robustness of our findings. The per protocol population consisted of patients who adhered to the terms of eligibility, interventions, and scheduled trial visits. Sub-group analyses on disease specific outcomes per IA diagnosis were also performed. To explore potentially relevant effect modifiers, stratified analyses on the co-primary endpoints were performed (37).

Flares were visualised by Kaplan-Meier cumulative incidence curves. Flare rates were assessed with a univariate Cox proportional hazards model; thereafter, a multivariable Cox model evaluated if diagnosis and biologics failure history were potential explanatory variables. Safety and harm outcomes were summarised as number and percentages with an estimate of the between group difference. All analyses were performed in SAS (version 9.4) or STATA (version 16).

RESULTS

Recruitment started in May 2018 and ended in April 2020 due to national implications of the COVID-19 pandemic. Among 204 patients screened for eligibility, 142 patients (69.6%) were enrolled and randomised to the tapering group (n=95) or the control group (n=47), Figure 1. Forty-three percentage (61/142) were diagnosed with RA, 18% (26/142) with PsA and 39% (55/142) with axSpA. Baseline characteristics were well-balanced, Table 1 and Supplementary Table S1. The majority received tumour necrosis factor inhibitors (TNFi), tapering group 93% (88/95) and control group 87% (41/47); the remanding received abatacept or tocilizumab. Patients treated with a non-TNFi were diagnosed with RA, more frequent females, older, had a higher HAQ-DI, and had experienced repeated biologic failure, Supplementary Table S2.

Overall, 94% (134/142) completed the study period, Figure 1. At 18 months, 37% (35/95) of the tapering group and 2% (1/47) of the control group had reduced their biological therapy by ≥50% compared to baseline; the absolute risk difference was statistically significant: 35% (95% confidence interval [95%CI]: 24% to 45%, Table 2). Thus, the first part of the co-primary endpoint was met. As presented in Supplementary Table S3, 34% of patients with RA, 36% of patients with PsA, and 48% of patients with axSpA achieved ≥50% biologic dose reduction at 18 months. However, the difference between IA diagnoses were not statistically significant, axSpA vs RA: 14% (95%CI: -8% to 37%) and axSpA vs PsA: 13% (95%CI: -18% to 43%). Nonetheless, these results must be interpreted with caution as the trial not was powered for analyses per diagnosis.

At 18 months, 27% (26/95) of the tapering group achieved a moderate dose reduction of 25-49% and 11% (10/95) a minor dose reduction <25% compared to 6% (3/47) and 9% (4/47) in the control group. Thus, 75% (71/95) in the tapering group and 17% (8/47) in the control group were able to taper their biologics. Total biologic withdrawal was possible for 15% (14/95) in the tapering group.

Disease activity was equivalent between the two groups at 18 months, mean difference 0.08, (95%CI: -0.12 to 0.29), as the 95%CI was within the prespecified equivalence margins of ±0.5, Table 2. Thus, the second part of the co-primary endpoint was also met. Figure 2 and Supplementary Figure S2 illustrates disease activity by diagnosis during the study period. At 18 months, no statistically significant difference in disease activity per diagnosis were observed between the tapering group and the control group: RA -0.04 (95%CI: -0.49 to 0.41), PsA -0.09 (95%CI: -0.56 to 0.38), and axSpA 0.24 (95%CI: -0.19 to 0.67). However, the trial is not powered for analyses per diagnosis; therefore, the results must be interpreted with caution.

As presented in Table 2, no difference in rates of remission or LDA were observed. Of noteworthy secondary findings, the tapering group had a slightly higher increase in Pain VAS between baseline and 18 months compared to the control group, mean difference: 4.7 mm (95%CI: 0.01 to 9.3). Moreover, CRP had increased slightly more in the tapering group between baseline and 18 months compared to the control group, mean difference: 2.4 mg/L (95%CI: 0.2 to 4.7). On the contrary, a small increase in tender joint count was observed in the control group compared to the tapering group, mean difference: -0.6 (95%CI: -1.2 to 0.00). Sensitivity analyses on the primary and secondary outcomes showed similar results (Supplementary Table S4-S5) with the exception of Pain VAS in the per protocol population as the difference no longer was statistically significant: mean difference 3.8 (95%CI: -0.7 to 8.4).

The only potential effect modifier for the co-primary endpoints was sex as females in the tapering group had lower disease activity at 18 months compared to the control group whereas the opposite was seen for males, between sub-group difference: -0.49 (95%CI: -0.97 to 0.001), Supplementary Table S6-7. Interestingly, baseline remission or LDA status was not an effect modifier. However, conclusions must be made with caution as the trial not was powered for the sub-group analyses.

Statistically significant more flares were observed in the tapering group: fulfilment of the flare criteria (41% [39/95] vs 21% [10/47], mean difference 20% [95%CI: 4% to 35%]) and symptoms of flare when not fulfilling the flare criteria (40% [38/95] vs 13% [6/47], mean difference: 27% [14% to 41%]), Table 3. Flares were treated with rescue therapy; only one patient (1%) in the tapering group and three patients (6%) in the control group had persistent flare. These patients were switched to another biological agent which managed the flare for the patient in the tapering group whereas one patient in the control group had persistent flare despite the switch and was switched to a third biological drug. The additional two patients switched therapy shortly before or at the 18 months visit; thus, data on flare reversibility was not available. Figure 3 illustrates the cumulative incidence of flare. Hazard ratios (HR) were high for all flare definitions: 1) Fulfilling flare criteria: crude HR 2.19 (95%CI: 1.09 to 4.40), 2) Symptoms of flare: crude HR 3.92 (95%CI: 1.66 to 9.30), and 3)

Total flares: crude HR 3.84 (95%CI: 2.22 to 6.65). Adjustment for diagnosis, and biologics failure history only had a small effect on the estimates: 1) Fulfilling flare criteria: adjusted HR 2.15 (95%CI: 1.07 to 4.33), 2) Symptoms of flare: aHR 4.05 (95%CI: 1.70 to 9.61), and 3) Total flares: aHR 3.84 (95%CI: 2.22 to 6.65).

AE and SAE were similar between the two groups, Table 3. Non-serious infections were the most frequent AE and observed in 55% (52/95) vs 51% (24/47). SAE in the tapering group were: ocular thrombosis (n=1), breast cancer (n=1), hospitalised due to stomach pain (n=1), hospitalised due to chest pain (n=1), and hospitalised due to surgery (n=1). SAE in the control group were: pulmonal infection (n=1), erysipelas (n=1), diagnosed with heart failure (n=1), paresthesia in the face (n=1), and hospitalised due to symptoms of stroke (n=1). No deaths occurred.

DISCUSSION

The BIODOPT trial demonstrated that a disease activity-guided tapering algorithm for biologics is an effective tool to achieve a substantial dose reduction in patients with IA while maintaining low disease activity. Sub-group analyses identified sex as a potential effect modifier as females in the tapering group had lower disease activity at 18 months compared to the control group whereas the opposite was seen for males. Just as important, baseline remission or LDA was not an effect modifiers; thus, providing evidence to the debate on when biologic tapering should be initiated (38,39). However, as the sub-group analyses are insufficiently powered conclusions are made with caution.

Strengths to the BIODOPT trial are: investigator-initiated, no pharmaceutical industry involvement, randomised design, comparable group monitoring, and few patients lost to follow-up. Exclusion criteria were kept to a minimum to allow inclusion of a broad spectrum of patients e.g., previous biologic failure, various lengths of LDA, and various co-morbidities. Thus, the study population is judged to resemble the real-life outpatient population. Another strength is the tapering strategy which easily can be implemented in routine care.

Results from BIODOPT are in line with previous trials evaluating disease activity-guided tapering of biologics as flare rates were high but resolved with rescue therapy and only few patients had persistent flare (11–16). In BIODOPT, 75% of the tapering group was able to reduce their biological therapy; thus, comparable to previously findings: 52-75% (11–16). Equivalent disease activity at 18 months was observed in BIODOPT. Similarly, low disease activity was maintained after disease activity-guided tapering in the majority of previous trials (11,12,14–18); however, STRASS reported non-equivalent disease activity at 18 months (13).

Recent meta-analyses did not find any statistically significant impact of biologic or janus kinase inhibitor (JAKi) tapering versus continuation in patients with RA or axSpA when evaluating serious

infection, SAE, malignancy, cardiovascular disease, or death (6,40). The BIODOPT safety rapports support these findings. Moreover, no increased risk of persistent flare or of flare in nail psoriasis, skin psoriasis, uveitis, or symptoms of IBD were observed; an aspect of great value for physicians and patients.

An equivalence approach for the co-primary endpoint 'disease activity' was chosen to allow for a two-sided testing of the research hypothesis. Potentially, tapering could improve patient satisfaction and quality of life as the disease is controlled with less drug doses (41) which could result in lower Patient Global Health VAS scores; thereby, lower disease activity. However, as the sample size not was met, a non-inferiority approach, which requires fewer participants, would have been more optimal. Attempts to reach target sample size was made by including additional sites and enrolment of patients in LDA. The latter based on evidence from Tweehuysen et al. where baseline disease activity not was found to be an effect modifier for successful tapering of biologics in patients with RA (38). Our study supports this conclusion, as sub-group analyses not found any statistically significant difference between patients in baseline remission or LDA when evaluating the primary efficacy outcomes (Supplementary Table 6-7). However, the sub-group analyses are insufficiently powered; therefore, conclusions are made with caution.

BIODOPT is not a strict equivalence study as the first part of the co-primary endpoint aims for superiority and the second for equivalence. As pre-specified in the SAP, the primary analyses were performed as ITT and a sensitivity analysis performed as per protocol was conducted to assess the implication of protocol violations (Supplementary Table S5). Similar results were observed with ITT and per protocol analyses; thus, strengthening the robustness of our findings.

Another possible limitation to discuss is the open-label design which potentially could lead to bias. However, as tapering is expected to increase the risk of flare, potential bias due to an unblinded trial design would most likely result in overestimation of flare in the tapering group; thereby, underestimating the proportion of patients able to taper their biological therapy.

The BIODOPT study population consisted of patients with different IA diagnoses which was chosen to evaluate the tapering algorithm in a patient population similar to the one most rheumatologists see in daily clinical practise. However, pooling data across IA diagnoses could introduce noise and complicate interpretation of results with the risk of overlooking important findings in one sub-group. Nonetheless, as presented in Supplementary Table S1, S3 and S6-S7, no substantial differences per diagnosis were identified but as the sub-group analyses not are adequately powered caution must be applied.

PsA-/axSpA-specific biologics (e.g., secukinumab, ixekizumab or JAKi) were not included due to limited use or availability (approval) when the protocol was drafted. Only few patients were treated

with a non-TNFi and these patients more frequent were females, older, had a higher HAQ-DI (maybe due to older age), and experienced repeated biologic failure. Thus, this limits the external validity of BIOFOPT to patients with IA treated with a TNFi.

Another limitation is that patients with PsA were monitored by DAS28-CRP and not a PsA-specific disease activity measure (e.g., DAPSA or MDA) as no flare criteria was defined for PsA when the protocol was drafted. However, the authors acknowledge that a PsA-specific disease activity measure would have been more preferable. The co-primary endpoint 'disease activity' was assessed by DAS28-CRP in patients with RA or PsA and by ASDAS in patients with axSpA. The difference in disease activity measurement was handled by the linear mixed-effects model for repeated measures framework as diagnosis was included as a fixed factor which enables the comparison within each condition i.e., as if it were three independent disease-specific trials.

At 18 months, a small but statistically significant difference in Pain VAS was observed between the trial groups; however, the difference was not judged to be of clinical relevance as the 95%CI of 0.01 to 9.3 was within the limits of the minimal clinically important difference of ±10 (42). Similarly, the 95%CI of the observed differences in CRP and tender joint count were very small and not judged to have clinical relevance.

No radiographs were performed in BIODOPT. The recent DRESS-PS trial reported similar radiographic progression in patients with PsA when comparing tapering to control (11). Moreover, a recent systematic review in patients with axSpA did not find a significant risk for radiographic progression when comparing TNFi treatment to no TNFi or to TNFi tapering (43). The DOBIS trial recently showed limited add-on value of magnetic resonance imaging (MRI) during TNFi tapering in patients with axSpA as the clinical flare criteria identified 106 out of 107 flaring patients (15). Furthermore, only minimal changes in radiographic outcomes not considered clinically relevant was found. Similarly, the ADOPT trial showed that 102 out of 104 patients with RA who flared while tapering biologics were identified by clinical flare criteria; one patient had solely MRI flare and another only progressed radiographically (14). However, a recent Cochrane review based on low-certainty evidence concluded that disease activity-guided tapering in RA may slightly increase the rate of minimal radiographic progression, relative risk: 1.45 (95% CI: 0.77 to 2.73) (5). Thus, radiographs may be valuable to identify patients with RA who progress despite judged not to have clinical flare.

In BIODOPT, more patients in the tapering group experienced a flare but reassuringly no increased risk of persistent flare was observed. Nonetheless, a flare can impact the individual patient's quality-of-life, including social activities and work life, considerably if not easily managed. Therefore, shared-decision between the physicians and the patients should take all aspects of

tapering or continuation into consideration as the potential benefits (minimise drug dose/potential side effects) for some patients may be outweighed by the risk of flare.

CONCLUSION

One-third of patients with IA achieved ≥50% biologic reduction at 18 months with disease activity-guided tapering whereas such reduction was rarely achieved with usual care. Furthermore, disease activity between groups was equivalent. Flares were more frequent in the tapering group but managed with rescue therapy; no increased risk of persistent flare was observed. Shared-decision between the physician and the patient taking all aspects of tapering into consideration is encouraged before initiating tapering.

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DATA AVAILABILITY STATEMENT

The authors commit to share relevant anonymised data on reasonable request. The trial protocol as well as the statistical analysis plan are available as supplementary documents to this manuscript.

LEGENDS

Figure 1: Flow-diagram of participant recruitment with reason for exclusion.

Figure 2: Disease activity during the study period by diagnosis. RA: Rheumatoid arthritis, LSMeans: least squares means. PsA: Psoriatic arthritis, axSpA: Axial spondyloarthritis.

Figure 3: Flare by trial arm visualised in Kaplan-Meier cumulative incidence curves. A) Fulfilling flare criteria, B) Symptoms of flare, and C) Total flares. Patients censored due to loss to follow-up are presented in parentheses after the number of patients with flare.

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Table 1: Baseline demographics and disease characteristics analysed "as observed" based on the ITT population.

Variable	Tapering group (*N* = 95)	Control group (*N* = 47)
General characteristics		
Female, n (%)	52 (55%)	20 (43%)
Age (years), mean (SD)	51.9 (15.4)	52.3 (15.9)
Smoking, n (%)	15 (16%)	9 (19%)
Body Mass Index (kg/m^2), median (IQR)	25.3 (23.2;29.2)	26.6 (23.1;29.4)
Arthritis characteristics		
Diagnosis:		
RA, n (%)	41 (43%)	20 (43%)
PsA, n (%)	18 (19%)	8 (17%)
AxSpA, n (%)	36 (38%)	19 (40%)
Disease duration (years), median (IQR)	11.3 (6.3;17.9)	12.4 (6.4;19.9)
Disease activity measures		
HAQ-DI (0.0-3.0), median (IQR)	0.13 (0.00;0.63)	0.13 (0.00;0.50)
Pain VAS (0-100 mm), median (IQR)	10.0 (2.0;17.0)	11.0 (5.0;21.0)
Fatigue VAS (0-100 mm), median (IQR)	16.0 (4.0;34.0)	25.0 (10.0;42.0)
Patient global health VAS (0-100 mm), median (IQR)	10.0 (2.0;21.0)	14.0 (5.0;28.0)
Short Form-36:		
Physical component summary (0-100), median (IQR)	52.0 (47.4;55.1)	49.8 (44.2;52.6)[1]
Mental component summary (0-100), median (IQR)	56.4 (47.3;59.5)	54.5 (48.5;59.6)[1]
Tender joint count (0-68), median (IQR)	0.0 (0.0;0.0)	0.0 (0.0;0.0)
Swollen joint count (0-66), median (IQR)	0.0 (0.0;0.0)	0.0 (0.0;0.0)
CRP (mg/L), median (IQR)	2.6 (0.8;3.9)	2.2 (0.6;3.9)
Physician global health VAS (0-100 mm), median (IQR)	0.0 (0.0;0.0)	0.0 (0.0;0.0)
Disease activity score[2], mean (SD)	1.47 (0.50)	1.51 (0.50)
In remission[3], n (%)	82 (86%)	40 (85%)
Arthritis treatment characteristics		
csDMARDs, n (%)	41 (43%)	22 (47%)
Combination csDMARDs, n (%)	2 (2%)	2 (4%)
MTX, n (%)	40 (42%)	20 (43%)
Duration of bDMARD (years), median (IQR)	5.1 (2.3;8.2)	4.2 (2.7;10.6)
Baseline bDMARD therapy:		
TNF-α inhibitor, n (%)	88 (93%)	41 (87%)
IL-6 inhibitor, n (%)	6 (6%)	3 (6%)
T-cell co-stimulation blocker, n (%)	1 (1%)	3 (6%)
Repeated bDMARD failure[4], n (%)	6 (6%)	3 (6%)

N: number, SD: standard deviation, kg: kilogram, m^2: square metre, IQR: interquartile range, RA: rheumatoid arthritis, PsA: psoriatic arthritis, axSpA: axial spondyloarthritis, HAQ-DI: Health Assessment Questionnaire Disability Index, VAS: Visual Analog Scale, CRP: C-reactive protein, mg: milligram, L:litre, csDMARDs: Conventional synthetic disease-modifying antirheumatic drugs, MTX: methotrexate, bDMARD: biologic disease-modifying antirheumatic drug, TNF: Tumour necrosis factor, IL: Interleukin.

[1]: Missing values: one value for SF-36 PCS and for SF-36 MCS.

[2]: RA and PsA: Disease Activity Score (DAS)28-CRP and axSpA: Ankylosing Spondylitis Disease Activity Score (ASDAS).

[3]: RA and PsA: DAS28-CRP <2.6 and axSpA: ASDAS <1.3.

[4]: I.e. on biological agent number three or higher.

Table 2: Comparison between groups at 18 months follow-up based on the ITT population.

Outcome	Tapering group N = 95	Control group N = 47	Difference between groups (95%CI)[1]
Primary outcome			
Biologics reduced by ≥50%[2], n (%)	35 (37%)	1 (2%)	0.35 (0.24 to 0.45)
Ln (disease activity score[3])	0.48 (0.07)	0.44 (0.08)	0.04 (-0.06 to 0.14)
Disease activity score[3]	1.84 (0.15)	1.75 (0.16)	0.08 (-0.12 to 0.29)
Key secondary outcomes			
In remission[4], n (%)	63 (66%)	33 (70%)	-0.04 (-0.20 to 0.12)
In low disease activity[5], n (%)	79 (83%)	41 (87%)	-0.04 (-0.16 to 0.08)
Other secondary outcomes			
ΔHAQ-DI (0-3)	0.06 (0.06)	0.000 (0.07)	0.06 (-0.02 to 0.15)
ΔPain VAS (0-100)	5.6 (3.2)	1.0 (3.5)	4.7 (0.01 to 9.3)
ΔFatigue VAS (0-100)	-1.2 (4.4)	-2.7 (4.7)	1.5 (-4.4 to 7.4)
ΔPatient Global Health VAS (0-100)	2.8 (3.9)	0.9 (4.2)	1.9 (-3.4 to 7.2)
ΔShort Form-36 PCS (0-100)	-2.1 (1.4)	-2.5 (1.5)	0.4 (-1.5 to 2.4)
ΔShort Form-36 MCS (0-100)	-1.6 (1.8)	-1.5 (1.9)	-0.1 (-2.6 to 2.4)
ΔPhysician Global Health VAS (0-100)	4.9 (2.1)	4.1 (2.3)	0.8 (-2.3 to 3.9)
ΔTender joint count (0-68)	-0.05 (0.4)	0.6 (0.5)	-0.6 (-1.2 to 0.00)
ΔSwollen joint count (0-66)	0.3 (0.2)	0.3 (0.2)	-0.02 (-0.3 to 0.3)
ΔCRP (mg/L)	3.2 (1.5)	0.7 (1.6)	2.4 (0.2 to 4.7)

N: number, CI: confidence interval, Ln: natural logarithm, Δ: Change between 18 months and baseline, HAQ-DI: Health Assessment Questionnaire Disability Index, VAS: Visual Analog Scale, PCS: physical component summary, MCS: mental component summary, CRP: C-reactive protein, mg: milligram, L: litre.

Dichotomous outcomes were analysed as crude risk difference for the between group comparison using generalised linear models for binomial data. Continuous outcomes were analysed using repeated-measures linear mixed-effects models as least squares means with standard error.

[1]: Analysed as tapering group – continuation group.

[2]: Compared to baseline biologic dose.

[3]: RA and PsA: Disease Activity Score (DAS)28-CRP, axSpA: Ankylosing Spondylitis Disease Activity Score (ASDAS).

[4]: RA and PsA: DAS28-CRP <2.6 and axSpA: ASDAS <1.3.

[5]: RA and PsA: DAS28-CRP ≤3.2and axSpA: ASDAS <2.1.

Table 3: Safety and harm summary analysed "as observed" based on the ITT population.

	Tapering group N = 95	Control group N = 47	Risk difference[1] (95% CI)
Total flares, n/N (%)	77/95 (81%)	16/47 (34%)	47% (31% to 63%)
Fulfil flare criteria, n/N (%)	39/95 (41%)	10/47 (21%)	20% (4% to 35%)
Symptoms of flare, n/N (%)	38/95 (40%)	6/47 (13%)	27% (14% to 41%)
Rescue therapy among the flaring patients:			
bDMARD dose escalation, n/N (%)	66/77 (86%)	6/16 (38%)	··
Glucocorticoid treatment[2], n/N (%)	24/77 (31%)	10/16 (63%)	··
NSAIDs, n/N (%)	23/77 (30%)	8/16 (44%)	··
Biologic switch due to flare, n/N (%)	1/95 (1%)	3/47 (6%)	-5% (-13% to 2%)
Adverse events of particular interest, n/N (%)	64[3]/95 (67%)	25/47 (53%)	14% (-3% to 31%)
Non-serious Infections, n/N (%)	52/95 (55%)	24/47 (51%)	4% (-14% to 21%)
Uveitis, n/N (%)	5/95 (5%)	3/47 (6%)	-1% (-9% to 7%)
Psoriasis skin flare, n/N (%)	4/95 (4%)	0/47 (0%)	4% (0.2% to 8%)
Psoriasis nail flare, n/N (%)	2/95 (2%)	0/47 (0%)	2% (-1% to 5%)
Flare in symptoms of IBD, n/N (%)	3/95 (3%)	0/47 (0%)	3% (-0.4% to 7%)
Discontinued bDMARD due to any AE, n/N (%)	5/95 (5%)	4/47 (9%)	-3% (-12% to 6%)
PsA/axSpA specific adverse events, n/N (%)	10[5]/54 (19%)	3/27 (11%)	7% (-8% to 23%)
Uveitis, n/N (%)	4/54 (7%)	3/27 (11%)	-4% (-17% to 10%)
Psoriasis skin flare, n/N (%)	3/54 (6%)	0/27 (0%)	6% (-1% to 12%)
Psoriasis nail flare, n/N (%)	1/54 (2%)	0/27 (0%)	2% (-2% to 5%)
Flare in symptoms of IBD, n/N (%)	3/54 (6%)	0/27 (0%)	6% (-1% to 12%)
Serious adverse events, n/N (%)	5/95 (5%)	5/47 (11%)	-5% (-15% to 5%)
Serious infections, n/N (%)	0/95 (0%)	2/47 (4%)	-4% (-10% to 2%)
Cardiovascular events, n/N (%)	1/95 (1%)	1/47 (2%)	-1% (-6% to 4%)
Malignancy, n/N (%)	1/95 (1%)	0/47 (0%)	1% (-1% to 3%)
Death, n/N (%)	0/95 (0%)	0/47 (0%)	0%
Other serious adverse events, n/N (%)	3/95 (3%)	2/47 (4%)	-1% (-8% to 6%)

N: number, CI: confidence interval, bDMARD: biologic disease-modifying antirheumatic drug, NSAIDs: Non-steroidal anti-inflammatory drugs, IBD: inflammatory bowel disease, AE: adverse event.

[1]: Analysed as Tapering group – Control group.

[2]: Intra-articular glucocorticoid treatment or if judged necessary by the physician intra-muscular or oral administration.

[3]: During the study period, three patients had an infection and an episode of uveitis, one patient had an infection and a psoriasis skin flare, one patient had an infection and a psoriasis nail flare, one patient had an infection and flare in symptoms of IBD, and one patient discontinued the bDMARD due to any AE and experienced flare in symptoms of IBD.

[4]: During the study period, four patients discontinued their bDMARD due to any AE and had an infection, and two patients had an infection and an episode of uveitis.

[5]: During the study period, one patient had both a psoriasis nail flare and an episode of uveitis.