Predicting successful biologics tapering in patients with inflammatory arthritis: Secondary analyses based on the BIOlogical Dose OPTimisation (BIODOPT) trial

Uhrenholt, Line; Duch, Kirsten; Christensen, Robin; Dreyer, Lene; Hauge, Ellen-Margrethe; Schlemmer, Annette; Taylor, Peter C; Kristensen, Salome

ORIGINAL ARTICLE

BJCP BRITISH PHARMACOLOGICAL SOCIETY

Predicting successful biologics tapering in patients with inflammatory arthritis: Secondary analyses based on the BIOlogical Dose OPTimisation (BIODOPT) trial

Line Uhrenholt[1,2,3] | Kirsten Duch[1,4] | Robin Christensen[3,5] |
Lene Dreyer[1,2] | Ellen-Margrethe Hauge[6,7] | Annette Schlemmer[7,8] |
Peter C. Taylor[9] | Salome Kristensen[1,2]

[1]Center of Rheumatic Research Aalborg (CERRA), Department of Rheumatology, Aalborg University Hospital, Aalborg, Denmark

[2]Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

[3]Section for Biostatistics and Evidence-Based Research, the Parker Institute, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark

[4]Unit of Epidemiology and Biostatistics, Aalborg University Hospital, Aalborg, Denmark

[5]Research Unit of Rheumatology, Department of Clinical Research, University of Southern Denmark, Odense University Hospital, Odense, Denmark

[6]Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark

[7]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

[8]Department of Rheumatology, Randers Regional Hospital, Randers, Denmark

[9]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK

Correspondence
Line Uhrenholt, Center of Rheumatic Research Aalborg (CERRA), Department of Rheumatology, Aalborg University Hospital, Reberbansgade 15, Aalborg 9000, Denmark.
Email: l.uhrenholt@rn.dk; line_uhrenholt@hotmail.com

Abstract

Aims: To evaluate predictors for successful biologic tapering among patients with inflammatory arthritis using baseline characteristics from the BIODOPT trial.

Methods: Adult patients with rheumatoid arthritis, psoriatic arthritis or axial spondyloarthritis on stable biologic dose and in low disease activity ≥12 months were enrolled. Participants were randomized (2:1) to disease activity-guided biologic tapering or continuation of baseline biologic. Patients achieving successful tapering reduced their biologic dose by ≥50%, had no protocol deviations and were in low disease activity at 18 months. Modified Poisson regression with robust variance estimator was applied.

Results: In total, 142 patients were randomized to tapering ($n = 95$) or control ($n = 47$). Successful tapering was achieved by 32 and 2%, respectively. Tapering group was the only statistically significant independent predictor for successful tapering, risk ratio (RR): 14.0 (95% confidence interval [CI]: 1.9 to 101.3, $P = .009$). However, higher Short Form Health Survey 36 mental component summary (SF-36 MCS) was observed to be a predictor of potential importance, RR: 1.06 (95% CI: 0.99 to 1.13, $P = .097$). When limiting the analyses to the tapering group only, none of the baseline variables were statistically significant independent predictors but SF-36 MCS was still considered to be of potential importance, RR: 1.05 (95% CI: 0.99 to 1.12, $P = .098$).

Conclusion: Successful tapering is a reachable target for 1 in 3 patients with inflammatory arthritis who are interested in reducing their biological therapy. No statistically significant predictors (besides allocation to tapering) were identified. Future research on mental health and tapering is encouraged.

KEYWORDS

arthritis, biologicals, clinical trials, drug utilization

The authors confirm that the principal investigator for this paper is Salome Kristensen and that she had direct clinical responsibility for patients.

1 | INTRODUCTION

The European Alliance of Associations for Rheumatology endorse physicians and patients with inflammatory arthritis (IA) to consider slowly tapering biologics when sustained remission is achieved over complete biologic withdrawal.[1–3] From a patient perspective, necessary visits to the outpatient clinic are reduced when the dosing interval is prolonged, which could lower the individual patient's time costs. Moreover, a lower risk of adverse drug reactions, including serious infections, is expected. From a societal perspective, tapering is expected to result in significant cost savings as biological therapies are expensive.

The evidence of biologic tapering is strongest in rheumatoid arthritis (RA) as multiple trials have been performed,[4–7] weaker in axial spondyloarthritis (axSpA) where fewer studies have been conducted (axSpA)[6–12] and sparse in psoriatic arthritis (PsA).[7,8,10,13] Across IA diagnoses, biologic tapering seem to be feasible and safe as a considerable dose reduction or interval prolongation can be achieved without losing the therapeutic response.[4–7,9–13] Moreover, the majority of patients who flare regain stable disease activity with rescue therapy (e.g. biologic dose escalation or glucocorticoids); only few patients need to be switched to another biological drug due to persistent flare.[4–7,11,12]

Recently, the BIODOPT trial evaluated disease activity-guided tapering of biologics to continuation of biologics as usual care among patients with RA, PsA or axSpA in sustained low disease activity (LDA) ≥ 12 months.[14] At 18 months follow-up, statistically significantly more patients in the tapering group had reduced their biologic dose ≥50% compared to the control group. Moreover, an equivalent disease activity state between the trial groups was demonstrated.

To date, little is known about potential predictors for successful biologic tapering as studies have reported no consistent predictors.[6,15] However, effort should be put into identifying possible predictive variables which can contribute to improve and individualize the tapering algorithm. Thus, this study evaluates baseline characteristics from the BIODOPT trial in an attempt to identify possible predictors for successful biologic tapering.

2 | METHODS

2.1 | Study design and participants

BIODOPT was an 18-month, pragmatic, randomized, open-label, equivalence trial conducted at 4 sites in Denmark and has previous

What is already known about this subject

- No consistent predictors for successful biologic tapering in patients with rheumatoid arthritis, psoriatic arthritis or axial spondyloarthritis nor across inflammatory arthritis (IA) diagnoses have been identified.
- No studies have yet evaluated possible predictors for successful biologic tapering in patients with IA, spanning from rheumatoid arthritis to psoriatic arthritis and axial spondyloarthritis, based on data from a randomized-controlled trial study.

What this study adds

- Other than allocation to tapering, no statistically significant predictors of successful tapering were identified. Thus, all patients with IA diagnoses are equally likely to have a successful course when tapering their biologics.
- Better baseline mental health seemed to be a nonsignificant predictor of potential importance and future research is encouraged.

been described extensively.[14,16] Adult patients diagnosed with RA, PsA or axSpA who had achieved sustained LDA on stable dose biologics ≥12 months were eligible. Baseline LDA was defined as absence of swollen joints and (i) RA: Disease Activity Score28-C-Reactive Protein (DAS28-CRP) ≤3.2[17]; (ii) PsA: Disease Activity in PSoriatic Arthritis (DAPSA) ≤14[18]; and (iii) AxSpA: Ankylosing Spondylitis Disease Activity Score (ASDAS) <2.1.[19] After written informed consent was obtained, patients were randomized in ratio 2:1 to the tapering group or the control group. In the tapering group, the biologic dosing interval (except for infliximab) was prolonged by 25% every 4 months after a disease activity-guided algorithm until flare or complete drug withdrawal. As previously described, the infliximab dosing interval was prolonged with 2 weeks at each infusion.[16] Patients in the control group maintained their baseline biologic dosing interval; however, as usual practice, a minor interval prolongation was permitted per patient request.
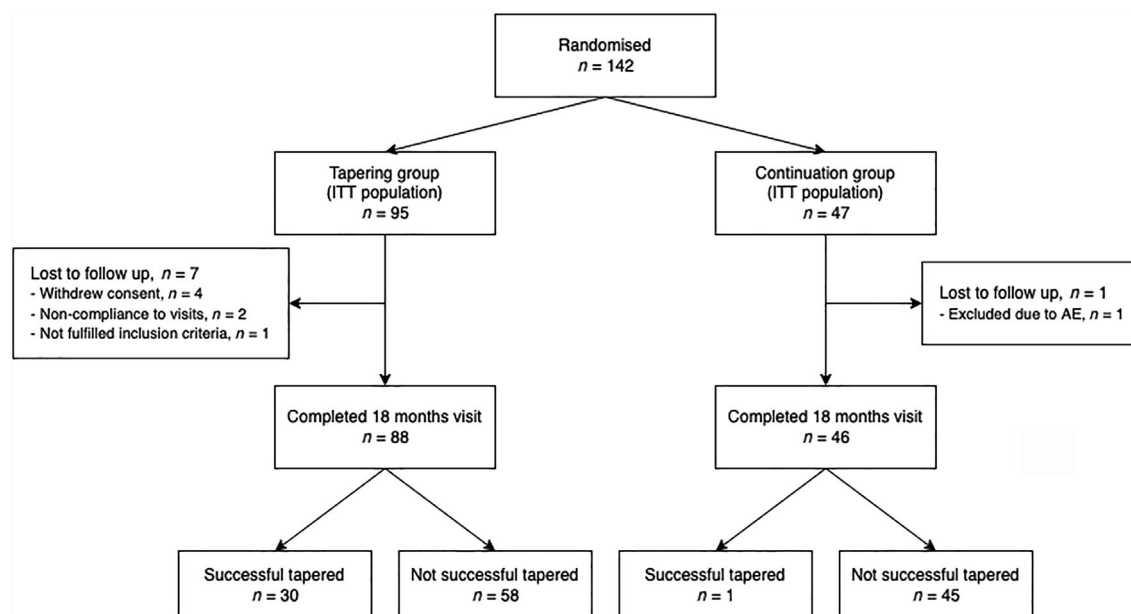
FIGURE 1 Flow-diagram over the study period.

In these secondary analyses, successful tapering at 18 months was predefined as: patients with no deviation from the trial protocol; who had reduced their biologic dose by ≥50% compared to baseline; and who still were in LDA. In compliance with the trial protocol, LDA at 18 months was defined by DAS28-CRP ≤3.2 (RA and PsA), and by ASDAS <2.1 (axSpA).

2.2 | Endpoint and predictors

This study aims to identify possible baseline predictive variables for successful tapering in patients with IA in sustained LDA who taper or continue biologics based on data from the BIODOPT trial.

Categorical baseline variables included in the regression model: tapering group, female sex, education status, tobacco use, body mass index classification, diagnosis, on ≥2 conventional synthetic disease-modifying antirheumatic drugs, on methotrexate, on tumour necrosis factor inhibitors (TNFi), on first biological agent, repeated biologics failure (on biological agent number ≥3), previous biologic tapering attempt and in remission (RA and PsA: DAS28-CRP <2.6, or axSpA: ASDAS <1.3).

Continuous baseline variables included in the regression model: age, body mass index, the Rheumatic Disease Comorbidity Index, disease duration, duration from diagnosis to start of arthritis treatment, duration of baseline biological therapy, duration of remission on baseline biologic, duration of LDA on baseline biologic, C-reactive protein (CRP) before first biologic, 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), SF-36 mental component summary (MCS), tender joints, Physician Global Health VAS and CRP.

2.3 | Statistical analysis

The BIODOPT sample size calculation has previously been reported in details.[14,16] These secondary analyses were performed in accordance with the prespecified statistical analysis plan (SAP),[20,21] inspired by the CONSORT statement[22,23] and reported according to the TRIPOD statement.[24,25] The intention-to-treat approach was applied i.e., all randomized participants with available baseline data independent of subsequent protocol deviations. Missing data for the primary outcome (i.e. successful tapering) was conservatively analysed as trial failure i.e. patients *were not able* to reduce their biologic dose by ≥50% and/or *did not* sustain LDA.

Univariable modified Poisson regression with robust variance estimator and the potential predictor as independent variables was used to estimate the relative risk (RR) with 95% confidence interval (95% CI) and *P*-value.[26] To identify relevant nonlinear predictors, all continuous variables were grouped into clinically relevant categories based on expert opinion and analysed as categorical variables. If no apparent evidence for nonlinearity was identified, the continuous variables were analysed as linear.

Two multivariable modified Poisson regression analyses using a robust variance estimator were performed. The data-driven model included all variables with a univariate *P*-value <.10. The clinical-driven model included variables selected from expert opinion to be of potential importance for achieving successful tapering which were: tapering group, female sex, age, repeated biologic failure and baseline remission. Pairwise correlation between predictors was investigated as collinearity may decrease the signal of correlated predictors. Presence of collinearity was evaluated using treelet transformation.[27] Results from the multivariable regression analyses were presented as RR with 95% CI.

TABLE 1 Baseline demographics and disease characteristics in the intention-to-treat 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)
Education status		
Unskilled worker, *n* (%)	13 (14%)	11 (23%)
Skilled worker, *n* (%)	31 (33%)	15 (32%)
Short-cycle higher education, *n* (%)	14 (15%)	6 (13%)
Medium-cycle higher education, *n* (%)	17 (18%)	6 (13%)
Long-cycle higher education, *n* (%)	20 (21%)	9 (19%)
Tobacco use		
Never, *n* (%)	42 (44%)	22 (47%)
Previous smoker, *n* (%)	32 (34%)	14 (30%)
Occasional smoker, *n* (%)	6 (6%)	2 (4%)
Daily smoker, *n* (%)	15 (16%)	9 (19%)
BMI (kg/m^2), median (IQR)	25.3 (23.2–29.2)	26.6 (23.1–29.4)
BMI classification		
Underweight (BMI <18.5 kg/m^2), *n* (%)	0 (0%)	0 (0%)
Healthy (BMI 18.5–24.9 kg/m^2), *n* (%)	38 (40%)	16 (34%)
Overweight (BMI 25.0–29.9 kg/m^2), *n* (%)	38 (40%)	20 (43%)
Obese (BMI ≥30.0 kg/m^2), *n* (%)	19 (20%)	11 (23%)
Comorbidity index,[a] median (IQR)	0 (0–1)	1 (0–2)
Arthritis characteristics		
Diagnosis		
Rheumatoid arthritis, *n* (%)	41 (43%)	20 (43%)
Rheumatoid factor positive, *n* (%)	26/41 (63%)	16/20 (80%)
Anti-citrullinated peptide antibody positive, *n* (%)	28/41 (68%)	17/20 (85%)
Psoriatic arthritis, *n* (%)	18 (19%)	8 (17%)
Axial spondyloarthritis, *n* (%)	36 (38%)	19 (40%)
Ankylosing spondylitis, *n* (%)	23/36 (64%)	14/19 (74%)
Disease duration (years), median (IQR)	11.3 (6.3–17.9)	12.4 (6.4–19.9)
Duration diagnosis to treatment start (months), median (IQR)	0 (0–1)	0 (0–1)
On ≥2 csDMARDs, *n* (%)	2 (2%)	2 (4%)
On methotrexate, *n* (%)	40 (42%)	20 (43%)
Biological agent class		
Non-TNF inhibitor, *n* (%)	7 (7%)	6 (13%)
TNF inhibitor, *n* (%)	88 (93%)	41 (87%)
On first biologic, *n* (%)	69 (73%)	32 (68%)
Repeated biologics failure, *n* (%)	6 (6%)	3 (6%)
Duration of baseline biologic (years), median (IQR)	5.1 (2.3–8.2)	4.2 (2.7–10.6)
Duration baseline biologic remission (years), median (IQR)	1.7 (1.0–4.1)	1.4 (1.0–2.6)
Duration baseline biologic LDA (years), median (IQR)	2.7 (1.5–5.7)	2.5 (1.2–5.5)
Previous attempt to taper biologic, *n* (%)	30 (32%)	12 (26%)
CRP before first biologic (mg/L), median (IQR)	11.0 (5.0–27.0)	14.0 (4.9–38.0)
Disease activity measures		
HAQ.DI (0–3), 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)

(Continues)

TABLE 1 (Continued)

Variable	Tapering group (N = 95)	Control group (N = 47)
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)
SF-36 PCS (0–100), median (IQR)	52.0 (47.4–55.1)	49.8 (44.2–52.6)[b]
SF-36 MCS (0–100), median (IQR)	56.4 (47.3–59.5)	54.5 (48.5–59.6)[b]
Physician global health VAS (0–100 mm), median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
No tender joints, n (%)	90 (95%)	43 (91%)
CRP (mg/L), median (IQR)	2.6 (0.8–3.9)	2.2 (0.6–3.9)
In remission,[c] n (%)	82 (86%)	40 (85%)

Abbreviations: BMI, body mass index; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; HAQ, Health Assessment Questionnaire Disability Index; IQR, interquartile range; LDA, low disease activity; MCS, mental component summary; PCS, physical component summary; SD, standard deviation; SF-36, Short Form-36; TNF, tumour necrosis factor; VAS, Visual Analogue Scale.
[a]Rheumatic Disease Comorbidity Index.
[b]Missing value: 1 value.
[c]RA and PsA: DAS28-CRP < 2.6 and axSpA: ASDAS < 1.3.

Leave-1-out cross-validation was performed and assessed using the concordance index (c-index) for binary outcome identical to the area under the receiving operator characteristic curve (AUC).[28] Lastly, classification trees were used to identify and illustrate the most relevant predictors; cross-validation was applied to identify the optimal sub-tree and the Gini index as a measure of node purity. All analyses were performed using STATA (version 16.1).

3 | RESULTS

Between May 2018 and April 2020, 142 patients were included; 95 patients were randomized to the tapering group and 47 patients to the control group. Figure 1 provides a modified overview of the study period including patients lost to follow-up. Baseline characteristics are presented in Table 1. In the tapering group and the control group, 41 (43%) vs. 20 (43%) were diagnosed with RA, 18 (19%) vs. 8 (17%) with PsA and 36 (38%) vs. 19 (40%) with axSpA. Most patients received treatment with TNFi (88 [93%] vs. 41 [87%], respectively), the rest were treated with abatacept or tocilizumab. The majority were in remission at baseline: 82 (86%) in the tapering group and 40 (85%) in the control group.

Data for the primary outcome (i.e., successful tapering) were missing for 10 patients as 8 patients were lost to follow-up (Figure 1) and disease activity was not registered for 2 patients due to investigator error. These patients were analysed as trial failures. At 18 months follow-up, 64% (61/95) of patients in the tapering group and 15% (7/47) of patients in the control group had tapered their biologic dose compared to baseline and maintained LDA. Interestingly, 32% (30/95) of patients in the tapering group had managed to taper their biologic dose ≥50% and maintained LDA; thus achieved successful tapering, compared to only 2% (1/47) of patients in the control group. When evaluating potential differences in achieving successful tapering between biological agents none was found as 32% (28/88) of patients in the tapering group treated with TNFi and

29% (2/7) treated with non-TNFi reached this target. Moreover, no differences were observed in the tapering group between the different IA diagnoses as 29% (12/41) of patients with RA, 28% (5/18) of patients with PsA and 36% (13/36) of patients with axSpA achieved successful tapering.

3.1 | Regression analyses on both study groups

The only continuous baseline variable which demonstrated clear non-linearity when assessed as grouped was *tender joints*. Thus, the variable was analysed as categorical based on the clinically relevant groups: 0 tender joints or ≥1 tender joints. As presented in Table 2, the univariable modified Poisson regression analyses revealed statistically significant associations (P < .10) between successful tapering and tapering group, HAQ-DI, Pain VAS, Fatigue VAS, Patient Global Health VAS, SF-36 PCS and SF-36 MCS. Interestingly, none of the baseline variables judged by expert opinion to be potentially important were statistically significant.

A data-driven multivariable modified Poisson regression model was applied which included the variables with a univariate P < .10: tapering group, HAQ-DI, pain VAS, fatigue VAS, patient global health VAS, SF-36 PCS and SF-36 MCS. Allocation to the tapering group was the only independent predictor for successful tapering that remained statistically significant, RR: 14.0 (95% CI: 1.9 to 101.3, P = .009). However, better mental health at baseline (higher SF-36 MCS) was judged to be a statistically nonsignificant but potentially important predictor, RR: 1.06 (95% CI: 0.99 to 1.13, P = .097). Thus, when comparing 2 patients who differed by 1 unit in SF-36 MCS (range 0–100), the patient with the higher SF-36 MCS score seem to have a 6% higher change of successful tapering. For explorative purpures, a sensitivity analysis on the data-driven model including only tapering group and SF-36 MCS (fewer baseline variables thereby more power) was performed. The sensitivity analysis found both allocation to the tapering group and higher baseline SF-36 MCS to be

TABLE 2 Univariable and multivariable regression analyses for prediction of successful tapering at 18 months.

Possible baseline predictors	Univariable analysis RR (95% CI)	Multivariable analysis Data-driven RR (95% CI)	Multivariable analysis Clinical-driven RR (95% CI)
Tapering group	14.8 (2.1 to 106.3), P = .007	14.0 (1.9 to 101.3), P = .009	14.9 (2.1 to 107.1), P = .007
Female	1.18 (0.63 to 2.21), P = .605		0.95 (0.48 to 1.87), P = .884
Age	1.00 (0.98 to 1.02), P = .773		1.00 (0.98 to 1.03), P = .784
Education status			
Unskilled worker	1 (ref.)		
Skilled worker	1.04 (0.40 to 2.72), P = .931		
Short-cycle higher education	0.72 (0.19 to 2.66), P = .622		
Medium-cycle higher education	1.04 (0.35 to 3.15), P = .940		
Long-cycle higher education	1.32 (0.50 to 3.53), P = .575		
Tobacco use			
Never	1 (ref.)		
Previous smoker	0.65 (0.31 to 1.39), P = .270		
Occasional smoker	0.47 (0.07 to 3.10), P = .433		
Present smoker	0.78 (0.32 to 1.90), P = .590		
BMI (kg/m^2)	0.99 (0.92 to 1.07), P = .813		
BMI classification			
Healthy (BMI 18.5–24.9 kg/m^2)	1 (ref.)		
Overweight (BMI 25.0–29.9 kg/m^2)	0.93 (0.47 to 1.83), P = .836		
Obese (BMI ≥30.0 kg/m^2)	0.69 (0.27 to 1.76), P = .440		
Comorbidity Index[a]	0.89 (0.66 to 1.21), P = .471		
Diagnosis			
Rheumatoid arthritis	1 (ref.)		
Psoriatic arthritis	0.90 (0.36 to 2.28), P = .828		
Axial spondyloarthritis	1.11 (0.56 to 2.19), P = .765		
Disease duration	0.99 (0.95 to 1.03), P = .542		
Duration diagnosis to treatment start	0.99 (0.96 to 1.01), P = .243		
On ≥2 csDMARDs	2.38 (0.84 to 6.70), P = .101		
On methotrexate	0.75 (0.39 to 1.45), P = .395		
On TNFi	0.94 (0.33 to 2.68), P = .909		
On first biologic	0.99 (0.50 to 1.97), P = .982		
Repeated biologics failure	1.02 (0.29 to 3.62), P = .977		1.02 (0.25 to 4.17), P = .974
Duration of baseline biologic	0.95 (0.88 to 1.02), P = .158		
Duration baseline biologic remission	1.03 (0.94 to 1.12), P = .551		
Duration baseline biologic LDA	0.96 (0.88 to 1.05), P = .389		
Previous attempt to taper biologic	0.69 (0.32 to 1.49), P = .349		
CRP before first biologic	1.00 (0.99 to 1.02), P = .503		
HAQ-DI	0.44 (0.20 to 1.00), P = .049	0.60 (0.26 to 1.37), P = .221	
Pain VAS	0.96 (0.93 to 1.00), P = .024	0.99 (0.94 to 1.04), P = .720	
Fatigue VAS	0.99 (0.97 to 1.00), P = .072	1.01 (0.99 to 1.02), P = .495	
Patient global health VAS	0.97 (0.95 to 0.99), P = .011	1.00 (0.97 to 1.03), P = .955	
SF-36 PCS	1.06 (1.00 to 1.11), P = .045	1.00 (0.93 to 1.07), P = .915	
SF-36 MCS	1.06 (1.01 to 1.12), P = .011	1.06 (0.99 to 1.13), P = .097	
Physician Global Health VAS	0.97 (0.85 to 1.12), P = .706		
No tender joints	2.03 (0.31 to 13.32), P = .461		
CRP	0.97 (0.85 to 1.10), P = .621		

(Continues)

TABLE 2 (Continued)

Possible baseline predictors	Univariable analysis RR (95% CI)	Multivariable analysis Data-driven RR (95% CI)	Multivariable analysis Clinical-driven RR (95% CI)
In remission[b]	1.53 (0.51 to 4.58), P = .447		1.47 (0.51 to 4.23), P = .472

Abbreviations: 95% CI, 95% confidence interval; BMI, body mass index; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; HAQ-DI, Health Assessment Questionnaire Disability Index; LDA, low disease activity; MCS, mental component summary; PCS, physical component summary; RR, relative risk; SF-36, Short Form-36; TNFi, tumour necrosis factor inhibitor; VAS, Visual Analogue Scale.
[a]Rheumatic Disease Comorbidity Index.
[b]RA and PsA: DAS28-CRP < 2.6 and axSpA: ASDAS < 1.3.

(A)

AUC: 0.72 (95%CI: 0.63 to 0.82)
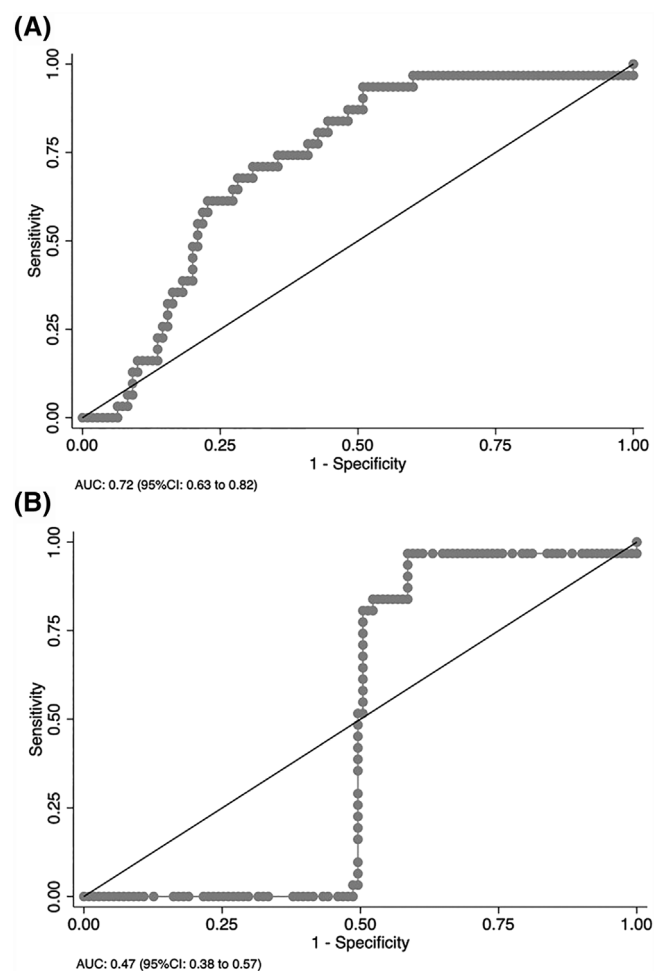
(B)

AUC: 0.47 (95%CI: 0.38 to 0.57)

FIGURE 2 Area under the receiver operator curve for the model including both trial groups with 95% confidence interval: (A) the data-driven model, (B) the clinical-driven model.

independent predictors for achieving successful tapering (tapering group: RR = 14.3 [95% CI: 2.0 to 101.9, P = .008], SF-36 MCS: RR = 1.06 [95% CI: 1.01 to 1.11, P = .009]), thus highlighting the potential importance of baseline mental health for reaching successful tapering. To explore potential differences for achieving successful tapering further, SF-36 MCS was dichotomised into low scores (≤50) and high scores (>50). *Posthoc* analyses demonstrated that successful tapering was achieved by 39% (26/66) of patients in the tapering

group with a high SF-36 MCS score and by 14% (4/29) with a low SF-36 MCS score, the difference was statistically significant: risk difference 26% (95% CI: 8% to 43%).

As illustrated in Figure 2, internal validation of the data-driven model was assessed with leave-1-out cross-validation which yielded an AUC of 0.72 (95% CI: 0.63 to 0.82). Thus, the model is judged to be valid and to provide reasonable prediction. Furthermore, another sensitivity analysis on the data-driven model was performed as high correlation was observed between pain VAS, fatigue VAS and patient global health VAS. The sensitivity analysis included tapering group, HAQ-DI, SF-36 PCS and SF-36 MCS in the original form and a score that combined the 3 VAS outcomes (obtained using treelet transformation). The results and conclusion were comparable to the data-driven model (data not shown); therefore, the data-driven model was judged to provide reasonable prediction. Figure 3 illustrates a classification tree, based on the data-driven model, which highlight the impact of the most relevant predictors for achieving successful tapering. The tree can provide the patient and the physician with additional insight when tapering is considered.

A clinical-driven model was also performed, which included variables judged by experts to be of potential importance for achieving successful tapering: tapering group, female sex, age, repeated biologic failure and baseline remission. None of the selected variables were correlated; thus, treelet transformation was not necessary. The clinical-driven multivariable modified Poisson regression analysis only identified tapering group, RR: 14.9 (95% CI: 2.1 to 107.1, P = .007), as a statistically significant independent predictor for successful tapering (Table 2). Leave-1-out cross-validation demonstrated an AUC of 0.47 (95% CI: 0.38 to 0.57, Figure 2); thus, the model is judged to predict successful tapering no better than chance. Furthermore, it was not possible to identify any prediction model with classification trees.

3.2 | Regression analyses on the tapering group

Posthoc analyses restricted to data on the tapering group were performed to explore predictors for this group alone. The univariable modified Poisson regression analyses found a statistically significant associations (P < .10) between successful tapering and HAQ-DI, Pain VAS, Patient Global Health VAS and SF-36 MCS (Table 3). Thus, these baseline variables were included in the data-driven multivariable
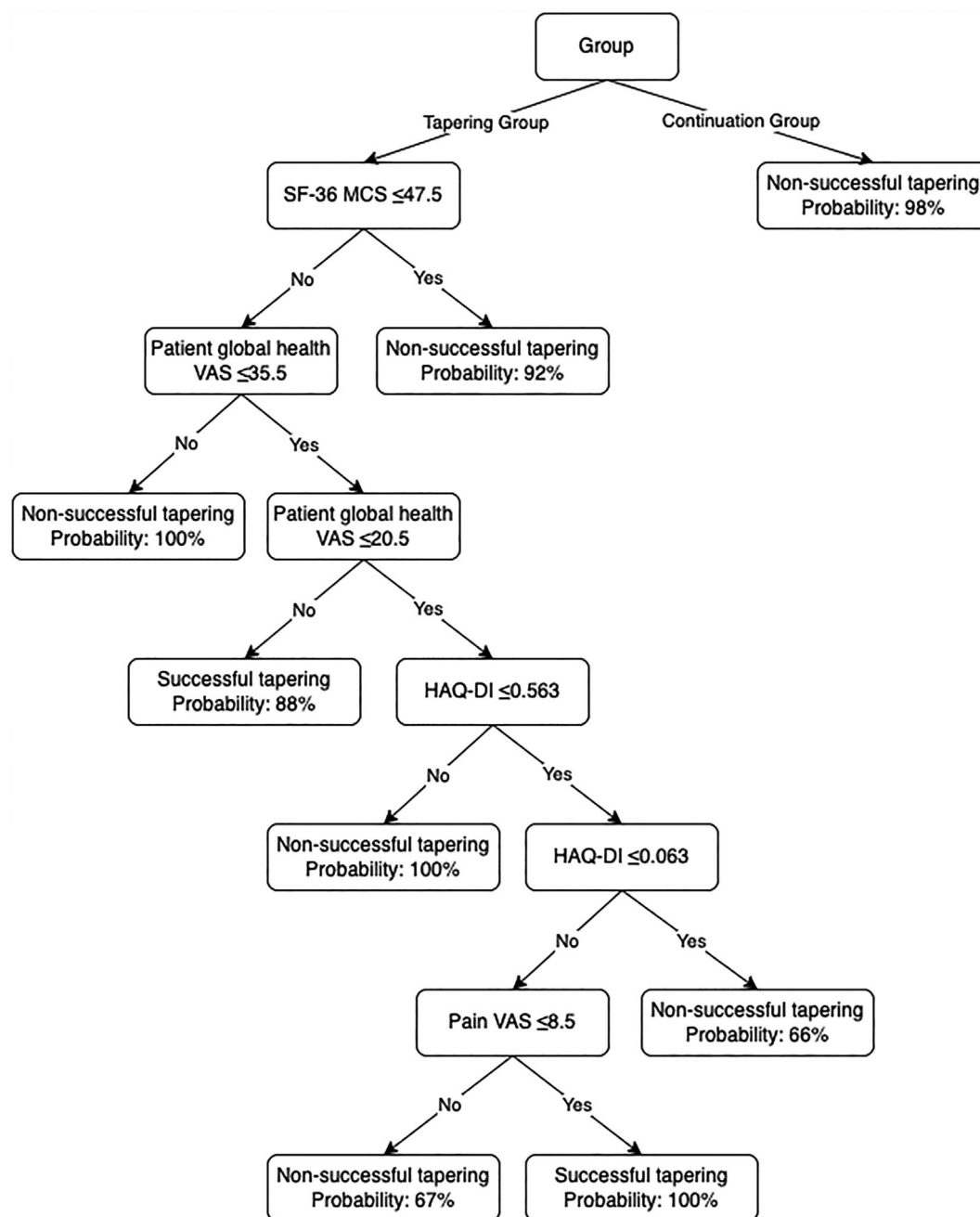
FIGURE 3 Classification tree identifying the most relevant predictors in the data-driven model including both trial groups.

modified Poisson regression model. As presented in Table 3, none of the variables were statistically significant independent predictors for achieving successful tapering but better mental health at baseline (higher SF-36 MCS) was still judged to be a potentially important non-significant predictor, RR: 1.05 (95% CI: 0.99 to 1.12, $P = .098$). Internal validation was assessed with leave-1-out cross-validation which yielded an AUC of 0.57 (95% CI: 0.45 to 0.69, Figure 4). Thus, the model is judged to predict successful tapering a little better than chance and therefore results must be interpreted with caution. Figure 5 illustrates a classification tree based on the model highlighting the most relevant predictors.

4 | DISCUSSION

This study is, as far as we know, the first to evaluate possible predictors for successful biologic tapering in patients with IA, spanning from RA to PsA and axSpA, based on data from a randomized-controlled trial (RCT) study. In the tapering group, 2/3 of patients who still were in LDA at 18 months managed to reduce their biologic dose and 1/3 manage to achieve a ≥50% dose reduction compared to baseline; thereby, obtaining successful tapering. Thus, a biologic dose reduction by at least half is an achievable goal for 1 in 3 patients with well-treated IA who consent to tapering after shared decision making. The

TABLE 3 Univariable and multivariable regression analyses for prediction of successful tapering at 18 months ONLY on data from the tapering group.

Possible baseline predictors	Univariable analysis RR (95% CI)	Multivariable analysis Data-driven RR (95% CI)
Female	0.95 (0.52 to 1.71), P = .853	
Age	1.00 (0.98 to 1.02), P = .904	
Education status		
Unskilled worker	1 (ref.)	
Skilled worker	0.84 (0.35 to 1.98), P = .689	
Short-cycle higher education	0.56 (0.16 to 1.89), P = .348	
Medium-cycle higher education	0.76 (0.28 to 2.11), P = .604	
Long-cycle higher education	0.91 (0.36 to 2.27), P = .840	
Tobacco use		
Never	1 (ref.)	
Previous smoker	0.54 (0.25 to 1.15), P = .110	
Occasional smoker	0.41 (0.07 to 2.58), P = .344	
Present smoker	0.82 (0.37 to 1.85), P = .638	
BMI index (kg/m^2)	0.99 (0.92 to 1.07), P = .845	
BMI classification		
Healthy (BMI 18.5–24.9 kg/m^2)	1 (ref.)	
Overweight (BMI 25.0–29.9 kg/m^2)	1.00 (0.53 to 1.87), P = 1.000	
Obese (BMI ≥30.0 kg/m^2)	0.62 (0.23 to 1.64), P = .332	
Comorbidity index[a]	0.93 (0.71 to 1.22), P = .616	
Diagnosis		
Rheumatoid arthritis	1 (ref.)	
Psoriatic arthritis	0.95 (0.39 to 2.31), P = .908	
Axial spondyloarthritis	1.23 (0.65 to 2.36), P = .525	
Disease duration	0.99 (0.96 to 1.03), P = .571	
Duration diagnosis to treatment start	0.99 (0.96 to 1.01), P = .283	
On ≥2 csDMARDs	1.60 (0.39 to 6.67), P = .516	
On methotrexate	0.69 (0.36 to 1.31), P = .254	
On TNFi	1.11 (0.33 to 3.76), P = .862	
On first biologic	1.04 (0.53 to 2.04), P = .918	
Repeated biologics failure	0.51 (0.08 to 3.17), P = .471	
Duration of baseline biologic	0.96 (0.89 to 1.04), P = .351	
Duration baseline biologic remission	1.02 (0.93 to 1.12), P = .689	
Duration baseline biologic LDA	0.97 (0.88 to 1.07), P = .542	
Previous attempt to taper biologic	0.66 (0.32 to 1.37), P = .264	
CRP before first biologic	1.00 (1.00 to 1.01), P = .322	
HAQ-DI	0.41 (0.17 to 0.99), P = .047	0.56 (0.26 to 1.22), P = .147
Pain VAS	0.97 (0.94 to 1.00), P = .049	0.99 (0.94 to 1.05), P = .808
Fatigue VAS	0.99 (0.97 to 1.00), P = .136	
Patient global health VAS	0.98 (0.96 to 1.00), P = .027	1.00 (0.97 to 1.04), P = .904
SF-36 PCS	1.04 (0.99 to 1.09), P = .102	
SF-36 MCS	1.06 (1.01 to 1.11), P = .012	1.05 (0.99 to 1.12), P = .098
Physician Global Health VAS	1.06 (0.94 to 1.20), P = .312	
No tender joints	1.61 (0.27 to 9.63), P = .601	
CRP	0.96 (0.85 to 1.10), P = .576	

TABLE 3   (Continued)

Possible baseline predictors	Univariable analysis RR (95% CI)	Multivariable analysis Data-driven RR (95% CI)
In remission[b]	1.43 (0.50 to 4.06), P = .505	

Abbreviations: 95% CI, 95% confidence interval; BMI, body mass index; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; HAQ-DI, Health Assessment Questionnaire Disability Index; LDA, low disease activity; MCS, mental component summary; PCS, physical component summary; RR, relative risk; SF-36, Short Form-36; TNFi, tumour necrosis factor inhibitor; VAS, Visual Analogue Scale.
[a]Rheumatic Disease Comorbidity Index.
[b]RA and PsA: DAS28-CRP < 2.6 and axSpA: ASDAS < 1.3.
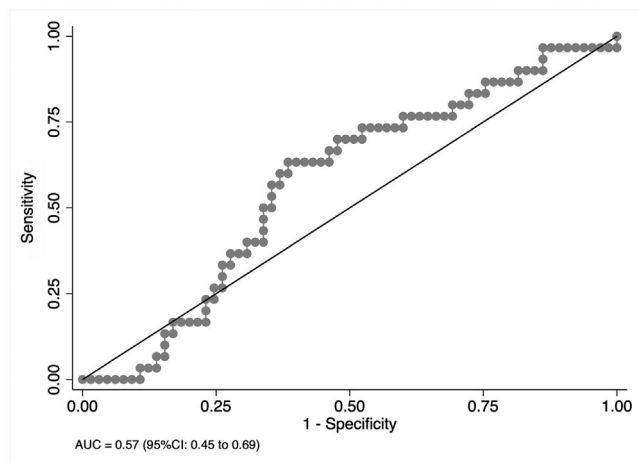

FIGURE 4   Area under the receiver operator curve for the data-driven model only including the tapering group with 95% confidence interval.

multivariable regression analyses did not reveal any statistically significant predictors (other than allocation to the tapering group). However, the analyses suggested that assessment of baseline mental health could be of potential importance as individuals with a better mental health state seem to achieve successful tapering more frequently. Future research is needed to address the impact of mental health during tapering.

The BIODOPT trial has several strengths as it was an investigator-initiated RCT with only few patients lost to follow-up. The eligibility criteria ensured a study population representative of the real-life outpatient population. An important strength to this study is that continuous variables were evaluated as recommended by TRI-POD i.e., kept in the continuous form unless significant nonlinearity was observed.[24,25] Nonlinearity was only found for *tender joints*, which then was handled as a categorical variable. Another strength is that possible collinearity was identified and handled by treelet transformation as highly correlated variables may decrease the signal of the correlated predictors. Thus, due to high correlation, VAS scores were combined into 1 score in a sensitivity analysis on the data-driven model. The analysis did not provide additional information. Lastly, internal validation was assessed with leave-1-out cross-validation; thereby, validating the data-driven model.

The SF-36 MCS and PCS provide an assessment of mental health and physical health ranging from 0 to 100 where higher scores equal better self-reported health.[29] The SF-36 MCS and PCS have been validated in RA, PsA and axSpA populations.[30–32] This study identified higher baseline SF-36 MCS as a nonsignificant predictor of potential importance for achieving successful biologic tapering in patients with IA in sustained LDA. *Posthoc* analyses found patients with SF-36 MCS > 50 to have a statistically significant higher chance for achieving successful tapering; thus, indicating that mental health could be important to consider before tapering is initiated and future research on this topic is encouraged. Previously, a literature review found patients with fibromyalgia to have significantly lower SF-36 MCS compared to the general population as well as patients with RA.[33] Recently, Matcham *et al.* demonstrated that a SF-36 MCS threshold of ≤38 in patients with RA could identify patients with present depression or anxiety.[34] *Posthoc* analysis on our data showed that only 1% (1/95) of patients in the tapering group achieved successful tapering if baseline SF-36 MCS was ≤38. Thus, patients with low SF-36 MCS might struggle with mental health issues or fibromyalgia, which could lead to greater coping difficulties with the treatment changes due to tapering. Similar to our study, the OPTTIRA trial demonstrated the importance of mental health when tapering TNFi in patients with RA.[35] However, only the SF-36 mental health subscale was found to be independently associated with the risk for flare whereas SF-36 MCS only was statistically significant in the unadjusted analysis.

A recent systematic review based on data from RCTs, reported no consistent predictors for successful biologic tapering/withdrawal or for flare in patients with RA or axSpA.[6] The most frequent predictors in RA trials were (number of studies): DAS28-CRP (n = 5), HAQ (n = 4), rheumatoid factor positivity (n = 2) and longer disease duration (n = 2); whereas great heterogeneity in the reported predictors was observed in the axSpA trials. In our study, HAQ-DI demonstrated significant univariate association but did not qualify as a statistically significant independent predictor for successful tapering in the data-driven multivariable model. Disease duration or disease activity (measured by remission or LDA) did not demonstrate statistically significant univariate prediction for successful tapering. In another systematic review, which was based on data from RCTs and observational studies in RA, higher adalimumab serum trough levels was the only predictor for successful biologic tapering.[15] However,
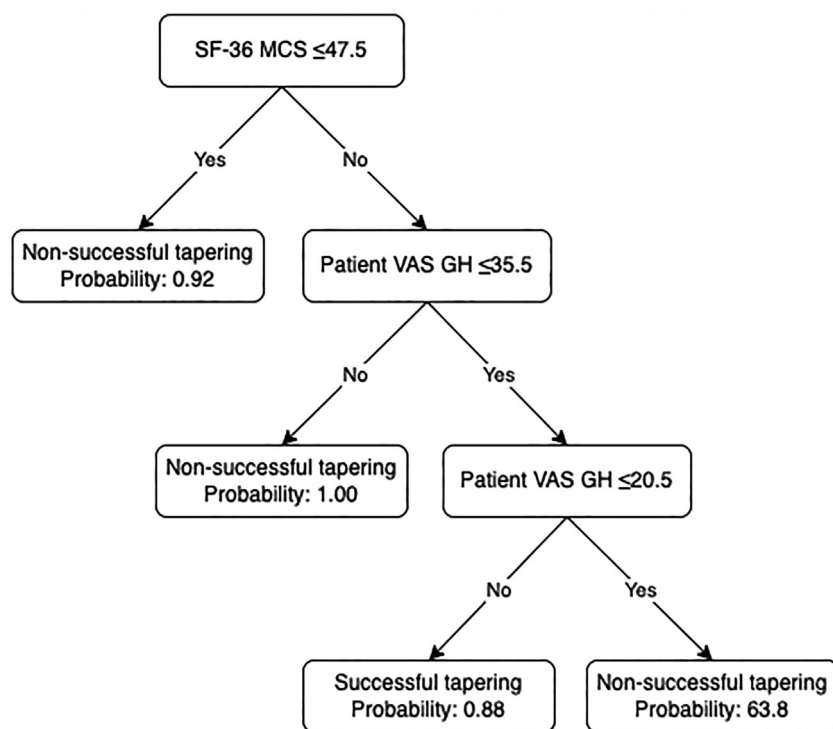
FIGURE 5   Classification tree identifying the most relevant predictors in the data-driven model including the tapering group.

the predictor was only evaluated in 2 studies and the level of evidence was labelled as limited; thus, conclusions must be made with caution.

An important limitation to the BIODOPT trial is that the sample size as the target population of 180 patients was not reached due to premature closure of enrolment because of the national implications of the COVID-19 pandemic. The lack of statistical power could lead to type II errors i.e., false negative results; thus, failure to detect relevant predictors. Therefore, the findings from this study must be interpreted with caution and future research is needed to provide additional insight. Another limitation to discuss is how predictors for the 2 models were selected i.e., variables with a univariate $P < .10$ and preselected variables based on expert opinion. Both methods come with a risk of type II errors as potentially important predictors can be rejected. Nonetheless, these methods were considered to be reasonable and preferable over e.g., backwards elimination as the data set and frequency of patients achieving successful tapering was relatively small. Another limitation to address is that patients with PsA were included based on DASPA LDA/remission but monitored during the trial by DAS28-CRP and the DAS28-based flare criteria. The authors acknowledge that a PsA-specific disease activity measure throughout the trial would have been more optimal. However, as no PsA-specific flare criteria were defined when the protocol was drafted, DAS28-CRP was chosen. Only endpoints that could be assessed in the whole IA population were evaluated in this study as sub-analyses would limit the statistical power further. Thus, disease specific variables, such as DAS28-CRP or ASDAS, were not included in the analyses. Lastly, the results of this study can only be generalized to patients treated with a TNFi as the majority of the BIODOPT study population received this treatment.

5 | CONCLUSION

One in 3 patients managed to reduce their biologic dose by ≥50% while maintaining low disease activity; thus, achieving successful tapering. No statistically significant predictors for achieving successful tapering were identified (other than allocation to the tapering group). Future research on mental health and tapering is needed to explore this topic further.

CONFLICTS OF INTERESTS STATEMENT

L.U. has received speaker's fee from AbbVie, Eli Lilly, Janssen and Novartis; L.D. has received speaker's fee from Eli Lilly, Galderma and Janssen, research grants from BMS; E.M.H. has received speaker's fee

DATA AVAILABILITY STATEMENT

Anonymised data will be shared upon reasonable request. The trial protocol and SAP are available as Supporting information documents.

ORCID

Line Uhrenholt https://orcid.org/0000-0002-4047-7175
Kirsten Duch https://orcid.org/0000-0002-5984-5134
Robin Christensen https://orcid.org/0000-0002-6600-0631
Lene Dreyer https://orcid.org/0000-0002-5156-2922
Ellen-Margrethe Hauge https://orcid.org/0000-0003-2562-9174
Peter C. Taylor https://orcid.org/0000-0001-7766-6167
Salome Kristensen https://orcid.org/0000-0001-5812-5234

REFERENCES

1. Smolen JS, Landewé RBM, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis*. 2020;79(6):685-699. doi:10.1136/annrheumdis-2019-216655

2. Gossec L, Baraliakos X, Kerschbaumer A, et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. *Ann Rheum Dis*. 2020;79(6):700-712. doi:10.1136/annrheumdis-2020-217159

3. Van der Heijde D, Ramiro S, Landewé R, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. *Ann Rheum Dis*. 2017;76(6):978-991. doi:10.1136/annrheumdis-2016-210770

4. Henaux S, Ruyssen-Witrand A, Cantagrel A, et al. Risk of losing remission, low disease activity or radiographic progression in case of bDMARD discontinuation or tapering in rheumatoid arthritis: systematic analysis of the literature and meta-analysis. *Ann Rheum Dis*. 2018;77(4):515-522. doi:10.1136/annrheumdis-2017-212423

5. Verhoef L, van den Bemt BJF, van der Maas A, et al. Down-titration and discontinuation strategies of tumour necrosis factor-blocking agents for rheumatoid arthritis in patients with low disease activity. *Cochrane Database Syst Rev*. 2019;5(6):CD010455. doi:10.1002/14651858.CD010455.pub3

6. Uhrenholt L, Christensen R, Dinesen WKH, et al. Risk of flare after tapering or withdrawal of b-/tsDMARDs in patients with RA or axSpA: a systematic review and meta-analysis. *Rheumatology (Oxford)*. 2022;61(8):3107-3122. doi:10.1093/rheumatology/keab902

7. Ruwaard J, L' Ami M, Kneepkens EL, et al. Interval prolongation of etanercept in rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis: a randomized controlled trial. *Scand J Rheumatol*. 2023;52(2):129-136. doi:10.1080/03009742.2022.2028364

8. Michielsens CAJ, den Broeder N, van den Hoogen FHJ, et al. Treat-to-target dose reduction and withdrawal strategy of TNF inhibitors in psoriatic arthritis and axial spondyloarthritis: a randomised controlled non-inferiority trial. *Ann Rheum Dis*. 2022;81(10):1392-1399. doi:10.1136/annrheumdis-2022-222260

9. Navarro-Compán V, Plasencia-Rodríguez C, de Miguel E, et al. Anti-TNF discontinuation and tapering strategies in patients with axial spondyloarthritis: a systematic literature review. *Rheumatology (Oxford)*. 2016;55(7):1188-1194. doi:10.1093/rheumatology/kew033

10. Michielsens CAJ, den Broeder N, Mulder MLM, van den Hoogen FHJ, Verhoef LM, den Broeder AA. Tumour necrosis factor inhibitor dose adaptation in psoriatic arthritis and axial spondyloarthritis (TAPAS): a retrospective cohort study. *Rheumatology (Oxford)*. 2022;61(6):2307-2315. doi:10.1093/rheumatology/keab741

11. Wetterslev M, Georgiadis S, Sørensen IJ, et al. Tapering of TNF inhibitors in axial spondyloarthritis in routine care—2-year clinical and MRI outcomes and predictors of successful tapering. *Rheumatology (Oxford)*. 2022;61(6):2398-2412. doi:10.1093/rheumatology/keab755

12. Arends S, van der Veer E, Kamps FBS, et al. Patient-tailored dose reduction of TNF-α blocking agents in ankylosing spondylitis patients with stable low disease activity in daily clinical practice. *Clin Exp Rheumatol*. 2015;33(2):174-180.

13. Ye W, Tucker L, Coates L. Tapering and discontinuation of biologics in patients with psoriatic arthritis with low disease activity. *Drugs*. 2018;78(16):1705-1715. doi:10.1007/s40265-018-0994-3

14. Uhrenholt L, Christensen R, Dreyer L, et al. Disease activity-guided tapering of biologics in patients with inflammatory arthritis: a pragmatic, randomised, open-label trial. *Scand J Rheumatol*. 2023;1-12. doi:10.1080/03009742.2023.2164979

15. Tweehuysen L, van den Ende CH, Beeren FMM, Been EMJ, van den Hoogen FHJ, den Broeder AA. Little evidence for usefulness of biomarkers for predicting successful dose reduction or discontinuation of a biologic agent in rheumatoid arthritis: a systematic review. *Arthritis Rheumatol*. 2017;69(2):301-308. doi:10.1002/art.39946

16. Uhrenholt L, Schlemmer A, Hauge EM, et al. Dosage reduction and discontinuation of biological disease-modifying antirheumatic drugs in patients with rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis: protocol for a pragmatic, randomised controlled trial (the BIOlogical dose OPTimisation [BIODOPT] trial). *BMJ Open*. 2019;9(7):e028517. doi:10.1136/bmjopen-2018-028517

17. Fransen J, Creemers MCW, van Riel PLCM. Remission in rheumatoid arthritis: agreement of the disease activity score (DAS28) with the ARA preliminary remission criteria. *Rheumatology (Oxford)*. 2004;43(10):1252-1255. doi:10.1093/rheumatology/keh297

18. Schoels MM, Aletaha D, Alasti F, Smolen JS. Disease activity in psoriatic arthritis (PsA): defining remission and treatment success using the DAPSA score. *Ann Rheum Dis*. 2016;75(5):811-818. doi:10.1136/annrheumdis-2015-207507

19. Machado P, Landewé R, Lie E, et al. Ankylosing spondylitis disease activity score (ASDAS): defining cut-off values for disease activity states and improvement scores. *Ann Rheum Dis*. 2011;70(1):47-53. doi:10.1136/ard.2010.138594

20. Christensen R, Langberg H. Statistical principles for prospective study protocols: design, analysis, and reporting. *Int J Sport Phys Ther*. 2012; 7:504-511.

21. Gamble C, Krishan A, Stocken D, et al. Guidelines for the content of statistical analysis plans in clinical trials. *JAMA*. 2017;318(23):2337-2343. doi:10.1001/jama.2017.18556

22. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010;340(mar23 1):c869. doi:10.1136/bmj.c869

23. Piaggio G, Elbourne DR, Pocock SJ, Evans SJW, Altman DG, CONSORT Group. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. *JAMA*. 2012;308(24):2594-2604. doi:10.1001/jama.2012.87802

24. Collins GS, Reitsma JB, Altman DG, Moons KGM. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *BMJ*. 2015;350(jan07 4): g7594. doi:10.1136/bmj.g7594

25. Moons KGM, Altman DG, Reitsma JB, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): explanation and elaboration. *Ann Intern Med*. 2015;162(1): W1-W73. doi:10.7326/M14-0698

26. Zou G. A modified Poisson regression approach to prospective studies with binary data. *Am J Epidemiol*. 2004;159(7):702-706. doi:10.1093/aje/kwh090

27. Gorst-Rasmussen A. Tt: treelet transform with Stata. *The Stata Journal*. 2012;12(1):130-146. doi:10.1177/1536867X1201200108

28. Shipe ME, Deppen SA, Farjah F, Grogan EL. Developing prediction models for clinical use using logistic regression: an overview. *J Thorac Dis*. 2019;11(S4):S574-S584. doi:10.21037/jtd.2019.01.25

29. Ware JE Jr. SF-36 health survey update. *Spine (Phila Pa 1976)*. 2000; (25):3130-3139. doi:10.1097/00007632-200012150-00008

30. Matcham F, Scott IC, Rayner L, et al. The impact of rheumatoid arthritis on quality-of-life assessed using the SF-36: a systematic review and meta-analysis. *Semin Arthritis Rheum*. 2014;44(2):123-130. doi:10.1016/j.semarthrit.2014.05.001

31. Leung YY, Ho KW, Zhu TY, Tam LS, Kun EWL, Li EKM. Testing scaling assumptions, reliability and validity of medical outcomes study short-form 36 health survey in psoriatic arthritis. *Rheumatology (Oxford)*. 2010;49(8):1495-1501. doi:10.1093/rheumatology/keq112

32. Yang X, Fan D, Xia Q, et al. The health-related quality of life of ankylosing spondylitis patients assessed by SF-36: a systematic review and meta-analysis. *Qual Life Res*. 2016;25(11):2711-2723. doi:10.1007/s11136-016-1345-z

33. Hoffman DL, Dukes EM. The health status burden of people with fibromyalgia: a review of studies that assessed health status with the SF-36 or the SF-12. *Int J Clin Pract*. 2008;62(1):115-126.

34. Matcham F, Norton S, Steer S, Hotopf M. Usefulness of the SF-36 health survey in screening for depressive and anxiety disorders in rheumatoid arthritis. *BMC Musculoskelet Disord*. 2016;17(1):224. doi:10.1186/s12891-016-1083-y

35. Bechman K, Sin FE, Ibrahim F, et al. Mental health, fatigue and function are associated with increased risk of disease flare following TNF inhibitor tapering in patients with rheumatoid arthritis: an exploratory analysis of data from the optimizing TNF tapering in RA (OPTTIRA) trial. *RMD Open*. 2018;4(1):e000676. doi:10.1136/rmdopen-2018-000676

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.