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Original article

Tumour necrosis factor inhibitor dose adaptation in psoriatic arthritis and axial spondyloarthritis (TAPAS): a retrospective cohort study

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Abstract

Objectives. We investigated the effect of disease activity-guided dose optimization (DAGDO) of TNF inhibitor (TNFi) on disease activity and TNFi dose in PsA and axial spondyloarthritis (axSpA) patients with low disease activity (LDA).

Methods. A retrospective cohort study was conducted in PsA and axSpA patients doing well on TNFi and eligible for TNFi DAGDO. Three different treatment periods were defined: (i) full dose continuation period, (ii) TNFi DAGDO period, and (iii) period with stable TNFi dose after DAGDO. A mixed-model analysis was used to estimate mean Disease Activity Score 28-joint count CRP (DAS28-CRP) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) during these periods, and a mean percentage of the daily defined dose (%DDD) was calculated as secondary outcome.

Results. Three hundred and twenty-four patients (153 PsA and 171 axSpA) were included, with a mean of 6.5 DAS28-CRP and 6.4 BASDAI measurements and a median follow-up duration of 46 and 44 months, respectively. A corrected difference of 0.06 (95% CI: −0.09, 0.21) in mean DAS28-CRP was found for the TNFi DAGDO period and 0.03 (95% CI: −0.14, 0.20) for the period with stable TNFi dose, compared with full dose continuation period. Differences for BASDAI were 0.03 (95% CI: −0.21, 0.27) and 0.05 (95% CI: −0.24, 0.34), respectively. The mean %DDD for the three treatment periods was for PsA 108%, 62% and 78%, and for axSpA 108%, 62% and 72%, respectively.

Conclusion. DAGDO of TNFi reduces drug exposure and has no negative effects on disease activity in PsA and axSpA patients compared with full dose continuation.

Key words: psoriatic arthritis, axial spondyloarthritis, TNF inhibitors, disease activity-guided, dose optimization, dose reduction, tapering, discontinuation, withdrawal, spacing

CLINICAL SCIENCE

Rheumatology key messages

- Disease activity-guided dose optimization does not increase disease activity in PsA and axSpA.
- A mean TNFi dose reduction of one-third is possible.

Introduction

TNF inhibitors (TNFi) have proven safe and effective in the treatment of spondyloarthritis (SpA), including PsA and axial spondyloarthritis (axSpA) [1, 2]. However, these drugs also have disadvantages such as an increased risk of infections, injection site reactions and the self-administration burden for patients, and high costs [3–6]. Disease activity-guided dose optimization (DAGDO) until complete withdrawal or flare could be a way to reduce these disadvantages [4]. However, there is still uncertainty concerning the effects of DAGDO and

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discontinuation of TNFi in PsA and axSpA patients with stable low disease activity (LDA) on long-term disease control and safety.

In RA, DAGDO of TNFi has been shown to be safe and (cost-)effective in multiple high quality trials [7, 8] and this strategy has been endorsed in recent recommendations [9]. For PsA and axSpA, both the evidence and recommendations are less clear. In PsA, no randomized controlled trials (RCTs) have been performed on DAGDO. One systematic review favoured DAGDO over discontinuation because of the substantial risk of losing remission of the latter [10]. Similar conclusions were derived from observational studies [11–14] and one recently published RCT on discontinuation in ixekizumab [15].

For axSpA, two systematic reviews [16, 17] and six RCTs [18–23] are available. The evidence is in line with that in PsA: TNFi reduction strategies are successful in maintaining clinical remission or LDA in a relevant proportion of patients, but discontinuation is dissuaded because it often leads to flares. However, the conducted studies in both PsA and axSpA investigate the possibility of fixed dose reduction or discontinuation often early after TNFi induction instead of DAGDO in patients with stable LDA. Literature on stepwise DAGDO strategies in prevalent PsA and axSpA patients is still lacking, with three randomized controlled trials on stepwise DAGDO strategies still ongoing [24–26]. Sample size is often an issue in these studies, with relatively small groups of patients participating in dose reduction or discontinuation and limited follow-up. Therefore, long-term follow-up data and a larger patient sample of DAGDO to explore the feasibility and efficacy in daily clinical practice is needed.

DAGDO or discontinuation of bDMARDs as a standard of care in adults with stable axSpA is currently discouraged by the ACR. These recommendations are, however, based on low quality evidence, which predominantly consists of observational studies with no direct comparison of tapered with non-tapered treatment, different patient selection (active disease at baseline) or a lack of DAGDO strategies [27]. The European Alliance of Associations for Rheumatology (EULAR) adopts a different view on tapering and discontinuation in PsA and axSpA. Considering the cost aspect, the guideline deems it appropriate to slowly taper bDMARDs in case of sustained remission [28, 29]. In summary, there is a lack of evidence regarding DAGDO in PsA and axSpA.

Since 2010, a specific TNFi DAGDO protocol has been implemented at our outpatient clinic for RA as well as for PsA and axSpA patients, together with standardized measurement of Disease Activity Score28-CRP (DAS28-CRP) in RA, and PsA patients and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) in axSpA patients. This allowed us to perform a controlled retrospective cohort study to explore the effect of DAGDO in a real life setting with regards to disease activity, (concomitant) medication use or switching, flare and infection rate.

Methods

Study design and patients

We conducted two parallel controlled retrospective cohort studies into the effect of DAGDO of TNFi on disease activity, (concomitant) medication use or switching, flare and infection rate, compared with full dose continuation in PsA and axSpA patients with stable LDA for $\geq$6 months (defined as DAS28-CRP $<$2.4 [or 2.9 in patients with disease duration $>$3 years] for PsA [30] or BASDAI $<$4 for axSpA [31] and/or according to the treating physician) and a minimal follow-up of 12 months. Patients $\geq$16 years, treated with TNFi (adalimumab, etanercept, certolizumab pegol, golimumab or infliximab) between April 2012 and October 2018 were enrolled at the rheumatology department of the Sint Maartenskliniek in Nijmegen, Woerden and Boxmeer, the Netherlands. Patients were considered eligible for inclusion if diagnosed clinically with PsA or axSpA by the treating rheumatologist (supported by the Classification for PsA [CASPAR] criteria for PsA and Assessment of Spondyloarthritis International Society [ASAS] criteria for axSpA).

Patients who attempted DAGDO before April 2012, who participated in other studies concerning DMARD adjustments during their inclusion, or who had fewer than two DAS28-CRP or BASDAI measurements were excluded. Patients with active extra-articular manifestations of disease, such as IBD, uveitis or psoriasis were also excluded, because these comorbidities being active would possibly preclude tapering. Other active extra-articular manifestations such as enthesitis were also considered to be active disease by rheumatologists, and therefore precluded tapering. Consent of all eligible patients for retrospective data collection was handled following an opt-out method (according to Dutch law [WGBO], article 458.2), and the study was judged not to require approval by the local ethics committee (CMO region Arnhem-Nijmegen, number 2020–6144).

We identified three TNFi treatment strategy periods, for which we compared the mean disease activity scores: (i) full dose continuation period, (ii) TNFi DAGDO period, and (iii) period with stable TNFi dose after DAGDO (at least 12 months after the last tapering attempt). We chose this subdivision because it was expected that patients who tapered might experience more short lived flares and thus higher disease activity while trying to achieve their optimal dose. By defining a period of stable TNFi dose after DAGDO, we avoid higher disease activity during tapering being masked by a longer period of LDA under a stable TNFi dose and thereby maximize the chance to find a potential negative effect of DAGDO compared with continuation. On the other hand, the estimation of the period with stable TNFi dose after DAGDO is also better for extrapolation of the results as short lived flares during DAGDO are no longer included in this period.

Treatment strategies

During the entire study period, a DAGDO protocol for TNFi was in use at the Sint Maartenskliniek. Treatment decisions were based on DAS28-CRP for PsA and BASDAI for axSpA. DAGDO was recommended when DAS28-CRP $<$ 2.4 (or 2.9 in patients with disease duration $>$3 years) for PsA patients and BASDAI $<$ 4 for axSpA patients had been reached for at least 6 months. TNFi were tapered stepwise according to a prespecified protocol for each drug (Table 1).

Patients, if eligible for DAGDO, were advised to taper their TNFi according to the protocol and could continue to taper at each subsequent visit while still in LDA. The protocol states every 3 months, but in clinical practice this was usually every 6–12 months.

PsA flare was defined (based on validated RA flare criteria [32]) as an increase of 1.2 points or 0.6 if DAS28-CRP score was $\geq$2.9 and axSpA flare as an increase of $>$2 points or $>$1 if BASDAI was $\geq$4. Although the latter criterion has not been formally validated, this was based on expert opinion. The axSpA flare criterion is based on the known cutoff of $\geq$4 (active disease) with a measurement error of 1.0 [33]. In cases of flare (based on the proposed flare criteria or as judged by the treating rheumatologist), intensification of treatment was advised. Temporary treatment with oral or intra-articular or intramuscular glucocorticoids or NSAIDs could be used. The protocol recommended the reassessment of patients after 1 month and the reinstatement of the last effective interval or dose in cases of persistent flare. If improvement of disease activity was insufficient, patients were switched to another TNFi or non-TNFi biologic (b)/targeted synthetic (ts)DMARDs.

Outcomes

The primary outcomes of this study were the differences in mean DAS28-CRP and BASDAI between the three treatment periods. Key secondary outcomes were differences in the TNFi use between the three treatment periods, by calculating the mean percentage of daily defined dose (%DDD); the difference in concomitant conventional synthetic (cs)DMARD use and bDMARD switching between the three treatment periods; the difference in oral or intra-articular/intramuscular glucocorticoid and NSAID use; and the difference in flares and infections. The percentage of patients discontinuing their TNFi because of remission was included as an additional secondary outcome.

Statistical analysis

Since we expected repeated and non-standardized timed disease activity measurements in this cohort, we chose to analyse the difference in mean DAS28-CRP for PsA and BASDAI for axSpA with a linear mixed-model using a random intercept to take into account correlations between multiple measures within patients. By choosing mixed-model analysis, we assumed gain of a more conservative estimation with this treatment period division, since patients with higher disease activity are expected to have more measurements. Possible confounders were added to the models: age, gender, baseline sacroiliitis (only for axSpA), disease duration, time since eligibility for DAGDO and use of concomitant csDMARDs. Descriptive statistics were used for demographic data and TNFi use, expressed as %DDD and compared between the three treatment periods. In addition, a sensitivity analysis was performed, wherein the %DDD was weighted by follow-up duration. These statistics were provided with mean (S.D.) or median (interquartile range, IQR) depending on distribution. For PsA, sensitivity analyses were performed with CASPAR positive only patients, regarding the mixed-model and %DDD. Mixed-model Poisson regression was used to determine the difference in the incidence rate ratio (IRR) of csDMARD escalation, TNFi switch, glucocorticoid initiation or escalation, NSAID initiation, flares and infections between the three treatment periods. In cases of a missing patient global visual analogue scale (VAS), DAS28-CRP measurements of PsA patients were calculated using the three-variable DAS28-CRP, which correlates strongly with the four-variable DAS28-CRP [34]. STATA/IC v13.1 (StataCorp, College Station, TX, USA) was used for all analyses.

Table 1 DAGDO strategy of TNFi in PsA and axSpA

TNFi	100%	66%	50%	33%	0%
Adalimumab/ certolizumab pegol	40 mg 2 week interval	40 mg 3 week interval	40 mg 4 week interval	40 mg 6 week interval	Stop TNFi
Etanercept	50 mg 1 week interval	50 mg 10 days interval	50 mg 2 week interval	50 mg 3 week interval	Stop TNFi
Golimumab	50 mg 1 month interval	50 mg 1.5 month interval	50 mg 2 month interval	50 mg 3 month interval	Stop TNFi
Infliximab[a]	3 mg/kg 8 week interval	2.25 mg/kg 8 week interval	1.5 mg/kg 8 week interval	Stop TNFi	Stop TNFi

[a]In our protocol, in line with RA, 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. axSpA: axial spondyloarthritis; DAGDO: disease activity-guided dose optimization; TNFi: TNF inhibitor.

Results

Patients

A total of 324 patients (PsA: $n = 153$; axSpA: $n = 171$) were included in this study (baseline characteristics depicted in Table 2). Clinical diagnosis was supported by classification criteria, with at least 60% of the PsA patients meeting the CASPAR and 80% of the axSpA patients the ASAS criteria. A similar mean number of disease activity measurements was available in both groups, respectively 6.5 DAS28-CRP (S.D. 3.0) and 6.4 BASDAI (S.D. 3.0) measurements. Median follow-up duration was 44 (IQR: 25–58) and 31 (IQR: 18–44) months, respectively for PsA and axSpA patients who never attempted dose reduction and 46 (IQR: 29–58) and 44 (IQR: 32–56) months, respectively, for those who did. Eighty-one percent of PsA and 68% of axSpA patients attempted dose reduction at least once, whereas 19% PsA and 32% axSpA patients did not, despite being eligible for dose reduction.

Disease activity and TNFi use

In PsA, the linear mixed-model resulted in a mean DAS28-CRP of 1.94 in the full dose continuation period (95% CI: 1.80, 2.08); 2.0 in the TNFi DAGDO period (95% CI: 1.89, 2.11); and 1.97 in the period with stable TNFi dose after DAGDO (95% CI: 1.86, 2.09). In axSpA, the mean BASDAI was 3.44 (95% CI: 3.18, 3.70) in the full dose continuation period; 3.47 (95% CI: 3.19, 3.74) in the TNFi DAGDO period; and 3.48 (95% CI: 3.19, 3.78) in the period with stable TNFi dose after DAGDO. No significant differences were found in either mean DAS28-CRP or BASDAI between the three treatment periods (Tables 3 and 4) and relevant differences were excluded by the 95% CI. Higher age ($P = 0.02$), longer disease duration ($P < 0.01$) and follow-up duration ($P = 0.04$) were significantly associated with a higher DAS28-CRP score in PsA. In axSpA, higher age ($P < 0.01$) and female gender ($P < 0.01$) were significantly associated with a higher BASDAI score. The mean %DDD for PsA was 108% in the full dose continuation

Table 2 Baseline characteristics of PsA and axSpA patients

Characteristic	PsA ($n = 153$)	axSpA ($n = 171$)
Female, *n* (%)	60 (39%)	68 (40%)
Age at inclusion, mean (S.D.), years	52 (11)	46 (13)
Disease duration at inclusion, median (IQR), years	7 (3–14)	12 (4–18)
Rheumatoid factor positivity (145/153), *n* (%)	12 (8)	—
Anti-CCP positivity (146/153), *n* (%)	9 (6)	—
HLA-B27 positivity (135/171), *n* (%)	—	115 (85)
CASPAR criteria, *n* (%)	92 (60)	—
ASAS criteria, *n* (%)	—	137 (80)
Erosions on radiographic imaging, *n* (%)	34 (22)	—
Sacroiliitis on radiographic imaging, *n* (%)	—	87 (51)
Number of previous bDMARD, *n* (%)		
0	103 (67)	90 (53)
1	39 (25)	50 (29)
2 or 3	11 (7)	31 (18)
Number of previous csDMARD, *n* (%)		
0	21 (14)	112 (66)
1	51 (33)	35 (20)
≥2	81 (53)	24 (14)
Current bDMARD use, *n* (%)		
Adalimumab	50 (33)	74 (44)
Etanercept	81 (53)	55 (32)
Golimumab	3 (2)	21 (12)
Infliximab	19 (12)	21 (12)
Current csDMARD use, *n* (%)		
None	71 (46)	152 (89)
Methotrexate	67 (43)	10 (6)
Leflunomide	12 (8)	1 (1)
Sulfasalazine	3 (2)	9 (5)
Hydroxychloroquine	1 (1)	0 (0)
Current NSAID use, *n* (%)	100 (65)	88 (52)
Duration of current bDMARD use, years, median (IQR)	3 (1–5)	3 (2–6)
Duration of follow-up, months, median (IQR)	46 (28–58)	41 (26–56)

ASAS: Assessment of Spondyloarthritis International Society; axSpA: axial spondyloarthritis; bDMARD: biologic DMARD; CASPAR: Classification for PsA; csDMARD: conventional synthetic DMARD; IQR: interquartile range.

Table 3 Mixed-model results PsA, estimation of mean DAS28-CRP between three treatment periods corrected for potential confounders

	Estimated effect (95% CI)	*P*-value
Gender (reference is male)	0.12 (0.06, 0.31)	0.19
Age (per year)	0.01 (0.00, 0.02)	0.02
Disease duration at baseline (per year)	0.02 (0.01, 0.03)	<0.01
Time since baseline (per year)	−0.04 (−0.09, −0.00)	0.04
csDMARD use (yes *vs* no, time varying)	0.05 (−0.12, 0.22)	0.54
Time period		
TNFi DAGDO *vs* full dose continuation	0.06 (−0.09, 0.21)	0.44
Stable TNFi dose after DAGDO *vs* full dose continuation	0.03 (−0.14, 0.20)	0.72

DAS28-CRP: Disease Activity Score 28-joint count CRP; csDMARD: conventional synthetic DMARD; DAGDO: disease activity-guided dose optimization.

Table 4 Mixed-model results axSpA, estimation of mean BASDAI between three treatment periods corrected for potential confounders

	Estimated effect (95 % CI)	*P*-value
Gender (reference is male)	1.08 (0.59, 1.56)	<0.01
Age (per year)	0.03 (0.01, 0.05)	<0.01
Disease duration at baseline (per year)	0.03 (0.00, 0.05)	0.07
Time since baseline (per year)	0.06 (−0.01, 0.13)	0.10
csDMARD use (yes *vs* no, time varying)	−0.04 (−0.59, 0.51)	0.89
Sacroiliitis at baseline (yes *vs* no)	−0.16 (−0.64, 0.32)	0.52
Time period		
TNFi DAGDO *vs* full dose continuation	0.03 (−0.21, 0.27)	0.82
Stable TNFi dose after DAGDO *vs* full dose continuation	0.05 (−0.24, 0.34)	0.75

axSpA: axial spondyloarthritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; csDMARD: conventional synthetic DMARD; DAGDO: disease activity-guided dose optimization.

period, 62% in the TNFi DAGDO period and 78% in the period with stable TNFi dose after DAGDO. For axSpA patients this was respectively 108%, 62% and 72%. The additional sensitivity analysis, calculating mean %DDD weighted by follow-up duration instead of disease activity, showed very similar results. The mean %DDD was 66% in the TNFi DAGDO period and 75% in the stable TNFi dose period after DAGDO for PsA; and respectively 66% and 73% for axSpA. The sensitivity analyses with only CASPAR positive PsA patients also showed no relevant differences in mean DAS28-CRP between the three time periods (TNFi DAGDO period: −0.03 [95% CI: −0.22, 0.17] and stable TNFi dose after DAGDO period: −0.07 [95% CI: −0.28, 0.15], compared with full dose continuation period) with similar %DDD (full dose continuation period: 111%; TNFi DAGDO period: 61%; and stable TNFi dose after DAGDO period: 76%).

Concomitant medication use, switching, flares and infections

In PsA patients, incidence of csDMARD dose escalation did not differ significantly between the three periods, with actually numerically lower rates during the tapering and stable dose period, nor did the rate of switching to another bDMARD differ between the three periods in PsA and axSpA (Table 5). The IRR of initiation or dose escalation of glucocorticoids did not differ in PsA, while in axSpA, glucocorticoid injections (0.42 [0.19–0.90], $P = 0.03$; 0.40 [0.17—0.93], $P = 0.03$) and NSAIDs (0.32 [0.21–0.49], $P < 0.01$; 0.31 [0.19–0.51], $P < 0.01$) were started significantly less frequently during the DAGDO period and stable dose period after DAGDO (Table 5). In PsA the IRR of disease flares was numerically higher (Table 5), and in contrast significantly lower in axSpA in the TNFi DAGDO period (0.60 [0.43–0.85], $P < 0.01$), compared with the full dose continuation period. In terms of safety, no significant differences were detected regarding the occurrence of infections (Table 5). Eighteen (12%) of the PsA patients discontinued their bDMARD as part of tapering, of whom 11 (61%) did not reinstate TNFi treatment during follow-up. Fifty-six (45%) of the tapered PsA patients eventually reinstated full dose TNFi. In axSpA, 16 (14%) of the patients discontinued their bDMARD as part of tapering, of whom 10 (63%) did not reinstate TNFi treatment during follow-up. Sixteen (14%) of the tapered axSpA patients eventually reinstated full dose TNFi.

Table 5 Poisson regression between three treatment periods in PsA and axSpA patients

	Incidence rate full dose continuation	Incidence rate ratio DAGDO		Incidence rate ratio stable TNFi dose after DAGDO	
	Events per patient year	Rate ratio compared with full dose continuation	*P*-value	Rate ratio compared with full dose continuation	*P*-value
PsA					
csDMARD escalation	0.04 (0.02, 0.09)	0.77 (0.34, 1.76)	0.54	0.86 (0.36, 2.07)	0.74
TNFi switch	0.03 (0.01, 0.07)	0.45 (0.11, 1.90)	0.28	1.32 (0.40, 4.32)	0.65
Oral glucocorticoid initiation or escalation	0.02 (0.01, 0.05)	0.75 (0.15, 3.74)	0.73	1.46 (0.33, 6.54)	0.62
Glucocorticoid injections	0.24 (0.17, 0.36)	0.87 (0.57, 1.33)	0.52	1.30 (0.85, 2.00)	0.23
Flares	0.12 (0.07, 0.20)	1.25 (0.73, 2.16)	0.41	1.31 (0.74, 2.32)	0.36
Infections, per patient year	0.04 (0.02, 0.10)	0.76 (0.30, 1.92)	0.57	0.77 (0.28, 2.10)	0.60
AxSpA					
TNFi switch	0.04 (0.02, 0.07)	0.46 (0.13, 1.65)	0.23	1.27 (0.47, 3.42)	0.64
Glucocorticoid injections	0.06 (0.03, 0.11)	0.42 (0.19, 0.90)	0.03	0.40 (0.17, 0.93)	0.03
NSAID initiation	0.48 (0.40, 0.58)	0.32 (0.21, 0.49)	<0.01	0.31 (0.19, 0.51)	<0.01
Flares	0.42 (0.36, 0.51)	0.60 (0.43, 0.85)	<0.01	0.74 (0.51, 1.06)	0.10
Infections, per patient year	0.02 (0.01, 0.05)	1.20 (0.38, 3.80)	0.75	1.33 (0.39, 4.53)	0.65

axSpA: axial spondyloarthritis; DAGDO: disease activity-guided dose optimization; TNFi: TNF inhibitor; csDMARD: conventional synthetic DMARD.

Discussion

This large and long-term retrospective cohort study indicates that DAGDO—in line with results in RA—is also effective and safe in PsA and axSpA patients who are doing well on their TNFi. This strategy resulted in lower doses of TNFi being used with no significant difference in disease activity score for both PsA and axSpA between the three treatment periods.

The mean TNFi %DDD was 62% in PsA and 62% in axSpA during the TNFi DAGDO period and respectively 78% and 72% in the period with stable TNFi dose after DAGDO. Compared with studies in RA [7, 35], this is a modest degree of tapering. Explanations for this difference could be that the full dose reduction potential was not met due to suboptimal execution of the local protocol, whereas in prospective intervention trials, protocol adherence is likely higher. A reason for lower protocol adherence might be that physicians taper carefully because RCTs in PsA and axSpA on the subject are lacking. Although it could be that further tapering was indeed not possible, this should be accompanied by higher rates of flares and the use of additional comedication as flare treatment and this was not the case in PsA and axSpA. In addition, the %DDD mean was weighted by the number of disease activity measurements to accurately reflect the relation between disease activity and TNFi dose, which could result in a higher estimated dose if patients doing well (and thus able to taper more) were measured less often. However, mean %DDD weighted by follow-up duration was very similar at 66% and 66% in the tapering period and 75% and 73% in the stable dose period for PsA and axSpA, respectively, so this effect was limited.

Our results showed that of the patients who tapered their TNFi as part of DAGDO, 45% of PsA and 14% of axSpA patients eventually reinstated full dose TNFi. A possible explanation for this higher number in PsA patients could be that the full dose optimization potential was not fully reached in our study, leading to an overestimation of this percentage. Open label tapering and use of (in part) subjective disease activity measures can well lead to a nocebo effect or a false causal attribution effect, which was clearly demonstrated in the study of Tweehuysen *et al.* [36]. The suggestion that this higher rate of reinstatement in PsA could be the result of a lack of real remission prior to discontinuation seems less likely. There are some data in RA that baseline disease activity is associated with lower chance of successful tapering, but effects are small and not consistent with a relevant proportion of patients with LDA being able to successfully taper [37]. Despite lacking data on predictors for successful tapering in PsA and axSpA, it seems unlikely that many patients starting DAGDO would have much remaining disease activity, and that this has led to less successful tapering.

In our study, the IRR of infections was relatively low, with only 0.04 (0.02–0.10) for PsA and 0.02 (0.01–0.05) for axSpA per patient year in the full dose continuation period. In comparison, other studies report ~0.6 for mild and 0.02 for severe infections per patient year [4, 5]. This low incidence is in part driven by under-reporting, inherent to the retrospective design of our study. Furthermore, our centre being a specialized rheumatology outpatient clinic, under-reporting of infections might occur due to the fact that our patients' possible infectious complications are often treated in other hospitals. Anyway, no differences between periods were found, in

line with earlier findings that effects of DAGDO on infection risk is marginal [5, 7].

In our population, a minimal 60% of the PsA patients met the CASPAR criteria. Although this number is relatively low, this does not hamper generalizability in our view. Firstly, it should be noted that the sensitivity of the criteria for PsA diagnosis is ~87%, and this—instead of 100%—would be the upper limit of CASPAR positive patients in clinical practice [38]. Furthermore, the retrospective nature of our study means that we have not been able to verify all elements of the criteria system, underestimating the number of patients meeting the criteria. Indeed, sensitivity analyses in CASPAR positive patients only showed no important differences in disease activity score and TNFi use compared with a full data set analysis.

The strengths of our study include firstly the considerable sample size of DAGDO in current clinical practice. Furthermore, disease activity was frequently assessed with validated disease activity measures. Follow-up was ample, respectively a median of 46 (IQR: 28–58) and 41 (IQR: 26–56) months, and much longer than in DAGDO RCTs in RA (12–18 months). Also, the decision to analyse three treatment periods instead of two enables us to estimate the disease activity and medication use not only during the DAGDO period but also after this period. The results in this stable period after DAGDO gives us more insight on the consequences of tapering on disease activity.

Limitations of our study are the open label nature with the possibility of nocebo effects, incorrect attribution and information bias, as it might be expected that disease activity was more often assessed in patients who actively tapered their TNFi, and that tapering itself would lead to more perceived flares due to nocebo effects and incorrect attribution of increase in disease activity to the tapering process. However, all these effects would bias our results towards higher disease activity and flare rate during DAGDO, which were not observed. Also the fact that choice of treatment was based on physician and patient preference rather than randomization could have resulted in confounding by indication. However, no important differences were seen between baseline patient characteristics in patients who attempted tapering at any time with those who did not taper. Only gender and the type of TNFi differed slightly between patients who tapered and who did not. Of these, gender was corrected for in our mixed model and the type of TNFi is unlikely to impact our primary outcome. Although we corrected for the most likely potential confounders, residual or unmeasured confounding cannot be ruled out in this retrospective study. Another limitation is the use of DAS28-CRP for PsA and BASDAI for axSpA as disease activity measurement tools instead of more modern disease activity indices, such as the PsA Disease Activity Score (PASDAS) and Ankylosing Spondylitis Disease Activity Score (ASDAS). However, the PASDAS and ASDAS were not available at the time of the study, and in published [39, 40] or ongoing [24–26] trials on DAGDO strategies in PsA and axSpA different DAGDO and outcome measures were used, as the field is still developing. Since the DAS28-CRP as disease activity score does not include the feet and extra-articular manifestations, disease activity could be underestimated. However, we expect this effect to be limited as the DAS28-CRP also incorporates patient global assessment and acute phase response. Furthermore, DAGDO was performed by rheumatologists well aware of the limitations of the DAS28-CRP, and they routinely assess skin and enthesitis, although not formally. Patients will also recognize increases in extra-articular disease activity, and request treatment intensification. Therefore, a relevant increase in disease activity, although only partly measured by DAS28-CRP, would most likely not be missed. Finally, potential underestimation of disease activity by DAS28-CRP is unlikely to differ between the DAGDO period and the full dose continuation period. Although both measures are now seen as suboptimal for measuring disease activity in PsA and AxSpA, we believe that the validity and reliability is high enough to still provide valuable information, when used in DAGDO and outcome assessment.

In conclusion, our study suggests that DAGDO is effective and safe in PsA as well as axSpA. However, in light of the limitations, more definite evidence should be provided by well-designed randomized prospective studies.

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Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author according to FAIR principles.

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