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Review

Tapering or discontinuation of biological disease-modifying antirheumatic drugs in axial spondyloarthritis: A review of the literature and discussion on current practice

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ABSTRACT

Biological disease-modifying antirheumatic drugs (bDMARDs) have taken up an important role in the management of axial spondyloarthritis. Once stable remission or low disease activity has been achieved with bDMARDs, it may be possible to maintain this state with lower levels of these drugs. Studies consistently demonstrate that tapering of tumor necrosis factor alpha inhibitors (TNFi) is not inferior to full-dose continuation in terms of maintaining treatment response, while data for tapering of interleukin-17 inhibitors (IL-17i) is lacking. Complete discontinuation of TNFi and IL-17i, however, often results in relapse and should not be recommended at this moment. Clear safety benefits of tapering or discontinuation have not been shown, although studies were typically not designed to address this. Current evidence does not support specific tapering or discontinuation strategies, although stepwise disease activity-guided regimens do allow for a more personalized approach and might be preferred. The definition of what constitutes an appropriate disease state to initiate tapering or discontinuation is unclear, and requires further study. Also, reliable predictors of successful tapering and discontinuation have not yet been identified. Fortunately, if tapering or discontinuation fails, most patients are able to regain disease control when reverted to the original bDMARD regimen. Finally, most patients indicate that, when asked, they would be willing to try tapering if the rationale is clear and if it is in their best interests. The decision to taper or discontinue should be made through shared decision-making, as this could improve the likelihood of success.

1. Introduction

The introduction of the first biological disease-modifying antirheumatic drugs (bDMARDs) over twenty years ago led to unprecedented change in the management of axial spondyloarthritis (axSpA). Pharmacological therapies available then, had limited effects on improving disease outcomes in axSpA. Biological DMARDs, initially of the tumor necrosis factor alpha inhibitor (TNFi) type, demonstrated good efficacy and acceptable safety. Since then, bDMARDs have taken up an important role in the management of axSpA [1].

It has become evident over the years that not all patients who achieve inactive disease or low disease activity with bDMARDs, require these to be continued at full dose to maintain their effect [2,3]. If the disease is in remission, it may be possible to keep that state with lower levels of the drug, or even without the drug. As such, some patients are overtreated. Dose reduction, by tapering or complete discontinuation, would be an alternative in these patients, and comes with multiple advantages for patients and society. Lower drug administration frequency could reduce the burden for the patient and the healthcare system, saving time and costs. The risk of bDMARD-associated adverse events could be lower, or even non-existent, once tapered or discontinued. Also, as bDMARDs are costly, any efforts to reduce their impact on the

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Box 1 : Methodology for this review

For the current review, data from two reviews on bDMARD efficacy and safety – conducted to inform the 2016 and 2022 ASAS-EULAR management recommendations for axSpA – were used [51,52]. As these reviews covered the period up to 2021, an additional PubMed search was conducted with the search terms "ankylosing spondylitis", "axial spondyloarthritis", "tapering", "discontinuation", "withdrawal", "TNF inhibitor", "biologic" and "bDMARD" (including variations) to identify recent studies on the topic. Furthermore, the EULAR 2022 Annual Congress abstract archive was checked for new studies. Finally, references of reviews on tapering and discontinuation in axSpA were reviewed for additional articles of interest. CW was responsible for article screening and review.

Box 2 : Definition of terms as used in this review

Term	Definition
Dose reduction	Any strategy that involves lowering and/or completely stopping the cumulative dose received by a patient
Tapering	Prolonging the interval between administrations (*spacing*) or reducing the administered dose
Stepwise tapering	Progressive dose reduction in multiple steps, often (but not necessarily) guided by disease activity at each step
Instant tapering	Tapering in one single step, either by *spacing* or by reducing the administered dose
Discontinuation	Completely stopping a bDMARD
Instant discontinuation	Discontinuation of a bDMARD from full dose at once, not preceded by any dose reduction by tapering
Tapering to discontinuation	Discontinuation of a bDMARD after dose reduction by tapering
Full dose, standard dose	Dose and frequency as approved and recommended for indication
Remission	Inactive disease with minimal symptoms, reflected by a very low disease activity score (clinical remission)
Flare, relapse	Increase in disease activity and/or symptoms that requires a change in treatment

management costs of axSpA would be desired. This would free up space in healthcare budgets. That is not to say that there are no potential disadvantages of dose reduction. The most obvious one would be the risk of relapse, affecting patient health and reducing the cost benefits of these strategies.

Over the last decade, an increasing number of studies explored tapering and discontinuation of bDMARDs in axSpA. This review (see Box 1 for methodology) aims to provide a comprehensive overview of the important evidence in this area.

2. Tapering and discontinuation

Throughout the literature on tapering of bDMARDs in axSpA, a variety of different terms are used (see Box 2 for definitions used in this review). Although studies typically focus on tapering or discontinuation, both can be considered part of same spectrum of strategies aimed at reducing the dose received by the patient over a period. Tapering can involve spacing, reduction of the administered dose or both (simultaneously or sequentially). Tapering or discontinuation strategies vary in complexity. Some are rather simple, for example instantly stopping a bDMARD. Others follow quite elaborate 'multiple-step' progressive regimens that can be adapted further depending on the individual's disease status while tapering (such as disease-activity guided tapering, where the dose is typically tapered until a flare occurs).

3. Effectiveness of tapering bDMARDs

Initial case series and observational studies showed the feasibility of tapering TNFi in axSpA without loss of response [2–5]. Since then, 11 randomized controlled trials (RCTs) in axSpA investigated bDMARD tapering (Table 1) [6–16]. These typically assessed whether tapering was non-inferior to standard-dose bDMARD continuation in terms of clinical effectiveness (i.e. maintaining a certain disease state or absence of flare, often based on ASDAS or BASDAI [17]). Importantly, TNFi were the only bDMARD class investigated. Some studies included an open-label induction phase, thus enrolling patients with active disease. These were then randomized to tapering or full-dose continuation only if they achieved a remission or low disease activity state after this induction phase. Other studies enrolled patients who already were in such a disease state in clinical practice. In two trials, patients could stop the TNFi after tapering (tapering to discontinuation, see "Effectiveness of discontinuation" below) [15,16].

Overall, the findings of these RCTs suggest that tapering of TNFi is possible, i.e. not inferior to standard-dose continuation, for maintaining response. The risk of relapse was often comparable in those who taper and those who do not (Table 1) [6,8,9,11–15]. These favourable results have been observed in both r-axSpA and nr-axSpA. Most studies used spacing as tapering method, which can be explained by the mode of administration of TNFi. For subcutaneously administered TNFi (adalimumab [ADA], certolizumab pegol [CZP], etanercept [ETN], golimumab [GOL]), spacing allows for a more pragmatic implementation, as it does not require changes to preparation of prefilled syringes. For intravenously administered TNFi (infliximab [IFX]), however, administered dose reduction is a more efficient way to maintain a minimal effective concentration [18].

Interestingly, in the only trial that strictly used reduction of the administered dose as tapering method (ANSWERS, 50% ETN dose), tapering was inferior [7]. Of note, this study only required patients to have treatment response at one point in time (6 months after ETN initiation), instead of a minimum period of stable remission. Patients might not have been in remission long enough before tapering.

When characterizing specific tapering schemes, earlier studies used a single-step approach, while more recent trials employed stepwise tapering, often disease-activity guided (Box 1, Table 2). An example is DRESS-PS, where TNFi were tapered according to a predefined protocol (mainly by spacing, except for IFX), and patients only moved on to the next step if low disease activity was maintained [12]. Also, the TNFi dose was increased again when a persistent flare occurred. Other stepwise schemes used similar approaches [11,14]. The advantage of stepwise tapering schemes is that, in case of relapse, one can revert back to the previous tapered dose and often regain control, while still maintaining some degree of tapering. Such schemes also allow for a more personalized approach. Due to heterogeneity between trials, it is difficult to judge whether certain tapering schemes are more effective than others, or whether there is a clear relationship between the extent of dose reduction (i.e. the percentage of full-dose equivalent that patients received) and the success of tapering (maintaining their initial clinical state). Regarding the latter, it should be noted that dose reduction percentages were in similar range for most trials, often $\geq$ 50% of full dose. It would be of interest to have multiple tapering strategies within the same trial. The only study that did include multiple tapering strategies (stepwise ETN tapering after 12 weeks of full-dose treatment, and delayed stepwise ETN tapering after 24 weeks of full-dose

Table 1
Randomized controlled trials investigating tapering of bDMARDs in axSpA.

Strategy Study	Drug(s)	Population	Tapering entry criteria[a]	Induction[b]	Intervention *Comparator*	N	Time (wks)[c]	Outcome definition	Outcome	Tapering success[d]
Spacing										
Lukas, 2021 [11]	ADA, CZP, ETN, GOL, IFX	axSpA	BASDAI < 4 for ≥ 6m	No	TNFi spacing *Standard-dose TNFi*	197 201	52	BASDAI < 4 at 52w (non-inferiority)	88.0% 91.5%	+
Cantini, 2013 [6]	ETN	r-axSpA	BASDAI < 4, no PD or uveitis, CRP/ESR ≤ ULN	Yes (2y)	ETN 50 mg Q2W *Standard-dose ETN*	22 21	91–95	Maintain remission (see entry criteria)	86.3% 90.4%	+
Li, 2016 [8]	ETN	r-axSpA + hip involvement	None reported	Yes (4w)	ETN 25 mg QW *Standard-dose ETN*	26 17	8	BASDAI at 8w	1.42 1.40	+
Ruwaard, 2022 [13]	ETN	r-axSpA[e]	ASDAS < 2.1 for ≥ 6m	No	ETN spacing[i] *Standard-dose ETN*	20 20	26	Maintain remission (ASDAS < 2.1)	55.0% 65.0%	+
C-OPTIMISE [15]	CZP	axSpA (early)	ASDAS < 1.3 at 32/36w and 48w of induction	Yes (48w)	CZP 200 mg Q4W *Standard-dose CZP*	105 104	48	Absence of flare[f]	79.0% 83.7%	NR
GO-BACK [16]	GOL	nr-axSpA (early)	ASDAS < 1.3 at 7m and 10m of induction	Yes (10 m)	GOL 50 mg Q2M *Standard-dose GOL*	64 63	52	Absence of flare[f]	68.3% 84.1%	–
BIODOPT[g] [14]	ADA, CZP, ETN, GOL, IFX	axSpA[g]	Remission/LDA (not specified) for ≥ 12m	No	TNFi spacing *Daily practice TNFi*	95 47	78	Superiority: dose ≥ 50% reduced at 78w Equivalence: ASDAS at 78w	36.8% 2.1% 1.75 1.84	+ +
Administered dose reduction										
ANSWERS [7]	ETN	r-axSpA	BASDAI 50% or ≥ 2 unit decrease, and spinal pain ≥ 2 unit decrease	Yes (26w)	ETN 25 mg QW *Standard-dose ETN (50 mg QW)*	23 24	26	Maintain response (see entry criteria, non-inferiority)	52.2% 83.3%	–
Combined[h]										
REDES-TNF [9]	ADA, ETN, GOL, IFX	axSpA	BASDAI ≤ 2, no PD, CRP ≤ ULN for ≥ 6m	No	TNFi tapering *Standard-dose TNFi*	55 58	52	BASDAI, PhGA. PtGA, night pain < 4 at 52w (non-inferiority)	81.3% 83.3%	+
DRESS-PS [12]	ADA, CZP, ETN, GOL, IFX	axSpA[e]	ASDAS < 2.1 for ≥ 6m	No	T2T with tapering[i] *T2T without tapering*	39 19	52	ASDAS < 2.1 at 52w (non-inferiority)	66.7% 73.7%	+
Zhang, 2020 [10]	ETN[j]	r-axSpA	Group A: ASDAS < 1.3	Yes (12w)	Group A: Stepwise ETN tapering *ETN discontinuation*	106 36	36	Absence of flare[f]	91.0% 68.2%	+
			Group B: 1.3 ≤ ASDAS < 2.1		Group B: Stepwise ETN tapering Delayed ETN tapering *ETN discontinuation*	53 19 21	36	Absence of flare[f]	83.3% 68.7% 57.1%	–

ADA: adalimumab; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; IFX: infliximab; LDA: low disease activity; M/m: months; NR: not reported (not formally tested); PD: peripheral disease; ULN: upper limit of normal; W/w: weeks; Y/y: years.

[a] Eligibility criteria for patients to be included in (tapering phase of) the trial.

[b] Induction phase with (open-label) treatment as part of trial.

[c] Time in weeks from start of tapering (excluding induction phase, if applicable).

[d] Result of statistical analysis, interpretation: (+) = tapering non-inferior to comparator, or comparator not superior to tapering; (–) = tapering inferior to comparator or comparator superior to tapering (depending on design)..

[e] Study also included patients with PsA (DRESS-PS), or RA and PsA (Ruwaard); randomisation was stratified by diagnosis, and results shown here are for the axSpA subgroup only.

[f] Flare defined as: ASDAS ≥ 2.1 at two consecutive visits or ASDAS > 3.5 at any visit (C-OPTIMISE), ASDAS ≥ 2.1 at two consecutive visits or ASDAS increase ≥ 1.1 at any visit (GO-BACK), ASDAS > 2.1 at any point (Zhang). For C-OPTIMISE, no formal statistical comparison was made between the reduced dose and full dose arms.

[g] Study also included patients with RA or PsA; randomisation was stratified by diagnosis, and results shown here are for the overall population only (axSpA subgroup results not yet published).

[h] Strategies used: REDES-TNF: spacing for ADA/ETN/GOL, spacing and administered dose reduction for IFX. Zhang: initial reduction of administered, followed by spacing. DRESS-PS: spacing for ADA/CZP/ETN/GOL, administered dose reduction for IFX.

[i] Trial allowed for complete discontinuation (see Tables 2 and 3).

[j] ETN biosimilar (Yisaipu).

Table 2
Tapering schemes used in randomized controlled trials of bDMARD tapering in axSpA.

Strategy Study	Approach[a]	Drug(s)	Full dose	Tapering scheme (from full dose)	Dose %[b]
Spacing					
Lukas, 2021 [11]	Stepwise, DAG[c]	TNFi (any)	NR	Increase interval (not defined)	NR
Cantini, 2013 [6]	Instant	ETN	ETN 50 mg QW	ETN 50 mg Q2W	50
Li, 2016 [8]	Instant	ETN	ETN 25 mg TW	ETN 25 mg QW	50
Ruwaard, 2022 [13]	Instant	ETN	ETN 50 mg QW/25 mg TW	ETN 50 mg Q2W/25 mg QW 6m → stop	50 → 0[d]
C-OPTIMISE [15]	Instant	CZP	CZP 200 mg Q2W	CZP 200 mg Q4W	50
GO-BACK [16]	Instant	GOL	GOL 50 mg QM	GOL 50 mg Q2M	50
BIODOPT [14]	Stepwise, DAG[c]	TNFi (any)	NR	Increase interval by 25% per 4m	80 → 67 → 57 → 50
Administered dose reduction					
ANSWERS [7]	Instant	ETN	ETN 50 mg QW	ETN 25 mg QW	50
Combined					
REDES-TNF [9]	Instant	ADA	ADA 40 mg Q2W	ADA 40 mg Q3W	67
		ETN	ETN 50 mg QW	ETN 50 mg Q10D	60–70
		GOL	GOL 50 mg Q4W	GOL 50 mg Q6W	67
		IFX	IFX 5 mg/kg Q6-8W	IFX 3 mg/kg Q8W	45–60
DRESS-PS [12]	Stepwise, DAG[c]	ADA	ADA 40 mg Q2W	ADA 40 mg Q3W 3m → Q4W 3m → stop	67 → 50 → 0[d]
		CZP	CZP 200 mg Q2W	CZP 200 mg Q3W 3m → Q4W 3m → stop	67 → 50 → 0[d]
		ETN	ETN 50 mg QW	ETN 50 mg Q10D 3m → Q2W 3m → stop	70 → 50 → 0[d]
		GOL	GOL 50 mg QM	GOL 50 mg Q1.5M 3m → Q2M 3m → stop	67 → 50 → 0[d]
		IFX	IFX 3 mg/kg Q8W	IFX 2.25 mg Q8W 3m → 1.5 mg Q8W 3m → stop	75 → 50 → 0[d]
Zhang, 2020 [10]	Stepwise	ETN[e]	ETN 50 mg QW	ETN 25 mg QW → 25 mg Q2W → 25 mg Q4W (12w/step)	50 → 25 → 13
	Stepwise, delayed	ETN[e]	ETN 50 mg QW	ETN 50 mg QW → 25 mg QW → 25 mg Q2W (12w/step)	100 → 50 → 25

ADA: adalimumab; CZP: certolizumab pegol; D: days; DAG: disease activity-guided; ETN: etanercept; GOL: golimumab; IFX: infliximab; M/m: months; NR: not reported; W/w: weeks.

[a] Tapering applied once (instant), or multiple steps (stepwise).

[b] Tapered dose expressed as percentage of full dose (e.g. ETN 50 mg Q2W = "50%" of full dose of 50 mg QW). If stepwise tapering, percentages are shown for each step, with the first percentage reflecting the first step of the scheme.

[c] Disease activity-guided: if disease activity increased, tapering was halted or (partially) reverted, until low disease activity or remission was re-achieved.

[d] Patients were allowed to discontinue TNFi after 6 months of successful tapering.

[e] ETN biosimilar (Yisaipu).

treatment), found the risk of flare to be higher for the delayed tapering group (Zhang et al., Table 1) [10]. However, interpretation of these results requires caution, as no full-dose continuation arm was included for reference and there was substantial loss to follow-up.

Most trials on bDMARD tapering in axSpA were not blinded, except for C-OPTIMISE and GO-BACK [15,16]. Patients and rheumatologists might consider tapering to be inferior to standard treatment, resulting in a perceived increase in disease activity if aware of the treatment received (nocebo). They might also incorrectly attribute non-related events to tapering [18]. Despite these effects, tapering was still non-inferior in most studies.

Some results from observational studies also deserve attention. A prospective study from Denmark (DOBIS) found that with a protocolized, disease activity-guided stepwise tapering-to-discontinuation scheme (16-week steps of 67%/50%/33%/stop of standard dose) in patients with low disease activity for at least one year, about half were still on a reduced dose after two years (yet only 1% was able to completely discontinue) [19,20]. Of note, almost all patients experienced a flare while tapering, but more than half did not do so before they were on one-third or less of the full dose. In another cohort study (KOBIO), heavy tapering (< 50% of full dose) compared to standard dose was associated with reduced odds of maintaining inactive disease, while mild tapering (50–99% of full dose) was not [21]. Finally, a propensity score-matched cohort study demonstrated that tapering could reduce costs by more than one third [22]. This study only considered differences in drug costs, however, and assumed that all other costs would be equal between groups. More sophisticated approaches that also consider other cost areas (healthcare resource consumption, work productivity) have been successfully used to demonstrate the economic advantages of tapering in rheumatoid arthritis (RA) and are needed in axSpA [23].

Trial data on tapering of interleukin 17 inhibitors (IL-17i), such as secukinumab and ixekizumab, is unavailable in axSpA. Although results for complete discontinuation of TNFi and IL-17i are comparable (see below), thus potentially indirectly supporting extrapolation of TNFi tapering results to IL-17i, additional studies are needed to demonstrate the viability of IL-17i tapering.

4. Effectiveness of discontinuation of bDMARDs

Historically, complete discontinuation of bDMARDs in axSpA was investigated (post-hoc) in trials of TNFi, where all patients stopped the drug after the main study period [24–28]. The frequency of relapse was very high in these initial studies (69% to 98% within 48 weeks), although interpretation of these numbers was hampered by the lack of a comparator group that continued the drug. Since then, several discontinuation trials were conducted. This includes five trials (four placebo-controlled) of *instant discontinuation* of bDMARDs (i.e. an immediate switch from standard-dose to stopping the drug altogether) and two open-label trials of *tapering to discontinuation* (Table 3) [12,13,15,16,29–31]. One of these included an IL-17i (COAST-Y; ixekizumab), while all others investigated TNFi [31]. In addition to these studies, one trial compared stepwise tapering to instant discontinuation, but without a full-dose continuation arm [10].

So far, the results of trials on bDMARD discontinuation have been rather disappointing. In the case of *instant discontinuation* without prior tapering, flare rates (primary outcome in all five trials) were significantly higher in those who discontinued their bDMARD (55–80%, median time to flare 16 weeks) compared to those who continued them (16–30%) [15,16,29–31]. Results were consistent across different axSpA subtypes, different disease stages (early/established), and different drug targets (TNF/IL-17). In addition to a higher risk of flare, disease activity in those without flare was also higher in the discontinuation group compared to the continuation group [32]. Two trials also had an instant tapering arm (C-OPTIMISE and GO-BACK, both with tapering dose 50% of full-dose) with flare rates that were significantly better than those for discontinuation and numerically comparable to those of full-dose continuation, suggesting that tapering is preferred over instant discontinuation [15,16]. Also, in the trial by Zhang et al. that directly compared tapering with discontinuation, tapering led to less flares [10].

Instant discontinuation trials were quite homogeneous regarding their design [open-label induction followed by (dis)continuation], entry criterion (remission during/after open-label remission induction) and primary endpoint (absence of flare, based on disease activity). Although none used the ASAS-endorsed definition of clinically important worsening – ASDAS increase $\geq$ 0.9 – as primary outcome [33], some studies added this post hoc, with similar results [29,31].

There are several important considerations when interpreting these studies. The open-label induction phases were rather short (24–48 weeks, Table 3), so that patients could have been in remission for a very limited period when stopping their bDMARD. This might have negatively affected the flare rates. Also, although the flare rate was substantially higher in those who discontinued compared to those who continued, a considerable proportion of patients (20–55%) remained in drug-free remission for up to a year in these studies. As such, while the 'risks' associated with complete discontinuation (i.e. flare) are high if applied in the overall axSpA population in remission, it could be a viable strategy if applied in the right subpopulation. Nonetheless, observed success rates could be an overestimation, as most studies were placebo-controlled (except for RE-EMBARK). In daily practice, the performance of discontinuation strategies could be lower due to nocebo effects and misattribution.

The trials discussed above focused on instant discontinuation. Hypothetically, a more prolonged strategy with careful tapering before complete discontinuation might be more successful. Two trials (Ruwaard trial and DRESS-PS) used such a strategy [12,13]. The first allowed patients to discontinue ETN after 6 months of one-step tapering, while the second used a stepwise TNFi tapering scheme over a 6-month period (Table 2). One year after initiation of tapering, only 14% (Ruwaard) to 21% (DRESS-PS) were still off-drug (Table 3). Both trials also included other rheumatic diseases (RA and/or psoriatic arthritis [PsA], in addition to axSpA). Interestingly, the observed rates of successful discontinuation were notably higher for RA/PsA compared to axSpA. Recent observational studies found 3% (DOBIS) and 63% (TAPAS) of those who attempted TNFi discontinuation after protocolized tapering-to-discontinuation, were able to maintain low disease activity off-drug [19,34].

5. Safety of tapering and discontinuation

If tapering would reduce the risk of bDMARD-associated adverse events, this would be an important benefit to patients. Although biologically plausible, this benefit has not been demonstrated in axSpA, possibly because studies were not designed to assess safety. In studies that formally compared (statistically tested) safety between groups, the risk of serious events, infections and infusion reactions were either similar for tapering and full-dose continuation groups [12,22], or slightly favoured tapering [9,35]. Meta-analyses of RCTs in RA and axSpA did not observe statistically significant differences in odds for serious adverse events, serious infections, malignancies, cardiovascular events or death for tapering/discontinuation compared with continuation [36,37]. Of note, numerically, pooled rates for some events were lower for

Table 3
Randomized/clinical controlled trials investigating discontinuation of bDMARDs in axSpA.

Strategy Study	Population	Discontinuation criteria[a]	Induction[b]	Intervention *Comparator*	*n*	Time (wks)[c]	Outcome (definition)	Outcome (%)	Discontinuation success[d]
Instant discontinuation									
ABILITY-3 [29]	nr-axSpA	ASDAS < 1.3 at 16–28w of induction	Yes (28w)	PBO Q2W (ADA stop)	153	40	Absence of flare[e]	47.1	–
				Continue ADA 40 mg Q2W	152			70.4	
C-OPTIMISE [15]	axSpA (early)	ASDAS < 1.3 at 32w/36w and 48 w of induction	Yes (48w)	PBO Q2 W (CZP stop)	104	48	Absence of flare[e]	20.2	–
				Continue CZP 200 mg Q2W[f]	104			83.7	
RE-EMBARK [30]	nr-axSpA	ASDAS < 1.3 at 24w of induction	Yes (24w)	ETN stop (no PBO)	119	40	Absence of flare[e]	25.2	–
				Continue ETN (EMBARK)	NR			> 75	
GO-BACK [16]	nr-axSpA (early)	ASDAS < 1.3 at 7m and 10m of induction	Yes (10 m)	PBO QM (GOL stop)	63	52	Absence of flare[e]	33.9	–
				Continue GOL 50 mg QM[f]	62			84.1	
COAST-Y [31]	axSpA	ASDAS < 1.3 at 16w/20w of induction, and < 2.1 at both	Yes (24w)	PBO Q2W	53	40	Absence of flare[e]	54.7	–
				Continue IXE 80 mg Q2/4W[g]	100			83.3	
Tapering to discontinuation[h]									
DRESS-PS [12]	axSpA[g]	ASDAS < 2.1 ≥ 6m pre-tapering, and maintained while tapering	No	T2T with TNFi tapering	39	52	No bDMARD use at 52w	20.5	NR
				T2T without TNFi tapering	19			5.3	
Ruwaard, 2022 [13]	r-axSpA[g]	ASDAS < 2.1 ≥ 6m pre-tapering, and maintained while tapering	No	ETN spacing → stop	20	26	No bDMARD use at 26w	14.3[i] (overall)	NR
				Continue ETN → spacing → stop	20				

ADA: adalimumab; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; IXE: ixekizumab; M/m: months; NR: not reported; PBO: placebo; W/w: weeks.

[a] Eligibility criteria for patients to discontinue bDMARD.

[b] Induction phase with (open-label) treatment as part of trial.

[c] Time in weeks from start of discontinuation (excluding induction phase).

[d] Result of statistical analysis, interpretation: (+) = discontinuation non-inferior or superior to continuation; (−) = discontinuation inferior to continuation; (NR) = no formal (statistical) comparison.

[e] Flare defined as: ASDAS ≥ 2.1 at two consecutive visits (ABILITY-3), ASDAS ≥ 2.1 at two consecutive visits or ASDAS > 3.5 at any visit (C-OPTIMISE, COAST-Y), ASDAS ≥ 2.1 at any visit (RE-EMBARK), ASDAS ≥ 2.1 at two consecutive visits or ASDAS increase ≥ 1.1 at any visit (GO-BACK).

[f] Study also included a third arm with reduced dose (CZP 200 mg Q4W for C-OPTIMISE; GOL 50 mg Q2M for GO-BACK), which was formally only compared against the discontinuation arm. Data from these arms is presented in Table 1, as these can be considered tapering.

[g] Study also included patients with PsA (DRESS-PS), or RA and PsA (Ruwaard); randomization was stratified by diagnosis, and results shown here are for the axSpA subgroup only.

[h] These studies allowed for tapering before discontinuation (see Table 2). Both studies had a non-tapering arm as comparator (not an instant discontinuation approach).

[i] In those who maintained low disease activity while tapering and started discontinuation.

tapering/discontinuation groups [37]. An obvious limitation is that these trials were primarily aimed at efficacy – and not safety – outcomes. They often have a limited follow-up (not long enough to detect relevant different between groups regarding safety), and they are underpowered to detect differences in safety. In addition, for both trials and observational studies, there is a risk of misattribution. Unrelated events could be wrongly attributed to bDMARDs, and events detected during tapering/discontinuation periods could be the result of the previous full-dose regimen. Finally, tapering and discontinuation are initiated in patients that have already been on the drug for a while, and patients more prone to experience adverse events are likely already filtered out [37]. Overall, although it seems biologically plausible that tapering and discontinuation reduce the rate of adverse events, the currently available evidence does not clearly show this.

6. When to consider tapering or discontinuation, and in whom

Only patients in a stable and acceptable disease state should be considered for tapering or discontinuation. Two aspects seem important: the disease state, and the time spent in that state. There is no formal definition of these aspects, although 'sustained remission' is often mentioned. The taskforce involved in the 2022 ASAS-EULAR management recommendations for axSpA considered being in an ASDAS inactive or low disease activity state for at least 6 months ('sustained') to be appropriate, although both are based on expert opinion [38]. Studies on tapering and discontinuation in axSpA employed a variety of different disease states and durations (Tables 1 and 3). For the disease state, some studies also considered a low disease activity state – and not only remission – as acceptable

[6,10–14]. Probably, the more stringent state (remission) would be the safe choice. However, sustained remission cannot be achieved in all patients. Also, there is no robust evidence in axSpA that remission – as opposed to low disease activity – as a requirement to initiate dose reduction leads to better results. One trial did not observe a lower risk of flare if patients had inactive disease (remission), compared to low disease activity, at start of tapering or discontinuation [10], while in a large observational study the probability of inactive disease after one year with tapering was comparable to full dose if tapering was started if in remission, but lower if started in (non-remission) low disease activity [21]. Furthermore, there are few studies in axSpA that directly investigate the required period to be in remission before tapering or discontinuation. One post-hoc analysis found that the risk of flare following discontinuation was lower – but still high – in patients with sustained remission (8–12 weeks) compared to those with remission at a single timepoint (60% vs. 84% after 40 weeks) [39]. Also, the study by Zhang et al. observed numerically higher flare rates with delayed versus non-delayed tapering (Table 1), but only in those with low disease activity (not remission), and interpretation requires caution as discussed above [10].

It seems likely that patient and disease characteristics also affect the success of dose reduction strategies. Disappointingly, studies that investigated potential predictors for success/failure of these strategies did not consistently identify any [9,10,15,19,24,26,29,31,40–44]. For tapering, female sex, lower/higher age, higher CRP, HLA-B27 negativity and higher physician global have been associated with higher failure rates in single studies, but not consistently [10,15,19,40,41]. For discontinuation, higher ASDAS/BASDAI at time of discontinuation was associated with higher flare rate in two studies [24,29], while results for CRP, age and disease duration were inconsistent [15,24,26,43,44]. Baseline sacroiliac joint MRI (MRI-SI) positivity was only investigated in a single study, and associated with higher relapse rate if present together with increased CRP [42]. Importantly, studies varied with regard to the methods used to investigate predictors, the type of predictors included and the reporting quality of these analyses. There is a clear need to identify predictors for successful dose reduction, especially discontinuation. Imaging biomarkers, for instance the presence of bone marrow edema on MRI-SI, have been rarely investigated in this context, and could be relevant.

The decision to taper or discontinue should be made jointly by the physician and the patient through a shared decision-making process. In one observational study, in 90% of patients the decision to taper was made by the patient alone or jointly with the care provider [41]. The tapering success rate was almost 95% in those who originally preferred to taper, and less than 50% in those who did not. Patient–physician communication and managing expectations (not only when discussing tapering and discontinuation, but already at the start of a bDMARD), could be important factors that influence patients' attitudes towards tapering and the success rate thereof.

7. If tapering and discontinuation fail

An important question is what happens when tapering or discontinuation fails. Fortunately, it seems that reverting to a higher dose (if tapered) or restarting the bDMARD (if discontinued) often results in regain of disease control. For tapering, this was 50% in one study [7], and 78% or even up to 100% in other studies [6,12,19,40,41,45]. For discontinuation, this varied from 52% to 93% [15,16,26,28–31,44]. On the one hand, these are reassuring observations for patients: if tapering or discontinuation fails, there is a reasonable chance that they will regain disease control. On the other hand, it also means that some patients will not be able to regain their initial response and need to switch to another drug. This could possibly limit their options in the future.

Importantly, studies typically reverted to the last effective dose or restarted the bDMARD in case of relapse, and then maintained this until the end of study. None investigated if – and when – to reconsider another attempt to taper or discontinue once a previous attempt failed. It makes sense to only consider a second attempt if the circumstances (either for the patient or the disease) somehow changed.

8. The patient's perspective

As discussed above, the patient's view on tapering or discontinuation is important, if not essential, for such a strategy to succeed [41]. Qualitative research on these strategies in axSpA is scarce, and mostly conducted in mixed populations (axSpA and other rheumatic diseases). Patients can be fearful of tapering or discontinuation, reflecting on their life before bDMARDs [46]. They consider risk of flare and delayed access to rheumatology services as sources of concern in relation to tapering, while only a minority seems worried about loss of efficacy after return to the original dose [47]. Despite these fears, most would be willing to try dose reduction if there was a clear rationale and if it was in their best interests (provided in a collaborative setting, with control over flexible dosing) [46]. Interestingly, most patients do not think less frequent injections would positively affect home life, working life or travel [47].

9. Concluding remarks

Over the last decade, the evidence bases on bDMARD tapering and discontinuation in axSpA have grown substantially. For tapering, strategies have evolved from simple instant dose reductions to elaborate stepwise disease-activity guided approaches. Current evidence indicates that tapering is a viable strategy in patients with axSpA who are in a sustained low disease activity or remission state. Spacing is supported by the most evidence and seems the most practical method. Future studies need to address, ideally by direct comparison, how long patients need to be in remission before they can taper and whether the patient's initial state (remission or low disease activity) affects the probability of success. Also, the economic advantages of tapering need to be confirmed.

For discontinuation, the risk of relapse seems too high to justify this approach in all patients in sustained remission. Although it is unclear if tapering before discontinuation drastically improves the success rate, it has the advantage that, if discontinuation fails, the patient can revert to – and possibly maintain – the reduced dose. It is also a more pragmatic approach in practice, where tapering (as supported by evidence) could be a first step towards dose reduction. Nonetheless, discontinuation seems to work in some patients. Future studies need to explore different discontinuation strategies and identify good candidates for these.

Healthcare providers have a societal responsibility to consider the costs incurred in the management of axSpA. Dose reduction, if done carefully, could free up valuable space in healthcare budgets and contribute to cost-effective use of bDMARDs [48]. The 2022 ASAS-EULAR recommendations for the management of axSpA acknowledge this responsibility, and also recommend to consider bDMARD tapering if a patient is in sustained remission [38]. Similar guidance regarding tapering is provided in the 2022 French Society for Rheumatology management recommendations for SpA [49]. The 2019 ACR/SAA/SPARTAN recommendations are against tapering as a standard approach, but also mention that tapering could be considered in those with prolonged stable disease (not further defined) [50]. Of note, a substantial part of the evidence in axSpA was published after development of these

recommendations. Obviously, the principle of best care outweighs any cost considerations [38]. Ultimately, the use (and probability of success) of any tapering or discontinuation strategy will depend on the individual's needs and their context. Shared decision-making is essential in this regard.

In conclusion, evidence indicates that tapering of TNFi, and especially spacing, in patients with axSpA in sustained remission is not inferior to full-dose continuation. If tapering fails, patients often can regain disease control. For IL-17i, the efficacy of tapering in axSpA needs to be demonstrated. Complete discontinuation of bDMARDs in those in remission more often than not results in relapse and should not be recommended until we know how to select optimal candidates.

Contributorship

CW conducted screening, selection and data extraction. All authors interpreted the results, revised the manuscript critically for important intellectual content and approved the final manuscript.

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Ethics approval and patient consent

None.

Data availability statement

All data relevant to this review are included in the article.

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