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REVIEW

bDMARD Dose Reduction in Rheumatoid Arthritis: A Narrative Review with Systematic Literature Search

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ABSTRACT

Introduction: Although bDMARDs are effective in the treatment of RA, they are associated with dose-dependent side effects, patient burden, and high costs. Recently, many studies have investigated the possibility of discontinuing or tapering bDMARDs when patients have reached their treatment goal. The aim of this review is to provide a narrative overview of the existing evidence on bDMARD dose reduction and to provide answers to specific dose-reduction-related questions that are of interest to clinicians.

Methods: We systematically searched for relevant studies in four scientific databases. Furthermore, we screened the references of reviews and relevant studies.

Results: Our searches resulted in 45 original studies of bDMARD dose reduction in RA patients (15 RCTs and 30 observational studies). Current evidence shows that bDMARD dose reduction can be considered in all RA patients who achieve stable (e.g., ≥6 months) low disease activity or remission. The best strategies seem to be disease-activity-guided dose optimization and fixed dose reduction, since direct bDMARD discontinuation (without restarting) results in a high flare rate, worse physical functioning, and more joint damage. When tapering the bDMARD treatment of a patient, disease activity should be monitored closely,

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and if a flare occurs, the dose should be increased to the lowest effective dose. Current evidence shows that restarting bDMARD treatment is effective and safe. Unfortunately, no clear predictors of successful dose reduction have been identified so far.

Conclusion: The current evidence and rising healthcare costs urge that dose reduction should be considered for eligible patients. However, the decision to start dose reduction should be made in shared decision-making. Future research should focus not only on a better understanding of the effects of dose reduction on clinical outcomes but also on the perspectives of patients and physicians as well as the implementation of this new treatment principle.

Keywords: bDMARDs; Discontinuation; Dose de-escalation; Dose reduction; Dose titration; Drug holiday; Rheumatoid arthritis; Spacing; Tapering; Treatment relaxation

INTRODUCTION

Background

The introduction of biological disease-modifying antirheumatic drugs (bDMARDs) almost two decades ago has improved the treatment of patients with rheumatoid arthritis (RA) by offering more treatment options to be used according to the tight control principle. bDMARDs improve clinical, functional, and radiographic outcomes, and are a welcome—although not clearly superior—addition to existing therapies with synthetic DMARDs (sDMARDs) such as methotrexate, leflunomide, and prednisone [1]. bDMARDs can be categorized into those that act as an inhibitor of tumor necrosis factor (TNFi) and those that have another mechanism of action (non-TNFi).

Although bDMARDs are effective in the treatment of RA, they are associated with high costs, patient burden, and dose-dependent side effects, such as an increased risk of infection [2–5]. Because of these downsides, many studies have recently investigated the possibility of discontinuing or tapering bDMARDs when patients have reached their treatment goal, which is most often low disease activity (LDA) or remission [6, 7]. Based on evidence from these studies, the EULAR and ACR have incorporated the option of dose reduction into their latest guidelines, the central axiom being "maintenance of treatment goal does not necessarily mean maintenance of treatment intensity" [8, 9].

For clinical practice, however, several questions about the optimal strategy for dose reduction/discontinuation need to be answered in order to properly implement bDMARD dose optimization. Therefore, the goal of this review is to provide a narrative overview of the existing evidence on this topic, to provide answers to specific dose-reduction-related questions that are of interest to clinicians, and to suggest topics for future research.

Questions

We aimed to answer the following clinically relevant questions when considering dose reduction of a bDMARD in an individual RA patient with low disease activity:

1. What are the mechanisms behind the possibility of bDMARD dose reduction in RA patients?
2. In which patients and when should we consider dose reduction?
3. What is the best dose-reduction strategy?
4. What proportion of the patients can be stopped or tapered, and can we predict successful dose reduction using patient or treatment characteristics?
5. What are the effects of dose reduction on function, quality of life, adverse events, and radiographic damage?
6. Which flare criterion is best to use when deciding whether to restart/re-escalate treatment, and how often should the patient be monitored?
7. Is it effective and safe to restart treatment?
8. What is the cost-effectiveness of dose reduction?
9. How can dose reduction best be implemented in clinical practice?

10. What is the patient perspective on bDMARD dose reduction?

METHODS

To find relevant studies for this review, we searched CENTRAL, MEDLINE, EMBASE, and Web of Science (only for TNFi) from January 1, 1995 to August 17, 2016. We performed separate searches for TNFi bDMARDs and non-TNFi bDMARDs. To be included in this review, studies had to address RA, dose reduction/discontinuation/tapering of bDMARDs after LDA or remission, and at least one of the topics that we identified for this review. Articles describing original research, ≥20 participants, and a follow-up of ≥6 months were included. Furthermore, we identified relevant reviews on the topic of bDMARD dose reduction. The search strategies are provided in Appendix 1 of the Electronic supplementary material (ESM).

We also sought relevant studies by screening the references included in reviews of this field and those included in the studies that had already been accepted for inclusion in this work. In addition, studies that were already known to the authors from previous research, meetings/conferences, or personal communications were considered for inclusion. No meta-analyses were performed because our aim was to answer several questions in a narrative manner and not to obtain summarized estimates for one or two outcomes. For the same reason, and also due to feasibility, we did not formally assess the risk of bias in the included studies.

Since this article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors, no ethical approval was necessary.

RESULTS

General Results

Our searches and the subsequent reference screening process resulted in 45 original studies of bDMARD dose reduction in RA patients after attainment of low disease activity or remission (Table 1). Fifteen of these studies were randomized controlled trials (RCTs) that were specifically designed to compare dose reduction with continuation of bDMARDs. The other 30 articles addressed research in which dose reduction was investigated in a nonrandomized manner (observational), or in which one arm of a randomized study fulfilled the inclusion criteria but a nontapering control group was not included. The first study of this subject was published in 2002, and there was an evident increase in the number of studies published on this topic in the years that followed. Most of the studies focused on TNFi reduction (especially etanercept and adalimumab). None of the studies investigated anakinra or golimumab reduction, and very few focused on certolizumab pegol reduction.

There is marked methodological heterogeneity among these studies (as has already been noted by Yoshida et al. and Fautrel et al. [6, 10]) in terms of, for example, the design itself (RCTs, extensions of RCTs, observational studies, and superiority versus non-inferiority designs), inclusion criteria for dose reduction (remission or LDA with variety in duration, with or without concomitant DMARD, tapering soon after the start of treatment or in a later phase), and the definition of flare. However, for the latter, criteria based on the Disease Activity Score in 28 joints (DAS28) were mostly used.

We found several reviews on the topic of bDMARD dose reduction. A Cochrane review was published in 2014 by van Herwaarden et al. that focused on down-titration and discontinuation of TNFi therapy [7]. However, its results were based on searches performed in September 2013. Because many new studies and full texts have been published since then, an update is needed. Some reviews have chosen to focus on dose reduction of both biological and synthetic DMARDs; examples include the recent reviews of Kuijper et al. and Schett et al. and a narrative review by Fautrel et al. [6, 11, 12]. Other reviews, such as those by Navarro-Millan et al., Yoshida et al., and Galvao et al. [10, 13, 14], only focus on bDMARD discontinuation.

Table 1 Original studies of bDMARD dose reduction in RA

References	Acronym	Design	Patients	Criteria for dose reduction	Drug(s)	Intervention(s)	*N*	FU (in years)	Primary outcome measure	Main results
Randomized controlled trials										
Kaine [15]	ALLOW	RCT db	RA	ΔDAS28 ≥0.6 after 12 weeks ABA	ABA	STOP	120 CON: 40 STOP: 80	0.5	Immunogenicity and safety	Immunogenicity rate: 7/73 (10%) STOP vs 0/38 (0%) CON; ($p = 0.119$). Safety comparable
Batticciotto (abstract) [16]	–	RCT	RA	Good–moderate EULAR response	RTX	FDR 50%	21 CON: 11 FDR: 10	1	Percentage of patients with LDA or in REM	Dose reduction to 2 × 0.5 g possible. % LDA or REM similar in both groups after fourth 70% FDR vs 73% CON $p = 1.0$ and fifth course 83% FDR vs 67% CON $p = 0.545$. No patient numbers reported
Smolen [17]	PRESERVE	RCT db	RA	LDA: DAS28 ≤3.2	ETA	STOP and FDR 50%	604 CON: 202 FDR: 202 STOP: 200	1	Proportion of patients with LDA	% LDA: 166/201 (83%) CON, 159/201 (79%) FDR, 84/197 (43%) STOP (CON vs STOP and FDR vs STOP $p < 0.0001$)
Smolen [18]	OPTIMA	RCT	ERA	LDA: DAS28 <3.2 for ≥4 weeks	ADA	STOP	207 CON: 105 STOP: 102	1	Proportion of patients with DAS28 <3.2 and radiographic nonprogression	DAS28 <3.2: 96/105 (91%) CON vs 82/101 (81%) STOP ($p = 0.0361$) Radiographic nonprogression (from baseline): 92/103 (89%) CON vs 79/98 (81%) STOP
Haschka [19]	RETRO	RCT	RA	REM: DAS28 <2.6 for ≥6 months	All DMARDs	STOP and FDR 50%	101 CON: 38 FDR: 36 FDR and STOP: 27	1	Sustained REM during 12 months	Overall, 67/101 (66%) patients remained in REM for 12 months. Prevalence of disease relapse: 6/38 (16%) CON, 14/36 (39%) FDR, 14/27 (52%) FDR and STOP. CON vs FDR $p = 0.036$, CON vs FDR and STOP $p = 0.003$
Mariette [20]	SMART	RCT ol	RA	Good–moderate EULAR response	RTX	FDR 50%	143 CON: 73 FDR: 70	1.5	DAS28-CRP AUC with a NI margin defined by 20%	Adjusted mean difference in DAS28-CRP AUC: 51.4 (95% CI −131.2 to 234), demonstrating noninferiority

Table 1 continued

References	Acronym	Design	Patients	Criteria for dose reduction	Drug(s)	Intervention(s)	*N*	FU (in years)	Primary outcome measure	Main results
Yamanaka [21]	ENCOURAGE	RCT	ERA	REM: DAS28 <2.6 for ≥6 months	ETA	STOP	99 CON: 49 STOP: 50	1	Maintenance of clinical REM (DAS <2.6), structural REM (total Sharp score <0.5 per year), and functional REM. (HAQ <0.5)	Clinical REM: 28/32 (88%) CON vs 15/28 (54%) STOP. Structural REM: 26/29 (90%) CON vs 19/23 (83%) STOP. Functional REM: 27/31 (87%) CON vs 18/28 (64%) STOP
Fautrel [22]	STRASS	RCT ol	RA	REM: DAS28 ≤2.6 for ≥ 6 months	ETA, ADA	TAP	137 CON: 73 TAP: 64	1.5	Standardized difference of DAS28 slopes	No equivalence in DAS28 (standardized difference 19% (95% CI −5% to 46%)). Prevalence of disease relapse: 49/64 (77%) TAP vs 34/73 (47%) CON, $p = 0.0004$
Galloway (abstract) [23]	OPTTIRA	RCT	RA	LDA: DAS28 <3.2 for ≥3 months	ETA, ADA	STOP and FDR 33% and 66%	103[a] CON: 50 FDR33%: 48 FDR66%: 38	0.5	Flare rate	Flare rate: 7/50 (14%) CON vs 6/48 (13%) FDR33% and 14/38 (37%) FDR66%. Flares increased with odds ratio of 4.1 (95% CI 1.3–14.5) in FDR66% vs FDR33%
Raffeiner [24]	–	RCT	RA	REM: DAS28 <2.6 for ≥12 months	ETA	FDR 50%	323 CON: 164 FDR: 159	3.6 ± 1.5	Clinical REM	Clinical REM: 130/159 (82%) FDR. No information provided for CON
van Herwaarden [25]	DRESS	RCT ol	RA	LDA: DAS28 ≤3.2 for ≥6 months	ETA, ADA	TAP	180 CON: 59 TAP: 121	1.5	Proportion of patients with major flare compared against a NI margin of 20%	Major flare: 14/119 (12%) TAP vs 5/50 (10%) CON (95% CI −12% to 12%), demonstrating noninferiority
van Vollenhoven [26]	DOSERA	RCT db	RA	LDA: DAS28 ≤3.2 for ≥11 months	ETA	STOP and FDR 50%	73 CON: 23 FDR: 27 STOP: 23	±1	Proportion of patients on 50 mg ETA versus placebo who were nonfailures after 48 weeks	Proportion of nonfailures: 12/23 (52%) CON vs 12/27 (44%) FDR vs 3/23 (13%) STOP. CON vs STOP $p = 0.007$, FDR vs STOP $p = 0.044$, CON vs FDR $p = 0.362$
Westhovens [27]	AGREE (substudy)	RCT db	ERA PP	REM: DAS28 <2.6	ABA	FDR 50%	108 CON: 58 FDR: 50	1	Relapse rate	Relapse rate: 18/58 (31%) CON vs 17/50 (34%) FDR; HR: 0.87 (95% CI 0.45–1.69)

Table 1 continued

References	Acronym	Design	Patients	Criteria for dose reduction	Drug(s)	Intervention(s)	*N*	FU (in years)	Primary outcome measure	Main results
Chatzidionysiou [28]	ADMIRE	RCT ol	RA	REM: DAS28 <2.6 for ≥3 months	ADA	STOP	31 CON: 16 STOP: 15	1	Proportion of patients in REM at week 28	Proportion of patients in REM: 15/16 (94%) CON vs 5/15 (33%) STOP ($p = 0.001$)
Moghadam [29]	POEET	RCT ol	RA	LDA: DAS28 <3.2 for ≥6 months	TNFi	STOP	819 CON: 286 STOP: 531	1	Flare rate	Flare rate: 272/531 (51%) STOP vs 52/285 (18%) CON ($p < 0.001$)
Non-randomized controlled trials										
den Broeder [30]	–	UC	RA	Not specified	ADA	TAP	21	0.75	Mean DAS28	Dose reduction of 67% in 15 patients (from 97.5 mg/week (range 46.3–125) to 32.5 mg/week (4.1–130)). No significant differences in mean DAS28 (3.5 (range 1.4–4.6) baseline vs 3.8 (range 2.0–5.1) end)
Quinn [31]	Part of RCT	UC	ERA	Not specified	IFX	STOP	20 CON: 10 STOP: 10	1	Reduction in synovitis compared with baseline (after 14 weeks)	Reduction in median total synovitis score: 5.5–3.4 CON vs 6.2–5.9 STOP ($p < 0.05$)
Brocq [32]	–	UC	RA	REM: DAS <2.6 for ≥6 months	TNFi (ETA, ADA, IFX)	STOP	21	1	Relapse rate	Relapse after 6 months 11/20 (55%) and after 1 year 15/20 (75%)
Saleem [33]	–	UC	RA	REM: DAS <2.6 for ≥6 months	TNFi	STOP	47	2	Disease flare	Disease flare after 2 years: 28/47 (60%)
Tanaka [34]	RRR	UC	RA	LDA: DAS28 <3.2 for ≥6 months	IFX	STOP	102	1	DAS28 and radiological progression	Sustained discontinuation >1 year without radiological progression: 56/102 (55%)
van den Broek [35]	Part of RCT (BeSt)	UC	RA	LDA: DAS ≤2.4 for ≥6 months	IFX	STOP	104	>1	Disease activity and joint damage progression	Sustained discontinuation: 54/104 (52%). Disease flare: 50/104 (48%) (42/50 (84%) regained LDA). No joint damage progression in the year after cessation

Table 1 continued

References	Acronym	Design	Patients	Criteria for dose reduction	Drug(s)	Intervention(s)	*N*	FU (in years)	Primary outcome measure	Main results
Harigai [36]	BRIGHT	C	RA	LDA: DAS28-CRP <2.7	ADA	STOP	46 CON: 24 STOP: 22	1	Percentage of patients who maintained discontinuation of biological agents and LDA for 52 weeks	Sustained discontinuation: 14/22 (64%). 4/22 (18%) maintained LDA
van der Maas [37]	–	UC	RA	LDA: DAS28 <3.2 for ≥6 months	IFX	TAP	51	1	Successful down-titration or discontinuation after 1 year	Successful down-titration: 23/51 (45%) patients (95% CI 31–59). Successful discontinuation: 8/51 (16%) patients (95% CI 6–26)
Aguilar-Lozano (abstract) [38]	–	UC	RA	REM: DAS28 ≤2.6	TCZ	STOP	45	1	Relapse rate	Relapse rate after 1 year: 25/45 (56%). Sustained REM: 20/45 (44%)
Detert [39]	Part of RCT (HIT-HARD)	UC	ERA	Not specified	ADA	STOP	82	0.5	DAS28	DAS28 before discontinuation: 3.0 ± 1.2. DAS28 after discontinuation: 3.2 ± 1.4
Hørslev-Peterson (abstract) [40]	Part of RCT	UC	ERA	Not specified	ADA	STOP	CON and STOP: not specified	1	DAS28	% REM before withdrawal 74% and 1 year after withdrawal 66%. No patient numbers reported
Kurasawa [41]	Part of RCT (BuSHIDO)	UC	RA	REM: DAS28 <2.6 for ≥6 months	IFX	STOP	55	2	Flare rate	Flare rate after 2 years: 7/22 (32%) for patients with concomitant MTX and BUC. 17/27 (63%) for patients with concomitant MTX
Rakieh (abstract) [42]	–	C	RA	REM: DAS28 <2.6 for ≥6 months	TNFi	STOP	69 CON: 51 STOP: 18	1	Flare rate	Flare rate: 13/51 (26%) CON vs 15/18 (83%) STOP ($p = <0.001$)
Huizinga [43]	Part of RCT (ACT-RAY)	UC	RA	REM: DAS28 <2.6 for ≥3 months	TCZ	STOP	238	1	Flare rate	Flare rate: 200/238 (84%)
Inui (abstract) [44]	RESUME	UC	RA	LDA: DAS28 <3.2	ETA	STOP	31	2	DAS28	13/31 (42%) withdrew due to inadequate response to ETA; 5/31 (16%) patients: no flare; 13/31 (42%) patients: achievement of LDA in 3.7 months on average after restarting ETA
Iwamoto [45]	–	UC	RA	REM: DAS28 <2.6	TNFi and TCZ	STOP	40	0.5	Relapse	Relapse: 16/40 (40%)

Table 1 continued

References	Acronym	Design	Patients	Criteria for dose reduction	Drug(s)	Intervention(s)	*N*	FU (in years)	Primary outcome measure	Main results
Maneiro [46]	–	UC	RA	REM: DAS <2.6 for ERA, LDA: DAS <3.2 for established RA	TNFi, ABA, TCZ	TAP	64	1.5	Time to relapse	Relapse rate: 5/51 (10%) at 6 months, 11/36 (31%) at 12 months, 12/27 (45%) at 18 months
Nishimoto [47]	DREAM	UC	RA	LDA: DAS ≤3.2	TCZ	STOP	187	1	Rate of DAS28 REM or LDA	REM: 17/187 (9%) LDA: 25/187 (13%)
van Herwaarden [48]	–	UC	RA	LDA: DAS28 <3.2	TCZ	FDR 50%	22	0.5	Successful dose reduction: dose reduction without losing disease control	Successful FDR: 17/22 (77% (95% CI 54–91)) after 3 months, 11/20 (55% (95% CI 32–76)) after 6 months
Atsumi [49]	Part of RCT (C-OPERA)	UC	ERA	Not specified	CZP	STOP	108	1	SDAI REM rate	REM rate 58% before discontinuation and 45% after 16 weeks. Stable thereafter. No patient numbers reported
Emery [50]	AVERT	UC	ERA	LDA: DAS28 <3.2	ABA (and MTX)	STOP	150	1	REM rate	REM rate at start of discontinuation: 73/84 (87%) patients MTX + ABA, 50/66 (76%) patients ABA. After 6 months: 18/73 (25%) patients MTX + ABA, 14/50 (28%) patients ABA
Marks [51]	–	UC	RA	REM: DAS28 <2.6 and no synovitis on PDUS for ≥6 months	TNFi	FDR 33%	70	1.5	Combined DAS28 and PDUS REM	Sustained REM: 67/70 (96%) after 3 months, 44/70 (63%) after 6 months, 26/70 (37%) after 9 months, 24/70 (34%) after 18 months
Murphy [52]	–	UC	RA	REM: DAS28 <2.6 for ≥6 months	ETA, ADA	FDR 50%	45	2	REM rate	REM rate (all included diagnoses: RA, PsA, and AS) in remission at 2 years was 44/79 (56%)
Naredo [53]	–	UC	RA	REM: DAS28 <2.6 for ≥12 months	TNFi	TAP	77	1	TAP failure	Failure rate after 6 months: 23/77 (30%) and after 1 year: 35/77 (46%)
Takeuchi [54]	–	C	RA	REM: DAS28-CRP <2.3	ABA	STOP	51 CON: 17 STOP: 34	1	Proportion of patients remaining biologic-free in discontinuation group	After 52 weeks, 22/34 (65%) patients were biologic-free

Table 1 continued

References	Acronym	Design	Patients	Criteria for dose reduction	Drug(s)	Intervention(s)	*N*	FU (in years)	Primary outcome measure	Main results
Tanaka [55]	HONOR	C	RA	REM: DAS28 <2.6 for ≥6 months	ADA	STOP	75 CON: 23 STOP: 52	1	Proportion of patients with LDA or in REM (DAS28)	%REM: 19/23 (83%) CON vs 25/52 (48%) STOP, $p = 0.0056$. %LDA: 21/23 (91%) CON vs 32/52 (62%) STOP, $p = 0.0122$
Alivernini [56]	–	UC	RA	REM: DAS44 <1.6 for ≥6 months	ETA, ADA	TAP	42	0.5	Relapse rate	3 months after TAP, 13/42 (31%) patients relapsed and 29/42 (69%) maintained REM and stopped TNFi. At 6 months 26/29 (90%) maintained REM
Bouman [57]	SONATA	C	RA	LDA: DAS28 <3.2	ABA, TCZ	TAP	89 CON: 32 TAP: 57	0.5	Successful TAP	Tapering was successful in 37% of ABA patients and 35% of TCZ patients. No patient numbers reported
Heimans [58]	Part of RCT (IMPROVED)	UC	RA	REM: DAS44 <1.6	ADA	TAP	66 (RA patients in arm 2)	2	Percentages of patients in DAS REM and DFR based on a DAS <1.6	After 2 years of remission-steered treatment, 24/78 (31%) patients (diagnosis of UA and RA) were in REM. DFR 7/78 (9%)
Wiland [59]	PRIZE	UC	ERA	REM: DAS28-ESR <2.6	ETA	STOP and FDR 50%	193	1	Patient-reported outcomes	Continuing combination therapy at a lower dose did not cause a significant worsening of patient-reported outcome response, but switching to MTX alone or placebo did

ABA abatacept, *ADA* adalimumab, *AS* ankylosing spondylitis, *AUC* area under the curve, *BUC* bucillamine, *C* controlled, *CI* confidence interval, *CON* continuation group, *CRP* C-reactive protein, *CZP* certolizumab pegol, *DAS* Disease Activity Score, *db* double blind, *DFR* drug-free remission, *DMARDs* disease-modifying antirheumatic drugs, *ERA* early RA, *ESR* erythrocyte sedimentation rate, *ETA* etanercept, *EULAR* European League Against Rheumatism, *FU* follow-up, *HR* hazard ratio, *IFX* infliximab, *LDA* low disease activity, *MTX* methotrexate, *N* number of patients, *NI* noninferiority, *ol* open label, *PDUS* power Doppler ultrasound, *PP* poor prognosis, *PsA* psoriatic arthritis, *RA* rheumatoid arthritis, *RCT* randomized controlled trial, *FDR* fixed dose reduction group, *REM* remission, *RTX* rituximab, *SC* subcutaneous, *SDAI* Simple Disease Activity Index, *STOP* direct discontinuation, *TAP* disease-activity-guided tapering/dose optimization, *TCZ* tocilizumab, *TNFi* tumor necrosis factor inhibitors, *UA* undifferentiated arthritis, *UC* uncontrolled, *US* ultrasound

[a] The numbers do not add up to 103 because patients in the CON group were able to move into the FDR group

Table 2 Terms used in this field

Terms	Definition
Dose reduction, treatment relaxation/de-intensification/de-escalation	Overarching term for all strategies using dose reduction or cessation of a bDMARD
Discontinuation, stopping	Directly stopping the bDMARD
Treatment holiday	Temporary discontinuation of all (or one specific) medication
Drug-free remission (DRF)	Remission without any type of DMARD treatment
Fixed dose reduction	Directly reducing the dose or increasing the interval of the bDMARD
Tapering	Reducing the dose or increasing the interval of the bDMARD stepwise
Disease-activity-guided dose optimization, dose titration	Tapering a bDMARD until loss of response. In the case of loss of response, the dose is increased again until response is regained
Flare, loss of response, relapse	Increase in disease activity of sufficient duration and severity to warrant treatment change. When this occurs after dose reduction, it is often called loss of response or relapse [60]

The terminology used in the studies varies considerably. Therefore, in Table 2 we propose definitions of several terms that we will use in this review to describe concepts of interest.

1. What Are the Mechanisms Behind the Possibility of bDMARD Dose Reduction in RA Patients?

Most bDMARDs are believed to work though the achievement of a certain drug level in the blood that remains above the minimal effective drug concentration during the whole interval between two administrations [61]. The dose needed to obtain such a trough drug level differs between patients due to variations in the volume of distribution and the half-life of the drug. Furthermore, the minimal effective drug concentration varies significantly between patients. Therefore, each patient has their own dose–response curve [6].

Several dose–response patterns might be possible (Fig. 1). While some patients have an "average" dose–response curve, other patients will have a curve that is shifted to the left (good clinical response on a lower dose) or shifted to the right (good response only on a higher dose). Also, it is conceivable that some patients have a partial response to the drug or do not respond to the medication at all. The latter patients are doing well irrespective of the drug, possibly due to the placebo effect (in RCTs), regression to the mean, or concomitant medication.

Conceptually, based on the possible response patterns, patients with a flat dose–response curve can discontinue the bDMARD, as the clinical effect is unrelated to treatment. For patients with an S-shaped dose–response curve, tapering is possible until the minimal effective concentration (the concentration below which disease activity increases) is reached. Patients with a partial response should be switched to another drug and patients with a dose–response curve shifted to the right would need a higher than standard dose. However, administering a higher dose is not a realistic option for bDMARDs, as the authorized dose of these drugs is based on maximal effect at the group level. So, the chance of response is low, and is in fact much lower than the chance of response after switching to another bDMARD. Also, this higher dosing will result in lower cost-effectiveness and increased risk of side effects [5, 6].

2. In Which Patients and When Should We Consider Dose Reduction?

For clinical practice, it is important to know which patients are eligible for dose reduction. Logically, dose reduction is only applicable in

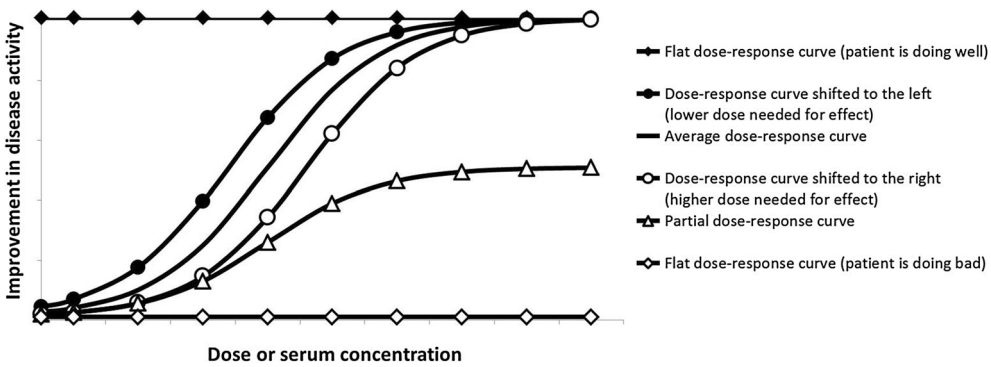

Fig. 1 Possible dose–response patterns for bDMARD treatment in RA patients (figure adapted from Fautrel et al. [6])

patients in whom the treatment goal is reached and treatment would normally remain unchanged. These are RA patients who have LDA or remission on treatment with a bDMARD.

Most of the studies included patients who showed sustained LDA or remission for ≥6 months. This period of 6 months seems reasonable, but this is based on expert opinion rather than evidence [6, 9]. It could be argued that dose reduction should only be performed in patients in clinical remission and not in patients with a low disease activity state. However, in a recent systematic review (mentioned in the section addressing question 4), neither DAS28-ESR nor DAS28-CRP at baseline demonstrated high predictive value for successful dose reduction or discontinuation of a bDMARD. Although deep remission is very nice to achieve, a less stringent goal of remission or low disease activity is a reasonable choice for many patients because (1) the patient-acceptable symptom state of RA disease activity is around a DAS28 of 3.2, (2) a subset of patients have a favorable prognosis with regard to joint damage, and thus do not need more intensive treatment, and (3) remission is not achievable in a subset of patients.

So, when the optimal effect of a bDMARD has been attained, it is possible to investigate whether this effect can be maintained with a lower dose of the drug. However, it is important to check that the bDMARD is not needed for any other condition such as Crohn's disease or psoriasis. Also, it is also important to address the order in which the tapering of medications should occur. Many patients use not only a bDMARD but also oral glucocorticoids and one or more sDMARDs. According to the EULAR recommendations, oral glucocorticoids should be tapered first, bDMARDs next, and sDMARDs last [9]. This recommendation is based on the safety and cost-effectiveness of each drug.

In conclusion, all RA patients with sustained (e.g., ≥6 months) LDA or remission, who do not need the bDMARD for any other condition, and who do not use high doses of steroids can be considered for bDMARD dose reduction.

3. What is the Best Dose Reduction Strategy?

There are several possible strategies for dose reduction of bDMARDs in RA patients. Many studies have investigated the possibility of direct discontinuation of the drug when a patient is in a low disease activity state. This is also called withdrawal, a "treatment holiday," or, when remission is maintained without any medication, drug-free remission (DFR); see also Table 2. Another option is a fixed dose reduction, for example halving the dose. The last and perhaps most sophisticated strategy is to taper the dose of the bDMARD step by step until disease flare or discontinuation of the medication. These last two strategies (fixed dose reduction or disease-activity-guided dose optimization) may be realized by either reducing the dose or increasing the interval between doses (spacing). Increasing the interval is the most practical approach for drugs administered through prefilled syringes, whereas dose reduction might be preferable for intravenous medication, as this is pharmacologically more

efficient when a minimal effective trough concentration must be obtained for a drug with first-order pharmacokinetics [6]. It should be noted, however, that in RA treatment the overarching strategy is characterized by tight control, so this should be incorporated into any dose-reduction strategy [62].

Based on most of the studies and reviews, it is evident that direct discontinuation of a bDMARD ultimately leads to a disease flare in many or even most patients [13, 17, 26, 28, 29]. At the group level, this strategy is therefore probably inferior to continuation of the bDMARD with respect to disease control, although no studies have investigated a strategy in which direct discontinuation was combined with restarting under tight control. However, direct discontinuation is feasible for at least a relevant subset of patients, which makes it interesting to identify these patients beforehand (see question 4).

Fixed dose reduction and disease-activity-guided dose optimization have often been found to be noninferior to continuation of the drug [7, 17, 22, 24–27, 63]. These strategies should therefore be considered in daily practice, as suggested by the EULAR and ACR in current guidelines [8, 9]. One strategy for disease-activity-guided dose optimization is to attempt tapering only once (as in the DRESS study [25]). Another option is to taper again after remission has been re-achieved (as in the STRASS study [22]). As it seems that patient dose–response curves are relatively stable over the short term, repeated tapering attempts are probably not favorable. This may be why the spacing arm in the STRASS study has a slightly higher mean DAS28 value than the maintenance arm. It may, however, be reasonable to expect (although this should be investigated) that another tapering attempt could be considered after a longer period, for example 1 or 2 years.

There is a discrepancy between the results of blinded fixed dose reduction of etanercept and open-label disease-activity-guided dose tapering: having the dose was shown to be just as effective as full-dose continuation (and thus feasible in nearly 100% of patients), while open-label tapering was not feasible in 30–40% of patients. An explanation for this may be that doubling the interval is not exactly the same as halving the dose. Another, more likely, explanation might be the nocebo and attribution effects that are introduced when dose reduction is not blinded. Patients might perceive dose reduction as being inferior and may feel worse as a result (nocebo), or unrelated events may be falsely attributed to the dose reduction (causal attribution) [6]. There are currently no known interventions for countering these effects of nocebo and false causal attribution, so open-label dose reduction strategies will probably underperform in clinical practice compared to what is biologically and pharmacologically possible.

To summarize the findings, open-label disease-activity-guided dose optimization seems to be the best strategy in clinical practice, although this probably underperforms compared to blinded dose halving as done in RCTs. It may be best to perform one attempt at tapering and thereafter maintain the lowest effective dose that was found, as multiple tapering attempts can result in higher disease activity. Fixed dose halving is a good alternative, but disease activity should be monitored, and of course the benefits are less compared to tapering until stop. Direct stopping can be attempted, but the relapse risk is much higher, and no studies have shown noninferiority of a stop strategy with restart in case of flaring compared to bDMARD continuation.

4. What Proportion of the Patients Can Be Stopped or Tapered, and Can We Predict Successful Dose Reduction Using Patient or Treatment Characteristics?

Although the percentage of patients who can successfully stop or taper varies considerably between studies, and depends on the flare criteria used (see question 6), many more patients can taper than can discontinue. For direct bDMARD discontinuation, the relapse risk after one year lies between 45% and 88% [6]. For fixed bDMARD dose reduction, these numbers are much lower—around 40% in the PRESERVE trial, 50% in the DOSERA trial, and 34% in the ALLOW study [17, 26, 27]. Two reviews conclude that halving the dose of etanercept and

rituximab is as effective as continuing with the full dose [7, 63].

For tapering strategies, the relapse rate should be interpreted differently, since tapering is continued until a patient flares (in order to find the optimal dose). In the DRESS study, the occurrence of short-lived flares was 73% in the tapering arm versus 23% in the continuation arm. However, there was no difference in persistent flares (longer than 3 months): 12% versus 10% in the tapering and continuation arms, respectively. The STRASS trial found comparable relapse rates: 77% (tapering) and 47% (continuation), although noninferiority could not be established due to lower than projected inclusion rates [22, 25].

The flare rate is thus lower for bDMARD fixed dose reduction versus bDMARD discontinuation. Open-label disease-activity-guided dose optimization leads to a high risk of short-lived flare versus continuation but comparable long-term disease control. Finally, fixed dose reduction seems as effective for two bDMARDs. These quantitative chances of successful dose reduction or discontinuation can be communicated to patients, and following shared decision-making (SDM), dose reduction can be attempted.

The chance of a successful dose reduction may differ between patient groups, depending on the patient or treatment characteristics. Therefore, many studies have also investigated possible predictors of success. Prediction of successful dose reduction or discontinuation of a bDMARD would provide several advantages. In patients who cannot use a lower dose, flares can be prevented by not tapering at all. For patients who are able to directly stop their bDMARD, accurate prediction would save time and medication since the dose-tapering phase can be skipped.

Regarding disease duration, a review by Kavanaugh reports that withdrawal appears possible for a subset of patients, especially those with early disease [64]. However, their conclusion is not consistent with a more recent review by Kuijper et al. in which the flare rate in studies including early RA patients was not consistently lower than that in patients with established RA [11].

Regarding the disease activity state before dose reduction, almost all studies use the DAS28 definition of LDA or remission when deciding upon patient inclusion [65]. Intuitively, it might seem logical that patients in remission have a higher chance of successful dose reduction compared to patients with low disease activity. However, in the RETRO trial, satisfying the ACR/EULAR Boolean remission criteria was not associated with a lower risk of relapse [6, 19]. Also, in the DRESS study, baseline disease activity was not a predictor of successful tapering [6, 25]. Therefore, all patients with LDA or in remission can be offered dose reduction with an equal chance of success.

Several dose-reduction studies have investigated various biomarkers for predicting successful tapering of bDMARDs. Some narrative reviews have demonstrated that it remains challenging to identify those patients who can taper their bDMARD without risking a flare [12, 66, 67]. In addition, the review of Schett et al. concludes that anti-citrullinated protein antibody (ACPA) negativity and the presence of "deep" remission such as absence of ultrasound synovitis and/or normal serum markers of inflammation are associated with greater chances of achieving drug-free remission [12].

A recent systematic review on this topic included 16 studies with a predefined tapering protocol and identified 64 and 52 different biomarkers for successful discontinuation and dose reduction, respectively. Among all the biomarkers investigated in more than one study, only three biomarkers were identified as predictive in two studies: a higher adalimumab trough level to predict successful dose reduction and a lower Sharp/van der Heijde erosion score and a shorter symptom duration at the start of a bDMARD to predict successful discontinuation [68]. The strength of this evidence was limited, since the latter two biomarkers (erosion score and symptom duration) showed a statistically significant but not strong association, and the first biomarker (adalimumab trough level) is questionable considering the extensive multiple testing performed in one study [69] and the disputed results of another study [70, 71]. Also, new data from the STRASS study could not confirm any predictive value of adalimumab

level [72]. In contrast to Schett et al., ACPA was not found to be a predictor in this systematic review, and ultrasound and several serum markers were only studied once. Some studies have been published recently on the Multi-biomarker Disease Activity (MBDA) score as a predictor of successful tapering, but they report conflicting results [73–76].

Thus, biomarker-based prediction is not ready for clinical practice yet. Assessment of subclinical inflammation by laboratory or imaging testing may provide a useful tool to determine a patient's risk of flare, but these biomarkers need to be validated first in other cohorts with a predefined tapering protocol before they can be considered to be predictive.

The type of bDMARD used might also be an effect modifier for successful dose reduction. Although some bDMARDs have been more extensively investigated than others, there do not appear to be any large differences in the effects of dose reduction. This may be due to the fact that for all bDMARDs, treatment using the authorized dose leads to overtreatment for at least a proportion of patients, since this dose is almost always chosen to be the highest effective dose at the group level. Some differences do seem to exist. For example, in the DREAM study with tocilizumab, relapse occurred quite rapidly [47].

Rituximab (RTX) is a rather different type of bDMARD. It is administered at intervals of at least 6 months due to the long B-cell depletion effect. The authorized RTX dosing for RA is also clearly much higher than needed. A recent systematic review revealed that half the authorized dose (1×1000 mg) is as effective as the full dose (2×1000 mg). This low dose is now widely used in clinical practice [77]. Several case studies and one case series suggest the possibility that a much lower dose of rituximab might be effective in the treatment of RA patients [78–81]. The effectiveness of these ultralow doses should be investigated further. Note that retreatment with RTX can be given on demand, but this results in repeated flaring and suboptimal disease control compared to fixed retreatment schedules or tight control treatment [82], as this approach essentially mimics repeated dose reduction attempts. So, while lower dosing can and should be used, in our opinion, retreatment should preferably be carried out either with a fixed interval or under strict tight control.

Regarding sDMARD use, Kavanaugh et al. suggest that patients who are MTX-naïve and receive an induction regimen of MTX with a TNF inhibitor may be better suited to dose reduction than those who do not respond to MTX sufficiently, improve upon the addition of a TNF blocker, and then are withdrawn from the bDMARD [64]. This seems logical, as response in these patients probably depends on MTX rather than the bDMARD. In the review by Kuijper et al., no relationship was observed between the use of a concomitant sDMARD and time to flare [11]. However, no information was reported on the order in which bDMARD and sDMARDs treatment was given before tapering. Therefore, no clear conclusion can be drawn on the effect of a concomitant DMARD treatment based on these reviews.

5. What Are the Effects of Dose Reduction on Function, Quality Of Life, Adverse Events, and Radiographic Damage?

Since fixed dose reduction and tapering of bDMARDs seem feasible in a large proportion of RA patients, and discontinuation for a smaller group, it is important to address the effects that are found on other important clinical outcomes such as function, quality of life, adverse events, and progression of joint damage.

Function (measured with the HAQ-DI) was found to be worse after discontinuation in the PRESERVE study, but not in two other RCTs, the OPTIMA and ADMIRE [17, 18, 28]. The ENCOURAGE study showed that fewer patients had HAQ <0.5 after discontinuation [21]. In the ALLOW study, physical function was slightly worse after withdrawal of abatacept, but this improved after reinstating treatment [15]. Function was found to be comparable to continuation after fixed dose reduction and tapering [17, 22, 25]. In the STRASS study, a small difference in quality of life remained at the end of the study [22].

The reduction of (dose-dependent) adverse events is one of the reasons to consider dose reduction of bDMARDs. Although several

studies have monitored adverse events, few have found significant differences between dose reduction and continuation [17, 18, 22, 25, 26, 28, 49]. This might be due to the fact that none of these studies were powered to detect differences in side effects, and clinical trials in general have a limited follow-up time. Also, tapering studies usually include patients who have been using the bDMARD for quite some time, thus selecting the patients who are less prone to adverse effects (healthy survivor bias). However, Raffeiner et al. did find fewer infections in the half-dose etanercept group compared to the full-dose group [24].

Several studies have assessed the effect of bDMARD dose reduction on radiographic structural damage progression. In the PRESERVE trial, discontinuation of etanercept led to increased joint damage. However, progression in the dose-halving group was similar to that in the continuation group [17]. These findings are in line with other studies which found that dose reduction/tapering did not lead to significant radiographic damage progression [22, 24, 34, 35, 54, 55]. In the DRESS study, a minimal increase in radiographic progression was found in the tapering group, but no patients had an outcome of relevant joint damage progression [25]. Kuijper et al. conclude in their systematic review that there are limited data on radiographic damage but that the current evidence shows that progression remains limited after treatment de-escalation [11].

In conclusion, discontinuation results in somewhat worse function and more joint damage. Fixed dose reduction and tapering does not seem to result in deterioration in these parameters. A reduction in adverse events has not been unequivocally shown, although this seems plausible, as bDMARD-induced infections have been shown to be dose-related [4].

6. Which Flare Criterion is Best to Use When Deciding Whether to Restart/Re-escalate Treatment, and How Often Should the Patient Be Monitored?

In the included studies, several different criteria for flares were used, although they were mostly based on the DAS28. The OMERACT working group performed a validation study of the DAS28-based RA flare criteria. They concluded that an increase in DAS28 >1.2, or >0.6 if DAS28 ≥3.2, appears to be the most discriminating and valid based on a set of predefined validation criteria [83]. It is therefore advisable to use this flare criterion in clinical practice. In addition, the OMERACT RA Flare group is developing a patient-reported flare questionnaire that could also be used in the future [84], especially in health care systems where travel distances are much higher than generally encountered in Western Europe. Other flare criteria could be used as well, but they may be either too sensitive or too specific, resulting in worse patient outcomes or conversely unjustified treatment re-escalation.

Since dose reduction may lead to a flare in (a proportion of) the patients, it is very important to closely monitor patients who are tapering their bDMARDs. When a flare occurs, the dose should be increased again to the lowest effective dose. Based on the methods of several trials, an interval of no more than 3 months appears necessary, with an extra consultation when patients experience a worsening of their symptoms [22, 24, 25].

7. Is It Effective and Safe To Restart Treatment?

When considering discontinuation or tapering until stop, it is essential to know whether restarting the bDMARD or intensifying treatment will be effective and safe. Regarding effectiveness, most patients are able to regain LDA or remission again after restarting the bDMARD treatment. Percentages of between 80% and 100% are described [85]. Also, most studies show that restarting a bDMARD after withdrawal is well tolerated and not associated with more adverse events or higher immunogenicity [15, 25, 35, 38, 44, 49, 55]. Data from tight control studies also support this notion, as the mean DAS28 for example in the DRESS study is similar for continuation and dose reduction after 18 months, while switching to other bDMARDs was rare [25]. Therefore, based on the current evidence, it seems that restarting bDMARDs after discontinuation is effective and safe.

It has been suggested in the literature that tapering of bDMARDs may lead to the

formation of anti-drug antibodies (ADAbs), which could then result in worse outcomes after restarting treatment. However, there does not seem any evidence supporting this statement [85, 86]. It is probable that the amount of "free" antibodies that is measured depends on the dose of the antigen (the drug). When administering a high dose, most of the ADAbs will be bound to the drug. When administering a low dose, more of the ADAbs will be unbound and are thus measureable in the blood. This does not automatically imply that the formation of these antibodies is increased, or that the presence of the ADAbs leads to a lower effect or side effects.

8. What is the Cost-Effectiveness of Dose Reduction?

Next to infection risk and patient burden due to regular self-injection, costs are one of the main reasons to look into dose reduction of bDMARDs after LDA or remission is reached. Surprisingly, not many of the studies that address this topic report a cost analysis of their strategy. This may be because the majority of the studies are funded by pharmaceutical companies, so there is perhaps a limited interest in demonstrating that dose reduction is cost-effective. While it seems logical that tapering a bDMARD will result in a substantial cost saving, the question is whether these savings outweigh the costs induced by increased monitoring, patient education, an increase in flares, and a subsequent deterioration in quality of life (as reflected in QALYs).

Only three of the RCTs included in this review describe a cost-effectiveness analysis: the STRASS and DRESS studies, which both investigated disease-activity-guided tapering of bDMARDs until discontinuation, and the PRESERVE study [22, 25, 87–89]. The STRASS study found that spacing resulted in a smaller gain in QALYs during the study period of 18 months compared to continuation. They calculated that 53,417 euros were saved per QALY lost. The authors indicate that it depends on the willingness to accept whether this is cost-effective [22]. In the DRESS study, the mean QALY loss was −0.02 in the tapering arm compared to the continuation arm, and the dose optimization strategy resulted in savings of approximately 8000 euros per patient per year. The savings per QALY lost were 390,493 euros. When the minimal QALY loss was adjusted to account for the upper limit of what society is willing to pay or accept in the Netherlands, the net savings were still high [25]. For the PRESERVE study, a Markov model was devised that incorporated data from the trial and extrapolated to 10 years follow-up, allowing a dose increase in the case of a flare and dose reduction in the case of remission according to tight control. Overall, the fixed dose halving strategy seemed most advantageous, mainly because half-dose etanercept showed a similar effectiveness to full-dose [89].

Three of the nonrandomized studies that we found reported costs [37, 44, 52]. In an uncontrolled study of infliximab tapering by van der Maas et al., a mean reduction of 3474 euros per patient was found [37]. In a strategy study by Inui et al., patients discontinued etanercept when disease activity was low and restarted when a flare occurred. In the 5 patients who maintained low disease activity without restarting etanercept, the savings were found to be approximately 35% [44]. Murphy et al. reported a cost saving of 600,000 euros after 2 years in their cohort of 79 patients (45 RA, 10 psoriatic arthritis, and 24 ankylosing spondylitis) that reduced the dose of etanercept or adalimumab [52]. That meant a saving of 3800 euros per patient per year—comparable to the savings found by van der Maas et al.

Overall, disease-activity-guided dose optimization results in large cost savings per patient per year and no or a small loss in QALYs. Cost-effectiveness estimates are, however, very sensitive to either no or very small changes in quality of life, so the precise cost-effectivenesses of different strategies remain to be established, although results seem very encouraging.

9. How Can Dose Optimization Best Be Implemented in Clinical Practice?

An often forgotten aspect of new treatment strategies is their implementation in clinical practice. Although several studies have shown the additional value of bDMARD dose reduction, and it has been incorporated into international recommendations [8, 9], this does not

automatically mean that clinicians will act on it [90, 91].

Several studies have investigated the current use of a lower-than-standard dose of bDMARDs in routine clinical practice. A systematic review into dose escalation and dose reduction of bDMARDs in clinical practice found that, for etanercept, 13.2% of patients used a lower-than-registered dose. For adalimumab and infliximab, this was 8.9% and 25%, respectively [92]. In a retrospective cohort of RA patients using Medicare claims ($n = 26{,}510$), approximately 10–20% of patients who initiated and adhered to etanercept and adalimumab for ≥12 months subsequently received reduced-dose therapy for an 12 additional months and beyond [93]. In the Ninja cohort ($n = 1037$), 7.4% of patients stopped bDMARD treatment due to remission [94] and 40% of patients in a tertiary hospital in Spain ($n = 96$) used a lower-than-registered dose while remaining at a low disease activity or in remission [95]. These data show that in routine clinical practice, outside of trials, bDMARD dose reduction is still relatively rare, and it is often implemented for reasons other than dose optimization (e.g., side effects), and the mean percentage of patients on a lower-than-registered dose probably lies somewhere between 10% and 25%.

Many factors can impede the use of new insights in clinical practice, such as barriers related to the innovation itself (e.g., complexity, relative advantage), the individual health care provider or patient (e.g., knowledge, attitude, skills, self-efficacy), incentives and resources (time, funding), or the organizational context (work climate, structures) [90, 96]. For dose reduction, it is conceivable that rheumatologists are not aware of the possibility of dose reduction (knowledge), do not agree with the evidence (attitude), or simply do not have the time or tools/protocols to adhere to the guidelines (practical barriers). The same holds true for patients. Since it is still difficult to predict successful dose reduction, tapering comes with a risk of (short-term) disease flare which makes the decision to taper very dependent on patient preference. Gaining insight into barriers and facilitators for patients and physicians could facilitate implementation.

Recently, a pilot study aiming at the implementation of tight control and bDMARD dose optimization was published [97]. A multicomponent strategy consisting of education, protocol development, and treatment advice was employed to improve the use of these principles in a tertiary hospital with two rheumatologists. The results showed an increase in DAS measurements and a large decrease in bDMARD use, while mean disease activity levels remained unchanged. Larger, preferably controlled, studies are necessary to assess the effectivenesses of implementation strategies.

10. What is the Patient Perspective on bDMARD Dose Reduction?

Since dose reduction of a bDMARD comes with an increased risk of short-lived disease flare, the decision to start tapering is also dependent on the preference of each individual patient. The physician can inform, educate, and motivate the patient based on the current evidence on dose reduction, but the final decision should be SDM-based. It is therefore important to investigate what patients' cognitions and emotions are regarding bDMARD dose reduction.

Three qualitative studies into the patient perspective on bDMARD dose reduction were identified [98–100]. These studies all found that dose reduction is associated with both positive and negative perceived aspects for patients. Positive aspects include the reduced risk of adverse events, reduced frequency of injections, and contributing to savings in the healthcare budget. Examples of negative aspects are the risk of a flare, a delay in access to previous doses, and fear of a loss of efficacy after restarting treatment.

While these qualitative studies all explore factors that are important to patients when considering dose reduction of a bDMARD, the preferences of individual patients will differ largely. However, the current evidence on dose reduction and the need to reduce medication costs urge that tapering in RA patients who reach a stable LDA or remission on bDMARD treatment should be discussed in shared decision-making. In clinical practice, a balance

must be found between patient concerns and the responsibility of hospitals and rheumatologists to contribute to savings in the healthcare budget.

Communication methods could help physicians in their daily work regarding bDMARD dose reduction. Patient expectations could be modified by informing them as early as possible about the option of dose reduction, for example at the start of their bDMARD treatment. Also, motivational interviewing or positive framing can be used in conversations about dose reduction with individual patients.

DISCUSSION

Based on the current evidence for this subject, we conclude that bDMARD dose reduction can be considered in all RA patients who have stably reached their treatment goals (e.g., ≥6 months LDA or remission) on treatment with a bDMARD. The best strategy seems to be disease-activity-guided dose tapering with fixed dose reduction as an alternative, since the risk of relapse was found to be highest for direct bDMARD discontinuation, and discontinuation results in worse physical functioning and more joint damage. Although bDMARD tapering seems to be (very) cost-effective, a reduction in adverse events after dose reduction is yet to be clearly demonstrated.

When tapering the bDMARD treatment of a patient, disease activity should be monitored closely, for example with a consultation every 3 months and extra consultations when necessary. The validated flare criterion (ΔDAS28 >1.2 or >0.6 if DAS28 ≥3.2) can be used to identify patients who have lost response due to the tapering. When a patient flares, the dose should be increased to the lowest effective dose. Current evidence shows that restarting bDMARD treatment is effective and safe. Unfortunately, no clear predictors of successful tapering have been identified so far. The evidence for bDMARD dose reduction and rising healthcare costs urge that dose reduction should be considered and attempted for eligible patients. However, patient values and preferences should be respected and a balance may be found using SDM.

This study has some limitations, as our searches for relevant articles were systematic but the data extraction and writing were performed in a narrative manner. Also, we did not perform a quality assessment of the included articles, and no formal meta-analyses were done. However, this review does provide a complete overview of the most important studies that have been performed on bDMARD dose reduction, and the questions that we address here could be of interest to a large group of clinicians involved in the treatment of RA patients.

Several new trends are visible regarding bDMARD dose reduction, such as the introduction of biosimilars, which will change the cost-effectiveness ratio for tapering [101]. Also, evidence on bDMARD dose reduction for other diagnoses in rheumatology is emerging, for example in relation to psoriatic arthritis and ankylosing spondylitis [102]. Furthermore, new methods of research are gaining interest, such as noninferiority trials (investigating whether a new strategy or treatment is no worse than the old one) and modeling studies (using existing data to answer new research questions, thus saving costs and limiting the burden on patients) [103, 104]. Lastly, it is clear that most of the research done on the topic of dose reduction is "hard science," and studies of the "soft science" associated with dose reduction (e.g., investigations of SDM and implementation) are lagging behind. Future research should focus not only on achieving a better understanding of the effects of dose reduction on important clinical outcomes but also on the perspectives of the patients and physicians as well as the implementation of this new treatment principle.

CONCLUSIONS

In conclusion, a lot of research has been done on the topic of bDMARD dose reduction in RA. The best dose-reduction strategies seem to be disease-activity-guided dose optimization and fixed dose reduction. The evidence for bDMARD dose reduction and rising healthcare costs urge

that dose reduction should be considered for and attempted in RA patients who have reached a stable state of LDA or remission. However, patient values and preferences should be respected, and a balance may be found using SDM.

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