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REVIEW ARTICLE

Tapering biologics in rheumatoid arthritis: a pragmatic approach for clinical practice

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Abstract Optimal rheumatoid arthritis (RA) therapy in daily clinical practice is based on the treat-to-target strategy. Quicker escalation of therapy and earlier introduction of biological disease-modifying anti-rheumatic drugs have led to improved outcomes in RA. However, chronic immunosuppressive therapy is associated with adverse events and higher costs. In addition, our patients frequently express a desire for lower dosing and drug holidays. Current clinical practice guidelines from the American College of Rheumatology and European League Against Rheumatism suggest that rheumatologists consider tapering treatment after achieving remission. However, the optimal approach for tapering therapy in RA, specifically de-escalation of biologics, remains unknown. This clinical review discusses biologic tapering strategies in RA. We draw our recommendations for everyday clinical practice from the most recent observational, pragmatic, and controlled clinical trials on de-escalation of biologics in RA. For each biologic, we highlight clinically relevant outcomes, such as flare rates, recapture of the disease control with retreatment, radiographic progression, side effects, and functional impact. We discuss the use of musculoskeletal ultrasound to select patients for successful tapering. In conclusion, we provide the reader with a practical guide for tapering biologics in the rheumatology clinic.

Keywords Biologic therapy · Discontinuation · Musculoskeletal ultrasound · Rheumatoid arthritis · Tapering · Treat to target

Introduction

Rheumatoid arthritis (RA) affects up to 2% of individuals worldwide and is associated with increased morbidity and mortality [1, 2]. Immune system dysfunction, with loss of self-tolerance, autoantibody production, and pro-inflammatory cytokine release, leads to proliferation of the synovial lining of joints causing progressive damage [3, 4]. The initiating phase of RA may involve lung or periodontal disease with a break in immune tolerance to self-antigens occurring due to neoantigen formation and epitope spreading [5, 6].

The goals of RA management include rapid control of inflammation, prevention of structural damage, and maintenance of function. Optimal RA therapy in daily clinical practice is based on treat to target (T2T) successfully translated from randomized controlled trials (RCTs) of biological disease-modifying anti-rheumatic drugs (bDMARD) [7, 8]. T2T is focused on successive escalation of immunosuppression, i.e., combination therapy with conventional synthetic DMARDs (csDMARDs) and earlier addition of bDMARD, to achieve remission (REM) or low disease activity (LDA) [7, 8]. T2T has led to significant improvement in outcomes for our patients. It is unclear, however, whether initial immunosuppression can be de-escalated, i.e., tapered, while maintaining treatment goals.

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This review discusses bDMARD tapering strategies in RA for everyday clinical practice. We draw our conclusions for everyday clinical practice from up to date publications in the last 5 years of pragmatic observational studies and RCTs on de-escalation of bDMARDs in RA.

Why consider de-escalating bDMARDs in RA?

Current practice guidelines suggest that rheumatologists consider tapering treatment after achieving REM in RA, while tapering is not recommended for LDA [7, 8]. The suggested order of tapering is (1) glucocorticoids, (2) bDMARDs, and (3) csDMARDs. However, the optimal approach to tapering bDMARDs remains unknown.

Long-term REM is now possible in over 50% of patients with the T2T strategy, raising concern for potential overtreatment [9, 10]. Over time, the risks of immunosuppression with bDMARDs may outweigh the benefits of continuing therapy, such as increased infection risk and possibility of malignancy development due to impaired immune surveillance. bDMARD pharmacodynamics may allow for selected patients to require lower-dose requirements compared to standard regiments [9, 11]. Finally, the health economics of long-term bDMARD use in RA are an important consideration, especially for countries with socialized health care systems such as Great Britain and Canada, where novel specialized therapy is scrutinized for cost-effectiveness.

Patients' concerns regarding long-term bDMARD use play a major role in our consideration to de-escalate therapy. Patients frequently report concerns regarding side effects, the injection process, and administration fatiguing; most importantly, they express desire for lower dosing and drug holidays [9]. Despite our best efforts, about 15% of patients with RA self-discontinue bDMARDs, with reasons being decreased pain, prior treatment with more than 1 biologic, self-administration of injections, negative beliefs about treatment, and lack of perceived medical and social support [12].

What are the potential risks of de-escalating bDMARDs in RA?

De-escalation of bDMARDs may lead to more disease flares, transient or persistent, with an immediate impact on our patients' quality of life, function, and productivity. As providers, we are concerned for disease progression especially in the long term and the inability to recapture disease control with reinstitution of prior bDMARD therapy [9, 10].

In order to start tapering bDMARDs in clinical practice, we need to know which bDMARD to select, i.e., anti-TNF vs non-TNF, what is the impact on clinical outcomes, and which are optimal patients to be selected. The best approach for de-escalating bDMARDs would also align both provider and patient goals for management of chronic RA.

De-escalation of anti-TNF therapy

Adalimumab de-escalation in early RA Three major studies have been published addressing discontinuation of adalimumab (ADA) in early RA [13–15].

HIT HARD was a double-blind two-phase randomized controlled trial (RCT) with 155 patients with early RA (duration 1.8 months) [13]. Patients were initially randomized 1:1 to combination ADA and methotrexate (MTX) or MTX monotherapy for 24 weeks, followed by discontinuation of ADA in all patients regardless of disease activity while continuing MTX for 6 months. Flares were defined as Disease Activity Score in 28 joints (DAS28) >2.6 (i.e., non-REM by DAS28). At 6 months, similar rates of REM by DAS28 occurred in both groups (43% in ADA + MTX vs 37% in MTX monotherapy) regardless of initial treatment with bDMARD. However, radiographic progression measured by Sharp-van der Heijde score (SHS) was slightly higher in the MTX monotherapy group.

The OPTIMA trial was a double-blind two-phase RCT which enrolled 207 patients with early RA (duration 3 months), initially randomized 1:1 to combination ADA and MTX or MTX monotherapy for 26 weeks [14]. Subsequently, patients achieving LDA by DAS28 were randomized 1:1 to continue or discontinue ADA, with flares defined as DAS28 >3.2. At 1 year of follow-up, patients were more likely to be in LDA (91 vs 81%) and REM (86 vs 66%) if they continued ADA therapy compared with stopping.

In HOPEFUL-2, an observational study with 188 RA patients with longer disease duration (1.3 years), patients' choice guided the decision to continue or discontinue ADA in a 1:1 ratio after open-label combination treatment with ADA and MTX for 52 weeks [15]. At entry into the observational phase, 85% were in LDA and 75% in REM by DAS28. Flares were defined as DAS28 >2.6. At 1 year of follow-up, patients were more likely to be in LDA (91 vs 74%) and REM (76 vs 60%) if they continued ADA compared with stopping. Deep REM (DAS28 ≤2.0) at time of entry was suggested as a predictor for successful discontinuation of ADA. Increased radiographic progression was noted in patients on MTX monotherapy during the initial RCT. More infections were observed in the ADA continuation group (27 vs 15%).

A summary of findings from HIT HARD, OPTIMA, and HOPEFUL-2, which focused on the discontinuation of ADA in patients with early RA, is presented in Table 1.

Table 1 Summary of anti-TNF tapering in rheumatoid arthritis

	Adalimumab	Etanercept	Other (CZP, IFX)
No flare if D/C	Early RA: 40–90% @ 1 year Est RA: 10–60% @ 1 year	Early RA: 55–70% @ 10 months Est RA: 10–40% @ 1 year	Early RA: NR Est RA: 30–50% @ 1 year
No flare if taper	Early RA: NR Est RA: 25–90% @12–18 months	Early RA: 80–90% @10 months Est RA: 25–90% @ 1 year	Early RA: NR Est RA: NR
Predictors of taper	Early/Est RA: deep REM	Early RA: Boolean REM Est RA: longer TNFi use	Low DAS, shorter Dz, non-smoker
Radiographic stability	✓	No if D/C ✓ if taper	✓
Functional stability	✓	✓	✓
Side effects decreased	✓	No	✓
Retreatment success	>90% @ 1 year	>80–90% @ 2–3 months	>90% @ 3 months

TNF tumor necrosis factor, *RA* rheumatoid arthritis, *CZP* certolizumab pegol, *IFX* infliximab, *Est* established, *D/C* discontinuation, *NR* not reported, @ at, *REM* remission, *DAS* Disease Activity Score, *Dz* disease, ✓ yes

Adalimumab de-escalation in established RA Three main studies, HONOR, ADMIRE, and POET, were published examining discontinuation of ADA in established RA [16–18].

In the observational HONOR study of 75 patients with established RA (duration ~7.5 years), patients who achieved REM (DAS28 <2.6) for 6 months on combination treatment with ADA and MTX were randomized 1:2 to continue or stop ADA [16]. Flares were defined as DAS28 ≥3.2. Both REM (83 vs 48%) and LDA (91 vs 62%) were significantly higher in the continuation group compared with discontinuing ADA at 1-year follow-up. Less flares were observed in the subgroup of patients in deep REM (DAS ≤1.98).

ADMIRE was an open RCT with 31 patients with established RA (~8 years) who were randomized 1:1 to ADA continuation or discontinuation if they were in REM by DAS28 (<2.6) for more than 3 months while on stable combination treatment with ADA and MTX [17]. Flares were defined as DAS28 >2.6 or increase of >1.2 between assessments. At 1 year, REM was significantly higher in patients continuing ADA compared with stopping (81 vs 13%), without significant impact on radiographic progression or side effects.

POET was the largest pragmatic open-label RCT of 817 patients with established RA (~11 years) treated initially with combination anti-TNF (≥1 year) and MTX (≥6 months) and subsequently randomized 1:2 to continue or stop their anti-TNF if they were in REM or LDA by DAS28 for ≥6 months [18]. Anti-TNFs were mainly ADA 50% and etanercept (ETN) 40%; a minority were on infliximab (IFX) 5%, golimumab (GOLI) 3%, and certolizumab pegol (CZP) 1%. Flares were objectively defined as DAS28 ≥3.2 and increase in DAS28 ≥0.6. At 1-year follow-up, patients who continued on anti-TNF were more likely to be flare-free (82 vs 49%) and in REM (57 vs 30%) compared with patients stopping anti-TNF. More flares were observed in patients with initial higher DAS28 (HR 1.4) and longer disease duration (HR 1.3) prior to stopping anti-TNF.

A summary of findings from HONOR, ADMIRE, and POET, which focused on the discontinuation of ADA in patients with established RA, is presented in Table 1.

Etanercept de-escalation in early RA The PRIZE study was a double-blinded three-phase RCT with 193 patients with early RA (~6.5 months) who received initial open-label combination ETN 50 mg subcutaneous (SQ) once weekly (ETN50) and MTX for 52 weeks, followed by randomization 1:1:1 to ETN 25 mg SQ once weekly and MTX (ETN25) or MTX monotherapy or placebo if in REM by DAS28 (<2.6) at entry [19]. Flares were defined as DAS28 >3.2. At 39 weeks follow-up, patients receiving ETN25 were more likely to be in LDA (89 vs 69 vs 46%) and REM (79 vs 54 vs 38%) compared to MTX monotherapy and placebo. Less flares were observed when patients were in deeper Boolean defined REM. A summary of findings from PRIZE is presented in Table 1.

Etanercept de-escalation in established RA PRESERVE, DOSERA, and POET studies focused on patients with established RA [20, 21].

The PRESERVE trial was the largest double-blinded two-phase RCT with 604 patients with established RA (~7 years) who were initially treated with combination ETN50 and MTX for 36 weeks, followed by randomization 1:1:1 to continue ETN50 and MTX or taper to ETN25 and MTX or MTX monotherapy if they achieved LDA (DAS ≤3.2) for 6 months [20]. Flares were defined as DAS28 >3.2. At 1-year follow-up, patients were more likely to maintain LDA if on either ETN50 or tapered to ETN25 (83 vs 79%, NS) compared to stopping ETN

(43%). Additionally, stopping ETN altogether was associated with increased radiographic progression.

The more recent DOSERA study was a smaller double-blinded RCT which enrolled 73 patients with established RA (disease duration 13 years) treated initially with combination ETN50 and MTX for at least 14 months, who achieved LDA (DAS28 <3.2) for 11 months and were then randomized 1:1:1 to continue ETN50 with MTX or taper to ETN25 with MTX or monotherapy MTX [21]. Definition of flares used in this study included DAS28 >3.2, physician assessment, and patient report. At 48 weeks of follow-up, patients on either ETN50 or ETN25 (52 vs 44%, NS) were more likely to be flare-free compared with stopping ETN (13%). Less flares were observed in subgroups of patients with initial lower pain score, less erosions, and longer treatment with ETN prior to de-escalation in therapy. A smaller proportion of patients in DOSERA compared with PRESERVE were at T2T goal, which can be accounted for by the use of more subjective definitions of flare (i.e., patient report) underestimating overall disease control. The POET study was described earlier. A summary of findings from PRESERVE, DOSERA, and POET is presented in Table 1.

Disease activity-guided de-escalation of anti-TNF Two landmark trials, DRESS and STRASS, were completed in patients with established RA on either ADA or ETN therapy who underwent disease activity-guided tapering of their bDMARD [22, 23].

The DRESS trial was a pragmatic open RCT of 180 patients with established RA (~10 years) treated with either ETN (~2/3) or ADA (~1/3) for at least 6 months to achieve LDA by DAS28 (<3.2) [22]. Patients were subsequently randomized 1:2 to continue usual care or taper their anti-TNF to discontinuation based on a disease activity-guided strategy. For example, a patient on initial ADA who maintained LDA at each assessment would increase the injection interval every 3 months from initial 2-week dosing to every 3 weeks, then to every 4 weeks and finally stopping. Flares were defined objectively as increase in DAS28 >1.2 or increase >0.6 with DAS28 >3.2 and were classified as major if lasting more than 3 months or short-term otherwise. At 1.5 years of follow-up, patients who tapered their ETN or ADA had similar major flare-free rates compared with usual care (88 vs 90%); however, short-term flares were more common in the tapering group (63 vs 27%) and accompanied by slight statistically significant increase in radiographic progression but not exceeding the minimal clinical important change.

The STRASS trial enrolled 138 patients with established RA (~10 years) previously treated with ETN (50%) or ADA (50%) with or without a traditional DMARD [23]. In contrast to DRESS, patients had to achieve REM by DAS28 (≤2.6) for 6 months prior to randomization 1:1 to either continue their anti-TNF or taper to discontinuation with a 5-step disease activity-guided strategy. Flares were defined as DAS28 >2.6 and increase in DAS28 >0.6; however, duration or severity of flare was not defined. At 1.5-year follow-up, patients continuing their anti-TNF at standard dose were more likely to be flare-free compared with the tapering group (54 vs 23%). There were no differences in neither radiographic progression nor safety. Unexpectedly, flare rates were higher in STRASS compared with DRESS despite the former trial enrolling patients in sustained REM; however, in STRASS, less patients were on standard dose of anti-TNF (20 vs 37%) and more patients had discontinued their anti-TNF (50 vs 20%) compared with DRESS, which may account for the observed difference in flare rates. A summary of findings from DRESS and STRASS is presented in Table 1.

Infliximab de-escalation in RA In a post hoc analysis of the BeSt study, a multicenter RCT of 508 patients on four different treatment strategies in DMARD-naïve active RA which included two arms with initial or delayed IFX, 104 patients with LDA (DAS44 ≤2.4) for 6 months discontinued IFX and were followed up (median 7.2 years) [24]. Flares were defined as DAS44 >2.4, and more patients remained in LDA if they were in the initial compared with delayed IFX arm (56 vs 41%). There was no radiographic progression; patients who stopped IFX had predictably less infections. Additional studies with IFX have been reviewed recently [25].

Certolizumab de-escalation in RA CERTAIN was a small observational study whereby all 23 patients with established RA, initially treated in the RCT with certolizumab pegol (CZP) and MTX, who achieved REM by the clinical Disease Activity Score (CDAI) ≤2.8 discontinued CZP [26]. Flares were defined as CDAI ≥11 at two consecutive assessments. At 7-month follow-up, only 18% of patients remained in REM. A summary of findings from BeST and CERTAIN is presented in Table 1.

De-escalation of non-TNF biologics

Abatacept de-escalation in early RA Two main studies have been published focusing on abatacept (ABA) de-escalation in early RA [27, 28].

AVERT was an observational study with 186 patients with early RA (~0.56 years), initially treated in an RCT randomized 1:1:1 to ABA SQ and MTX or ABA SQ monotherapy or MTX monotherapy for 12 months [27]. Subsequent to the RCT, all treatment was discontinued in

patients in LDA (DAS28 <3.2) who were enrolled in the observational study. Flares were defined as a two-fold increase in swollen and tender joint counts or increase in DAS28 >1.2, or based on physician assessment. At 6-month follow-up, slightly more patients in the initial ABA groups were in REM compared with MTX group (25–28 vs 17%).

In the AGREE trial, 108 patients with early RA in REM (DAS28 <2.6) were randomized 1:1 to continue (10 mg/kg/dose) or decrease by half (5 mg/kg/dose) ABA intravenous (IV) dose [28]. All patients had early RA (≤2 years) initially and received ABA IV (10 mg/kg/dose) and MTX for 1 year prior to enrollment. Flares were defined as DAS28 ≥3.2, or ≥2 episodes requiring high-dose steroids or physician switch to full-dose ABA. At 1-year follow-up, flare-free rates were similar (69 vs 66%), while REM rates were slightly higher (47 vs 36%) in patients continuing full-dose compared with taper to half-dose ABA. Of note, the AGREE trial did not use specific power calculations in their analysis due to small sample size.

Abatacept de-escalation in established RA Takeuchi et al. performed a prospective single-arm observational study in 51 patients with established RA (~12.5 years), initially treated in an RCT with either ABA IV or placebo in combination with MTX for 24 weeks followed by open-label ABA IV in all patients for an additional 38 months. Patients achieving deeper REM (DAS28 <2.3) were given a choice to continue or stop ABA (1:2 ratio) [29]. Flares were defined as DAS28 >2.7 or by physician assessment. At 1-year follow-up, patients who continued ABA IV were more likely to be flare-free (94 vs 59%) and to be in REM (65 vs 41%) compared with stopping.

In summary, findings from studies of de-escalation of ABA in RA suggest that after initial treatment with ABA monotherapy or combination therapy with MTX and achieving T2T goal of REM or LDA, discontinuation of ABA leads to no flares in 40–60% of patients and tapering of ABA leads to no flares in 40–70% of patients by 1 year. A summary of findings from studies on de-escalation of ABA is presented in Table 2.

Tocilizumab de-escalation in RA The DREAM trial was an open single-arm study with 187 patients with established RA (7.8 years), initially treated in several RCTs with tocilizumab (TCZ) monotherapy, who discontinued TCZ at enrollment if in REM or LDA (by DAS28) [30]. Flare definitions included DAS28 >3.2 or adding DMARDs or patient request to reinitiate TCZ or by physician assessment. At 1-year follow-up, only 9% of patients were in REM and 13% in LDA. However, a subgroup of patients with both decreased serum interleukin-6 (IL-6) and matrix metalloproteinase 3 (MMP-3) was more likely to maintain disease control at both 24 weeks (71%) and 52 weeks (38%) compared to patients with abnormal serum levels of IL-6 and MMP-3. Hence, low IL-6 (HR 0.41) and low MMP-3 (HR 0.29) were postulated to be predictors of successful discontinuation of TCZ in selected patients. Radiographic progression and side effects were not reported. The follow-up RESTORE trial focused on retreatment with TCZ for patients who flared during DREAM, with 96 and 89% achieving LDA and REM by 3 months, respectively [31]. A summary of findings from DREAM and RESTORE is presented in Table 2.

Ultrasound-guided de-escalation of biologics

Three main studies have evaluated the use of musculoskeletal ultrasound (MSUS) during de-escalation of bDMARDs in RA [32–34].

Iwamoto et al. aimed to assess predictors of flare by MSUS after discontinuation of bDMARD in a prospective observational cohort of 42 patients with established RA treated with combination bDMARD (~75% anti-TNF, ~25% TCZ IV) and MTX, who achieved REM (DAS28 < 2.6) and were given the choice to stop bDMARD [32]. MSUS was performed in 40 joints for grayscale (GS) synovitis, and power Doppler (PD) positivity assessments scored 0–3 at each site. Flares were defined as DAS28 >3.2 and accompanied by increase in DMARD therapy. At 6 months, 60% of patients were flare-free after stopping their respective bDMARD. Total GS and PD scores by MSUS were significantly greater in relapsers compared with flare-free patients. After receiver operating characteristic (ROC) curve analysis for prediction of flare at 6 months, relapse was more likely in patients with greater total GS (≥14) or PD (≥3) scores at time of stopping bDMARD, suggesting that MSUS use can predict the likelihood of subsequent flare.

Naredo et al. studied MSUS predictors of failure to taper bDMARDs in a prospective observational cohort of 77 patients with established RA (~13.1 years), who achieved REM for 12 months after initial treatment with bDMARD and nbDMARD for 6 months [33]. Biologics were anti-TNF (80%), ABA (10%), and TCZ IV (10%), which were tapered by an increase in interval by 50% every 6 months if not flaring. Flares were defined as non-REM (by DAS or simplified disease activity index) or reincrease in bDMARD or nbDMARD or prednisone >5 mg daily. MSUS was performed for GS synovitis and PD assessment in 42-joint, 12-joint, and wrist-metacarpophalangeal (MCP)-ankle-metatarsophalangeal (MTP) examinations. At 6 and 12 months of follow-up, patients were flare-free in 70 and 55%, respectively, with increased flares in patients with DAS28 ≥2.2 at time of stopping bDMARD. The presence of PD-positive synovitis in any joint at baseline was

Table 2 Summary of biologic tapering in rheumatoid arthritis

	Anti-TNF	Abatacept	Tocilizumab
No flare if D/C	Early RA: 40–90% @1 year Est RA: 10–60% @ 1 year	Early RA: 25% @ 1 year Est RA: 40–60% @ 1 year	Early RA: NR Est RA: 10–13% @ 1 year
No flare if taper	Early: 80–90% @ 1 year Est RA: 25–90% @ 1 year	Early RA: 36–66% @ 1 year Est RA: NR	Early/Est RA: NR
Predictors of taper	Deep/Boolean REM, early > Est RA	Low DAS, low HAQ	Low IL-6/MMP-3
Radiographic stability	✓	✓	NR
Functional stability	✓	✓	✓
Side effects decreased	No	No	NR
Retreatment success	>90% @ 1 year	90% @ 1 year	>90% @ 3 months

TNF tumor necrosis factor, *RA* rheumatoid arthritis, *CZP* certolizumab pegol, *IFX* infliximab, *Est* established, *D/C* discontinuation, *NR* not reported, @ at; *REM* remission, *DAS* Disease Activity Score, *HAQ* Health Assessment Questionnaire, *IL-6* interleukin-6, *MMP-3* matrix metalloproteinase-3, *Dz* disease, ✓ yes

predictive of flare during the study period. Thus, the absence of PD signal evaluated by MSUS may help physicians select the most appropriate patients for de-escalation of bDMARD without adverse outcomes.

Finally, Alivernini et al. assessed de-escalation of anti-TNF treatment in an observational cohort of 42 patients with established RA (~11.2 years) for MSUS predictors of flare [34]. Initially, patients in stable clinical REM (by DAS <1.6) were tapered by increased interval of their anti-TNF for 3 months; for example, ADA's interval was increased from every 2 to every 4 weeks. At 3 months, in patients remaining in stable clinical REM with negative PD signal on MSUS assessment, anti-TNF was stopped and they continued on MTX monotherapy for an additional 6 months. Flares were defined as an increase in DAS >1.2. MSUS was performed for GS synovitis and PD signal assessment in bilateral MCP-PIP-wrist-knee-MTP. At 3-month follow-up, 69% of patients who tapered anti-TNF were flare-free; relapses were more likely in patients with higher baseline synovial hypertrophy by GS at their second MCP and fifth MTP joints. At 9-month follow-up, after discontinuation of anti-TNF, 90% of patients in clinical REM and PD negative maintained REM; relapses were more likely in patients with higher baseline synovial hypertrophy by GS at the fifth MTP. These findings suggest that the use of MSUS for GS and PD in combination with clinical REM may predict successful tapering and possible discontinuation of anti-TNF therapy in the short term.

A pragmatic approach to biologic tapering in the clinic

In everyday clinical practice, current clinical guidelines have provided a systematic approach to treatment of RA

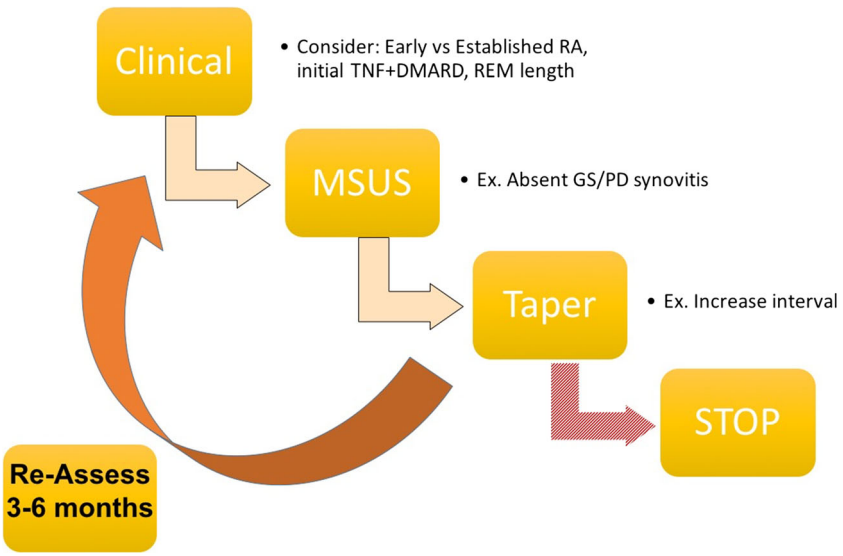

Fig. 1 A pragmatic approach to biologic tapering in rheumatoid arthritis. *RA* rheumatoid arthritis, *TNF* anti-tumor necrosis factor, *DMARD* disease-modifying anti-rheumatic drug, *REM* remission, *MSUS* musculoskeletal ultrasound, *GS* grayscale, *PD* power Doppler

with the goal of achieving rapid and sustained disease control [7, 8]. This T2T strategy has revolutionized treatment of RA and has led to significant improvements in outcomes for our patients. After achieving the desired treatment target for an individual patient with RA, providers should subsequently consider de-escalation of bDMARD therapy, after weighing the benefits and risks of decreased therapy with their patient.

Based on the summary of studies on de-escalation of bDMARDs in RA (Tables 1 and 2), the clinical information which we find to be helpful when selecting the optimal patient for successful de-escalation of bDMARD includes the following:

1. RA disease duration (early RA is favored to established RA)
2. Initial DMARD treatment (upfront induction anti-TNF with MTX is favored)
3. Current bDMARD used (most evidence-based data is available for anti-TNFs, ABA, and TCZ)
4. Concomitant nbDMARD (continuation of backbone treatment with nbDMARD is preferred)
5. Depth and length of disease control (deeper sustained REM for 6–12 months is favored)
6. MSUS assessment (absence of GS and PD synovitis is preferred)

Once a patient is selected for de-escalation of therapy, we recommend providers start tapering bDMARD therapy, i.e., reducing dose, rather than stopping bDMARD given the significantly higher rate of flares with discontinuation (Table 2). Backbone therapy with nbDMARD (i.e., MTX or similar) should be continued. Tapering of bDMARD is achieved by a multistep disease activity-guided increase in the interval of self-injections (i.e., doubling the time between doses) while maintaining the same dose per injection. Patients should be educated by their rheumatologist on the early signs of an RA flare-up and instructed to be reevaluated immediately in the clinic if they are flaring.

Careful clinical monitoring should occur for 3 to 6 months following the dose reduction to ensure that disease control is maintained without a major flare. If disease control is maintained, then tapering of bDMARD should continue until a balance of disease control and personalized dosing is achieved. Full discontinuation of bDMARD should be avoided given the high rate of flares. If disease control is lost, then a reincrease of the same bDMARD to the prior effective dosing interval should be pursued, since recapture of disease control is achieved in over 90% of patients by 3 to 6 months. A reattempt at further tapering should not be pursued further while on the same bDMARD. Our pragmatic approach to bDMARD tapering is summarized in Fig. 1.

Conclusion

Based on the current data, rheumatologists should consider de-escalation, i.e., tapering, of bDMARD therapy in selected RA patients in REM. Tapering of bDMARDs, such as anti-TNF, ABA, and TCZ, is possible for the majority of our patients without short-term adverse outcomes. Flares are manageable with a simple reincrease in bDMARD dosing. Further study of the predictors of successful tapering, such as genetic drug targets and use of MSUS, is needed to personalize the approach for our patients.

Compliance with ethical standards

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