Tapering of disease-modifying antirheumatic drugs: an overview for daily practice

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Tapering of disease-modifying antirheumatic drugs: an overview for daily practice

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In this Review, we discuss the possibility of drug tapering in patients with rheumatoid arthritis in remission or low disease activity, for glucocorticoids and disease-modifying antirheumatic drugs. We review international guidelines and recommendations, as well as remaining uncertainties, and provide an overview of the current literature. Three strategies of tapering are discussed: (1) tapering by discontinuation of one of the drugs in combination therapy regimens, (2) tapering by reducing the dose of one of the drugs in combination therapy regimens, and (3) tapering by dose reduction of monotherapy with disease-modifying antirheumatic drugs. We discuss the outcomes and robustness of evidence of trials and observational cohorts, and we give a trajectory for further research and drug tapering in daily practice.

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Introduction

Due to early referral and diagnosis, new therapeutic options, and treat-to-target strategies with rapid treatment escalation steps, disease activity in rheumatoid arthritis can often be effectively suppressed. Effective disease suppression results in improved long-term outcomes, with prevention of joint damage and maintenance of functional ability.[1] Subsequently, new challenges and opportunities have arisen. Long-term continuation of escalated treatment, once the disease is effectively suppressed, might result in overtreatment, risking adverse events and unnecessary costs. Therefore, concepts of tapering (de-escalating the dose or number of medications, or both, that result in the patients remaining in a state of remission or at least low disease activity) or even discontinuing treatment have been tested in trials and daily practice. Three methods of drug tapering are possible. One method consists of tapering by discontinuing one of the drugs in combination therapy, while maintaining the dose of any other drug used. This approach is mostly applied to glucocorticoids, but sometimes also to biological, targeted synthetic, or conventional synthetic disease-modifying antirheumatic drugs (DMARDs), which are stopped while other DMARDs are continued unchanged. The second method involves tapering by reduction of the dose of one of the drugs in combination therapy regimens. This method is most often done by halving the dose or extending the dose interval of a biological or targeted synthetic DMARD while the conventional synthetic DMARD remains unchanged. The third method involves tapering by gradual dose reduction of a single DMARD in monotherapy until the lowest effective dose is reached, without discontinuation; this method is mostly evaluated in treat-to-target study designs. In theory, and sometimes in practice, a tapering strategy can entail a sequence of (some of) these tapering steps. Ultimately, discontinuation of the last (tapered) DMARD can result in a state of drug-free remission, which is only briefly discussed in this Review, when this information was included in a trial investigating our tapering definition. Tapering or discontinuation of treatment because of side-effects or inefficacy falls outside of the scope of this Review. We did a literature search, restricted to trials and cohorts of patients with rheumatoid arthritis, including the terms stopping, tapering, discontinuation, and reducing, focusing on oral glucocorticoids and any approved conventional, biological, or targeted synthetic DMARD published in the past 5 years. We discuss the design and the outcomes regarding the success of the tapering strategy, and the strength of evidence from these studies. We also suggest future studies and steps to be made for the implementation of tapering strategies in daily practice.

Glucocorticoid tapering and discontinuation

Over time, weighing the benefits and risks of glucocorticoids has resulted in various international recommendations for the management of rheumatoid arthritis. The 2010 and 2019 European Alliance of Associations for Rheumatologists (EULAR) recommendations both recommend initial use of glucocorticoids; however, the 2019 recommendations put more emphasis on the short-term use of glucocorticoids as a bridging therapy and tapering glucocorticoid use as rapidly as clinically feasible, aiming for complete discontinuation (with or without continuation of other DMARDs) within 3 months.[2,3] The 2015 American College of Rheumatology (ACR) guidelines recommended physicians to consider using glucocorticoids in patients with moderate or high disease activity starting on a conventional synthetic DMARD, and advised using the lowest possible dose and the shortest possible duration. However, the recently updated 2021 ACR guidelines conditionally recommend to start DMARD treatment without short-term glucocorticoids, stating that the toxicity associated with glucocorticoids outweighs potential benefits.[4,5] The 2018 updated Asia-Pacific League of Associations for Rheumatology (APLAR) recommendations on the treatment of rheumatoid arthritis also advise timing the tapering of glucocorticoids "once symptoms improve", postponing discontinuation until remission is achieved.[6] Thus, there appears to be little discussion about the efficacy of initial treatment with glucocorticoids,[7,8] and more about

	Publication period of included studies	Studies reviewed*	Results	Conclusion
Glucocorticoid tapering or discontinuation, or both				
Wallace and colleagues[13] (letter; July, 2019)	August, 1997, to June, 2016	14 studies included in letter: NORD-STAR (n=812), STAR (n=122), CareRA (n=442), ACT-ALONE (n=68), CORRA (n=386), COBRA (n=400), CURE (n=251), RICE (n=43), SEMIRA (n=259), BeSt (n=508), CARDERA (n=467), Pincus and colleagues (n=31), Hickling and colleagues (n=128), and Tengstrand and colleagues (n=58)	11 ongoing studies evaluating oral glucocorticoid tapering in patients with rheumatoid arthritis since September, 2008, were found as well as five studies from a previous systematic literature review (none of the studies directly compared glucocorticoid tapering strategies); two studies were still ongoing at the time of publication of the letter	Tapering of glucocorticoids is not sufficiently investigated to give guidance to clinicians
Biological DMARD tapering or discontinuation, or both				
Kerschbaumer and colleagues[14] (systematic literature review; February, 2020)	January, 2016, to March, 2019	Nine studies included in review: RRRR (n=337), ADMIRE (n=32), POET (n=817), C-OPERA (n=179), SURPRISE (n=102), C-EARLY (n=289), OPTTIRA (97), DRESS (n=172), and TARA (n=189)	Success of tapering measured with: (major) flare rate (25–80%); change in DAS28 (−0·14 to 0·3); change in mTSS (0·66–3·01); biological DMARD-free rate (21–67%); flare-free rate (39–53%); proportion (%) of people with DAS28 <2·6 (33%); and proportion (%) of people with DAS28 ≥3·2 (51%)	Tapering of bDMARDs is achievable in patients with long lasting deep remission. Remaining disease activity can cause tapering failure. However, remission can mostly be obtained again after re-initiation of therapy
Schett and colleagues[15] (review; June, 2016)	February, 1996, to February, 2015	28 studies included in review: Saleem and colleagues (n=47), Brocq and colleagues (n=21), Aguilar-Lonzano and colleagues (n=45), Naredo and colleagues (n=77), Iwamoto and colleagues (n=40), Alivernini and colleagues (n=42), van der Maas and colleagues (n=51), van Herwaarden and colleagues (n=22), ten Wolde and colleagues (n=285), Ahern and colleagues (n=38), HONOR (n=75), RRR (n=102), DREAM (n=187), 20TNF (n=20), BeSt (n=243), IDEA (n=14), EMPIRE (n=9), ACT-RAY (n=238), HIT-HARD (n=155), OPTIMA (n=207), GUÉPARD (n=69), AVERT (n=222), RETRO (n=101), PRIZE (n=193), STRASS (n=137), PRESERVE (n=604), DOSERA (n=91), and DRESS (n=180)	Preferable dose tapering phase followed by gradual withdrawal instead of immediate withdrawal	The ideal patient characteristics for tapering remain unclear
Conventional synthetic DMARD tapering or discontinuation, or both				
Kerschbaumer and colleagues[14] (systematic literature review; February, 2020)	April, 2016, to June, 2019	Seven studies included in review: MUSICA (n=309), CAMEO (n=205), JUST-ACT (n=164), COMP-ACT (n=294), ACT-TAPER (n=272), CareRA (n=58), and Pope and colleagues (n=81)	Studies evaluate csDMARD continuing *vs* stopping in patients treated with (bDMARD or csDMARD) combination therapy; non-inferiority of methotrexate stopping *vs* continuing was shown in three trials with tocilizumab; non-inferiority was not shown for methotrexate dose reduction *vs* full dose in patients initiating adalimumab	Tapering of csDMARDs is mostly studied in the context of combination therapy (bDMARD or csDMARD); tapering or stopping csDMARD therapy can cause an increase in disease activity, although response can mostly be regained after re-initiation of the tapered drug
Tornero-Molina and colleagues[16] (systematic literature review; October, 2020)	January, 2013, to January, 2019	Eight studies included in review (regarding tapering): PRESERVE (n=604), OPTIMA (n=207), PRIZE (n=131), TARA (n=189), ACT-TAPER (n=272), JUST-ACT (n=164), SMART (n=58), and AGREE (n=81)	For patients with rheumatoid arthritis with sustained (at least 6 months) remission, the panel recommends tapering of bDMARDs before csDMARDs	Tapering should be considered individually for every patient
Schett and colleagues[15] (review; June, 2016)	February, 1996, to February, 2015	Five studies included in review: BeSt (n=243), ten Wolde and colleagues (n=285), Ahern and colleagues (n=38), RETRO (n=101), and PRIZE (n=193)	Preferable dose tapering phase followed by gradual withdrawal instead of immediate withdrawal	The ideal patient characteristics for tapering remain unclear

bDMARD=biological synthetic disease-modifying antirheumatic drugs. csDMARD=conventional synthetic disease-modifying antirheumatic drugs. DAS28=disease activity score for 28 joints. DMARD=disease-modifying antirheumatic drug. *n=reported number of patients included in the study as referred to in corresponding review. Definition of tapering: de-escalating the dose and number of medications, or both, that have resulted in the patients being in a state of remission or at least low disease activity. Definition of discontinuation: stopping the administration of the drug completely.

Table 1: **Reviews of articles on DMARD tapering or discontinuation, or both, in rheumatoid arthritis from the past five years**

how to weigh the use of glucocorticoids against the risk of side-effects, even regarding short-term use. Continued reports show that even relatively low dosages, as low as 5 mg/day, can increase the risk of sleep disturbance, skin changes, or infection, and that there is a (cumulative) dose–response effect for many side-effects.[9–11] With regard to this cumulative dose–response effect, glucocorticoids differ from most other DMARDs and, generally, patients and physicians agree on minimising the prolonged use of glucocorticoids.[12]

To our knowledge, no comparative studies between various tapering strategies for dose reduction or

complete glucocorticoid discontinuation have been published, and no study data are available on the benefit of discontinuation versus continuation of (very) low-dose steroids. Information is often indirectly derived from individual treat-to-target studies, in which glucocorticoids as well as other DMARDs have been tapered and discontinued as part of the treatment strategy. This information was summarised by Wallace and colleagues[13] (table 1). Observational studies report the use of glucocorticoids for over 12 months from diagnosis in up to 60% of patients with rheumatoid arthritis, suggesting complete discontinuation in daily practice is difficult.[17,18] However, in the protocolised setting of strategy studies, between 70% and 90% of patients discontinued glucocorticoids used as bridging therapy without the need to restart treatment for disease flares.[19–21] In the SEMIRA trial,[22] 259 patients with established rheumatoid arthritis, who were treated with glucocorticoids and the anti-interleukin 6 receptor antagonist tocilizumab (with or without concomitant conventional synthetic DMARDs), were randomly assigned to blinded glucocorticoid continuation (prednisone 5 mg/day, n=128) or glucocorticoid tapering (reducing the dose by 1 mg every 4 weeks to zero, n=131), while continuing treatment with other DMARDs. After 24 weeks, a significantly greater increase in Disease Activity Score for 28 joints-erythrocyte sedimentation rate (DAS28-ESR) was reported in the discontinuation group (difference 0·61 [95% CI 0·35–0·88]; p<0·0001). Low disease activity was maintained in 99 (77%) of 128 patients who continued compared with 85 (65%) of 131 patients who tapered prednisone (relative risk 0·83 [95% CI 0·71–0·97]; table 2).[22] During follow-up, which was limited to 24 weeks, no clinically relevant differences in adverse events were reported between the groups. No other randomised controlled studies comparing glucocorticoid continuation with tapering or discontinuation have been published. Future studies should clarify which patients can discontinue glucocorticoids, and what is the best tapering strategy to allow for successful and safe discontinuation. Or, if attempts to discontinue glucocorticoids results in an increase in disease activity, future studies should clarify the lowest effective dose for long-term use that is safe, and determine the best follow-up treatment step after glucocorticoid tapering.

Biological DMARD tapering and discontinuation

Although biological DMARDs can provide rapid clinical improvement and prevent radiographic damage later, biological DMARDs are not routinely used as bridging therapy. Also, when used as rescue treatment in patients who do not respond sufficiently to conventional synthetic DMARDs, the high treatment costs of biological DMARDs,[29] and risk of (infectious) side-effects with continued use, provide strong incentives to taper these drugs once the desired treatment goal has been reached. The most recent ACR, APLAR, and EULAR recommendations suggest that tapering can be tried, and EULAR refers to possible discontinuation of biological DMARDs when remission is achieved for a sufficiently long time.[2,4,6] Continued treatment with conventional synthetic DMARDs is preferred,[2,6] or advised.[4] All recommendations caution that flares might occur, potentially causing radiographic damage.

Various trials have studied biological DMARD tapering by dose reduction, interval spacing, and (eventually) discontinuation, and these trials were recently summarised and evaluated in preparation for the 2019 update of the EULAR recommendations[14] (table 1). Tapering by discontinuation of the biological DMARD while continuing a conventional synthetic DMARD (tapering strategy 1) was studied mostly in open-label studies. These studies reported that discontinuation versus continuation resulted in around 30–33% more flares, and loss of remission or low disease activity in up to 66% of patients.[30,31] The randomised, placebo-controlled trials[32,33] reported fewer flares overall, with smaller differences (up to 10%) in flare rate between the discontinuation (placebo) and continuation groups than reported in the open-label studies.

Tapering the biological DMARD by dose reduction while continuing other DMARDs (tapering strategy 2) has only been studied in open-label studies. In the OPTTIRA trial,[34] patients with a DAS28 of less than 3·2 for more than 3 months who were randomly assigned to a 66% dose reduction (n=21) of either the tumour necrosis factor (TNF) inhibitor adalimumab or etanercept had a reduced time to flare (defined as a DAS28 increase of ≥0·6, resulting in a DAS28 >3·2, and an increase in swollen joint count) compared with controls (n=50) who continued TNF inhibitors unchanged (hazard ratio [HR] 2·81, 95% CI 0·99–7·94). In addition, patients who reduced their TNF inhibitor dose by 66% had a higher risk of disease flare compared to patients who were randomly assigned to a 33% dose reduction (n=26; HR 5·10, 95% CI 1·81–21·95]; p=0·029). However, in the DRESS study,[35] no significant difference was reported with regard to major flare incidence (defined as an increase in DAS28–C-reactive protein [CRP] of >1·2 or a ≥0·6 increase and current DAS28-CRP >3·2, persisting for >12 weeks) between reducing the dose of TNF inhibitor (by 3-monthly increase in dosing interval; n=115) or continuing treatment unchanged (n=57) during the 3 years of follow-up (10% *vs* 12%). l'Ami and colleagues[36] reported non-inferiority in maintenance of disease control (change in DAS28-ESR <0·6) of interval increase from 2 weeks to 3 weeks of adalimumab (n=27), compared with continuing at every 2 weeks (n=27) in patients with high serum adalimumab concentrations (>8 µg/mL). The STRASS study,[37] an open-label, non-inferiority trial in which patients were randomly assigned to continue (n=73) or progressively space (n=64) etanercept

	Number of patients	Patient characteristics	Treatment groups	Primary outcome(s)	Secondary outcome(s)
Glucocorticoid tapering or discontinuation, or both					
Burmester and colleagues[22] (July, 2020); SEMIRA	259	Patients with rheumatoid arthritis and stable low disease activity with tocilizumab and glucocorticoids (5–15 mg)	Continue prednisone 5 mg/day *vs* taper masked prednisone (decreased by 1 mg every 4 weeks) to 0 mg/day	Estimated mean increase in DAS28 over 24 weeks was significantly greater in the tapered *vs* the continuation group (difference 0·61 [95% CI 0·35–0·88], p<0·0001)	Maintenance of DAS28 ≤3·2 without flare was lower in the tapered (65%) *vs* the continuation (77%) group
Conventional synthetic DMARD tapering or discontinuation, or both					
Cohen and colleagues[23] (November, 2019); ORAL Shift	533	Moderate to severe rheumatoid arthritis with low disease activity on tofacitinib and methotrexate	Tofacitinib + placebo (group 1) *vs* tofacitinib + methotrexate (group 2)	LSM change of DAS28-4-ESR from week 24 to week 48 was greater in group 1 (0·3, 95% CI 0·2–0·5) than in group 2 (0·0, 95% CI –0·1 to 0·2), but the difference was below the non-inferiority margin	LSM change of DAS28, SDAI, CDAI, SJC, PtGA, and VAS pain were greater in group 1 from week 24 to week 48; LSM changes, HAQ, and CRP were greater in group 1 from week 24 to week 36
Lillegraven and colleagues[24] (May, 2021); ARCTIC REWIND	155	Patients with rheumatoid arthritis and stable 12-month remission on a combination of csDMARDs	Half dose of (all) csDMARD(s) *vs* stable-dose of (all) csDMARD(s)	Proportion (%) of patients with a DAS-defined flare (DAS increase of ≥0·6 and increase of ≥2 swollen joints, and loss of DAS remission); 25% flared in half-dose group *vs* 6% in the stable-dose group (risk difference, 18%, 95% CI 7–29)	Change in area under the curve for the different disease activity composite indices; adverse events were similar between the groups
Biological DMARD tapering or discontinuation, or both					
Sanmarti and colleagues[25] (April, 2019); TOZURA	179	Patients with rheumatoid arthritis in remission receiving 162 mg tocilizumab per week	Continue tocilizumab 162 mg/week *vs* taper to tocilizumab 162 mg every 2 weeks	Extension study week 24–48 had no primary reported outcomes (the primary outcome of the initial phase of the study did not focus on tapering and was therefore not included in this review)	Proportion of patients in maintained remission at week 48 (24 weeks after randomisation) was higher in patients who continued tocilizumab 162 mg weekly (90%) compared with those who received tocilizumab every 2 weeks (73%); other efficacy measures, including mean change from baseline in DAS28, SDAI, CDAI, TJC, SJC, CRP, ESR, patient and physician global assessment of health, HAQ, and patient pain score, were similar
Emery and colleagues[26] (May, 2020); PREDICTRA phase 4	122	Patients with rheumatoid arthritis in stable remission receiving adalimumab 40 mg every 2 weeks for ≥12 months	Taper to 40 mg adalimumab every 3 weeks *vs* discontinue adalimumab (placebo)	No association between baseline MRI and hand and wrist synovitis, osteitis, and flare occurrence	Time to flare was longer in taper *vs* withdrawal group (not significant); at week 40, 36% in the taper group flared *vs* 45% in the withdrawal group
Curtis and colleagues[27] (November, 2020); SEAM-RA	253	Patients with rheumatoid arthritis in sustained (24 weeks) SDAI remission receiving methotrexate and etanercept	Methotrexate monotherapy (group 1) *vs* etanercept monotherapy (group 2) *vs* methotrexate and etanercept (group 3)	SDAI remission at 48 weeks in significantly more patients in group 2 (50%) compared with group 1 (29%), and there were more patients in remission in group 3 (53%) *vs* group 1 (29%)	Time to disease worsening was significantly shorter for group 1 (median 198 days) compared with group 2 and group 3 (medians not estimable); restitution of SDAI remission with rescue therapy: 70–80% in each group
Targeted synthetic DMARD tapering or discontinuation, or both					
Takeuchi and colleagues[28] (September, 2018); RA-BEYOND	559	Patients with rheumatoid arthritis in stable LDA or remission receiving 4 mg baricitinib with or without csDMARDs	Continue baricitinib 4 mg/day *vs* taper to 2 mg baricitinib	Maintained LDA and remission were higher in the continuation group (88% LDA; 40% remission) *vs* the tapered group (67% LDA; 33% remission)	Dose reduction resulted in increased disease activity and earlier and more frequent disease flares

CDAI=Clinical Disease Activity Index. csDMARD=conventional synthetic disease-modifying antirheumatic drug. CRP=C-reactive protein. DAS=disease activity score. DAS28=disease activity score for 28 joints. DMARD=disease-modifying antirheumatic drug. ESR=erythrocyte sedimentation rate. HAQ=Health Assessment Questionnaire. LDA=low disease activity. LSM=least squares mean. PtGA=patient global assessment of disease activity. SDAI=simplified disease activity index. SJC=swollen joint count. TJC=tender joint count. VAS=Visual Analogue Score. Definition of tapering: de-escalating the dose and number of medications, or both, that have resulted in the patients being in a state of remission or at least low disease activity. Definition of discontinuation: stopping the administration of the drug completely.

Table 2: **Clinical trials on DMARD tapering or discontinuation in patients with rheumatoid arthritis from the past five years not included in reviews**

or adalimumab dosages reported similar DAS28 and radiographic damage progression over time, but an increased risk for disease relapse (defined as a DAS28 >2·6 and an increase of >0·6 in DAS28) was shown in the spacing group (HR 2·37, 95% CI 1·47–3·83; p=0.0004). In the TOZURA study,[25] patients randomly assigned to continue tocilizumab 162 mg weekly (n=89) more often maintained remission (a DAS28 score of less than 2·6) compared with patients who were randomly assigned to spacing to 162 mg biweekly (n=90; 90% *vs* 73%), but most other efficacy measures were similar. The level of evidence of these studies was limited due to open-label design, small numbers of study participants, and, in some, an

inadequate sample size to provide the power to substantiate the results.

In 2020, two studies compared methods of tapering rather than investigating if tapering is feasible (table 2).[26,38] In the double-blinded, placebo-controlled PREDICTRA study[26] in patients who were in remission for at least 6 months, a disease flare occurred in 37 (36%) of 102 patients who tapered (by increasing the interval from 2 weeks to 3 weeks) adalimumab, compared with 9 (45%) of 20 patients who discontinued adalimumab (ie, switched to placebo). The single-blinded TARA trial[38] randomly assigned patients with well controlled disease receiving a combination of a TNF inhibitor and conventional synthetic DMARDs to either taper and stop the TNF inhibitor first (n=95) or the conventional synthetic DMARDs first (n=94), while continuing the TNF inhibitor; the remaining DMARD was then tapered and stopped in the second year. The proportion of patients with a disease flare (defined as DAS >2·4 or swollen joint count >1; the primary outcome), the mean DAS, and Health Assessment Questionnaire scores were similar between the groups. After 2 years, 19 (20%) patients in the conventional synthetic DMARD-first group were in drug-free remission versus 10 (11%) in the TNF inhibitor-first group.

In the 2019 EULAR guideline update, biological DMARDs were reported to carry a higher risk of serious infectious adverse events compared with conventional synthetic DMARDs. This recommendation was based on two studies, discussed by Sepriano and collegues,[39] with moderate or high risk of bias. A meta-analysis showed that tapering (by either dose reduction or interval spacing) of biological or targeted synthetic DMARDs did not lower the risk of serious infections in patients with rheumatoid arthritis compared with patients who continued the treatment dose (risk difference 0·01, 95% CI 0·00–0·02).[40] Also, in the later PREDICTRA, TARA, and SEAM-RA studies, tapering or stopping biological DMARDs did not reduce the number and burden of adverse events.[26,27,38] However, considering the relative rarity of serious adverse events, the numbers of patients selected and the follow-up time (maximum of 2 years) of these studies might have been insufficient to find a benefit in tapering or stopping.

Notably, assessment of flare risk when considering biological DMARD tapering or discontinuation would help to support treatment decisions. Generally, in patients with early rheumatoid arthritis versus those with established rheumatoid arthritis, or in patients who are auto-antibody negative versus those who are auto-antibody positive, or in patients who do not have shared epitopes versus those who do have the shared epitopes, tapering and stopping biological DMARDs is more likely to be successful.[41–43] Anti-citrullinated protein antibodies are associated with worse disease outcomes, but why they affect flare risk is unknown. On an individual clinical level, it is still not possible to predict which patients can safely taper or discontinue biological DMARDs.

Targeted synthetic DMARD tapering and discontinuation

In the double-blinded RA-BEYOND study,[28] patients with sustained low disease activity (Clinical Disease Activity Index [CDAI] of ≤10) or remission while receiving the Janus kinase inhibitor baricitinib were randomly assigned to continue full-dose baricitinib (4 mg; n=281) or reduce to half-dose baricitinib (2 mg; n=278) while continuing conventional synthetic DMARDs or glucocorticoids, or both (table 2). Compared with those in the half-dose group, more patients in the full-dose group maintained low disease activity and remission (67% *vs* 80% maintained low disease activity; 33% *vs* 40% maintained remission). Furthermore, fewer patients in the full-dose group flared (and patients in this group also flared later) compared with those in the half-dose group (23% *vs* 37%, p=0·001). After restoring the full dose in patients who did not retain low disease activity or remission, 67% regained low disease activity or remission. More information on targeted synthetic DMARD tapering might emanate in the coming years, but to our knowledge there are currently no ongoing interventional trials evaluating tapering or discontinuation of targeted synthetic DMARDs.

Conventional synthetic DMARD tapering and discontinuation

The 2019 updated EULAR recommendations state that conventional synthetic DMARDs in monotherapy, if they are tolerated, should not be discontinued but that dose reduction can be considered.[2] This recommendation is based on a double-blinded, placebo-controlled study from 1996,[44,45] in which patients with longstanding, mostly erosive rheumatoid arthritis and stable low disease activity were randomly assigned to continuation or discontinuation of the conventional synthetic DMARDs of the time. The cumulative incidence of flares was higher in the discontinuation group (53 [37%] of 143) compared with the continuation group (30 [21%] of 142).[44] Rapid improvement occurred after restarting medication.[45] No other discontinuation studies, including treatment strategies reflecting current standard of care, or placebo-controlled studies on stopping conventional synthetic DMARDs as monotherapy have been done since. Several studies, summarised in 2020 by Kerschbaumer and colleagues[14] (table 1), have investigated the option to taper or stop conventional synthetic DMARDs, while continuing biological DMARDs. Open-label studies showed contradicting results in their non-inferiority designs,[46,47] whereas the randomised, placebo-controlled trials all showed non-inferiority of discontinuing (versus continuing) methotrexate while continuing the biological DMARDs.[48–50] In the more recent double-blinded, placebo-controlled SEAM-RA study,[27] patients in stable

remission (defined as a Simple Disease Activity Index [SDAI] score of ≤3·3) receiving methotrexate in combination with etanercept were randomly assigned to receive either etanercept monotherapy (discontinuation of methotrexate; n=101), methotrexate monotherapy (discontinuation of etanercept; n=101), or methotrexate plus etanercept combination therapy (n=51). Patients who discontinued etanercept were more likely to lose SDAI remission compared with patients who discontinued methotrexate (72 [71%] of 101 patients *vs* 51 [50%] of 101 patients, p<0·01). Also, in the TARA study, tapering a conventional synthetic DMARD first versus the biological DMARD first resulted in similar efficacy outcomes.[38] An open-label, randomised, non-inferiority study compared stopping the conventional synthetic DMARD while continuing the TNF inhibitor certolizumab pegol (n=45) with continuing both (n=43).[47] For DAS28 less than 3·2 and a change of DAS28 of 1·2 or more at 18 months, the cutoff for non-inferiority was not met, and comparisons on CDAI and Health Assessment Questionnaire-Disability Index showed similar results in both groups.[47] In 2019, the double-blind phase of the ORAL Shift non-inferiority study[23] showed that in patients who had CDAI low disease activity with methotrexate combined with the Janus kinase inhibitor on conventional synthetic DMARDs tofacitinib, discontinuation of methotrexate (n=267) was non-inferior to continuation (n=266) regarding change in DAS28-4-ESR (the primary endpoint; difference 0·30 [95% CI 0·12–0·48]) (table 2), which was in line with previous studies.[48,49]

The 2021 open-label ARCTIC REWIND trial[24] randomly assigned patients with stable DAS remission (either monotherapy or combination conventional synthetic DMARDs) to continue on stable dose conventional synthetic DMARDs (mean methotrexate dose 19·5 mg/week, 66 [85%] of 78 patients receiving methotrexate monotherapy) or switch to half-dose (mean methotrexate dose 19.0 mg/week, 61 [78%] of 78 patients receiving methotrexate monotherapy) conventional synthetic DMARD therapy. During the 12-month study period, 19 (25%) of 77 patients in the half-dose group versus 5 (6%) of 78 patients in the stable-dose group had at least one flare (risk difference 18%, 95% CI 7–29). Dosages were restored after a flare. After 12 months follow-up, 63 (85%) of 74 patients in the half-dose group and 67 (92%) of 73 patients in the stable-dose group were in DAS remission. More (non-serious) adverse events were reported in the stable-dose group than in the half-dose group.[24]

Gradual tapering of conventional synthetic DMARDs in monotherapy (tapering strategy 3), ultimately to zero, was investigated in several treat-to-target studies. In the first 5 years of the single-blinded BeSt study,[51] in which treatment was tapered (as long as a DAS of less than 2·4 was maintained) and then discontinued (when remission was maintained), 115 (23%) of 508 patients achieved drug-free remission. Although 53 (46%) of 115 patients later lost remission, restart of the last discontinued conventional synthetic DMARD rapidly restored remission in 39 (74%) patients and restored low disease activity in another 11 (21%). Tapering to drug-free remission seemed more successful if the initial therapy had been with a combination of conventional synthetic and biological DMARDs (18% drug-free remission *vs* 8–14% drug-free remission; results from the first 4 years).[42] In the open-label RETRO study,[43] patients with established rheumatoid arthritis, in remission (DAS28 <2·6) for at least 6 months receiving conventional synthetic or biological DMARDs, or both, were randomly assigned to DMARD continuation (n=38), to halving the dosages of all DMARDs (n=36), or to first halving, followed by discontinuing all DMARDs (n=27). At the interim analysis, 15·8%, 38·9%, and 51·9%, respectively, had a flare over 12 months follow-up.[43] The study is ongoing, but the interim results show the feasibility of tapering or stopping conventional synthetic DMARD therapy (mostly methotrexate), although flare rates were substantially lower if therapy was continued (15·8% in continuing group *vs* 44·4% overall in the two tapering groups). During 2 years in the open-label tREACH study,[52] in patients with early arthritis, after protocolised tapering of conventional synthetic DMARDs, 34 (21%) of 159 patients achieved drug-free remission. Of these, 27 patients flared within 6 months and restarted treatment. In the single-blinded IMPROVED study,[53] patients with early arthritis received targeted treatment to attain DAS remission (DAS <1·6); 387 (63%) of 610 patients were in remission after 4 months and were then tapered to drug-free remission. During 5 years follow-up, 159 (26%) of 610 patients had sustained (≥1 year) drug-free remission at least once, but independent predictors for long-term successful tapering to drug-free remission could not be identified.[54]

Patient perspectives

Based on a 2020 review about patient perspectives on treatment changes in rheumatoid arthritis,[55] it was concluded that patients are most afraid of disease flares and limited access to health care after tapering treatment. Also, a cumulative effect of earlier negative experiences with increased rheumatoid symptoms in the past made patients more reluctant of treatment tapering. Fear of flaring is an important reason to remain on a treatment scheme that has shown to be successful in achieving the desired treatment target. The safety of continued monitoring of disease activity and the possibility of rapid treatment escalation (if necessary) are conditions that should be guaranteed before tapering should be attempted. Patients have declared that information provision and shared decision making are important for them to be convinced to taper their medication.[56–58] Patients also want to know that the biological or targeted

	Trial title	Target size	Follow-up time	Patient characteristics	Treatment groups	Primary outcome(s)	Secondary outcome(s)
Glucocorticoids							
Double-blinded, parallel-group, randomised controlled clinical trial; STAR (NCT02997605)	Comparison of two strategies of glucocorticoid withdrawal in rheumatoid arthritis patients	122	12 months	Rheumatoid arthritis (ACR/EULAR 2010 criteria)on stable csDMARD or bDMARD and glucocorticoids for at least 3 months	Prednisone tapering by 1 mg dose reduction per month + placebo hydrocortisone *vs* prednisone replacement with hydrocortisone (20 mg/day) + prednisone placebo tapering	Proportion of patients who could withdraw from prednisone and hydrocortisone at 1 year	Differences in proportion of patients withdrawn from prednisone, proportion of acute adrenal insufficiency, proportion of biological adrenal insufficiency, rescue therapy, proportion of flares, proportion of DAS28 remission and LDA, median HAQ, RAID, EQ5D, and FACIT-F scores, and proportion of serious adverse events
Biological DMARDs							
Single-blinded, non-inferiority, randomised clinical trial; ADDORA-low (NCT04222920)	Adalimumab dose reduction aiming low serum concentration with control of disease activity	89	24 weeks	Rheumatoid arthritis (ACR 1987 or EULAR 2010 criteria) using adalimumab (serum concentration >5 mg/L)	Dose reduction aiming at adalimumab serum concentration of 5 mg/L *vs* dose reduction aiming at adalimumab serum concentration of 2 mg/L	Difference in mean time weighted DAS28-CRP after 24 weeks	Differences in mean time DAS28-CRP after 12 weeks, number of flares, direct medical costs, and drug levels
Open-label, randomised controlled trial; ADDORA (NCT04194827)	Adalimumab drug optimisation in rheumatoid arthritis using therapeutic drug monitoring	267	80 weeks	Rheumatoid arthritis (ACR 1987 or EULAR 2010 criteria) initiating adalimumab	Concentration-guided dose reduction *vs* disease activity-guided dose reduction	Direct medical costs associated with adalimumab dose reduction (52 weeks)	Differences in mean time weighted DAS28-CRP, direct medical costs, indirect medical costs, patients with DAS28-CRP <2·9, number of flares, number of dose-interval shortenings, and drug levels
Randomised controlled, open-label, parallel-group, equivalence study; BIODOPT (EudraCT 2017–001970–41)	Dose reduction and discontinuation of biological therapy in patients with rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis	180	18 months	Rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis treated with a bDMARD and in clinical remission or LDA for 12 months	Disease activity-guided tapering (not further specified) *vs* continuation of bDMARD(s) as usual care	Difference in proportion of patients that reduced bDMARD dose to ≤50% while maintaining remission or LDA at 18 months	Differences in proportion of patients in remission with reduced dose bDMARDs and discontinued bDMARDs, changes in DAS28, CDAI, and SDAI for rheumatoid arthritis, changes in patient-reported outcomes, and changes in patient global assessment
Open-label, randomised controlled trial; TapERA (EudraCT 2012–004631–22)	TapERA: maintaining remission in RA while tapering etanercept	120	12 months	Established rheumatoid arthritis treated with etanercept and in DAS remission for at least 6 months	Decreasing dose of etanercept to 50 mg every 2 weeks *vs* continuation of etanercept dose at 50 mg weekly	Difference in proportion of patients remaining in remission at 6 months	Differences in proportion of patients in remission at 6 months and at 1 year according to the Boolean and SDAI definition, proportion of patients regaining remission when retreated in case of flare, safety (adverse events), evaluating usefulness FLARE-RA self-administered questionnaire, and exploring predictors for maintenance of remission
Open-label, randomised, non-inferiority trial; TODORA (NCT03895879)	Use of tocilizumab drug levels to optimise treatment in RA	98	52 weeks	Rheumatoid arthritis (ACR 1987 or 2010 criteria) using tocilizumab 162 mg/week for at least 6 months	Increasing tocilizumab dosing interval to every 2 weeks (group 1) *vs* continuation of tocilizumab weekly (group 2); all patients with a concentration of <15 mg/L will continue tocilizumab weekly	Difference in mean time DAS28 after 28 weeks (between group 1 and 2)	Differences in: mean time DAS28-ESR at 52 weeks; CDAI, SDAI, HAQ, direct medical costs, number of flares, and number and severity of adverse events, after 28 weeks and 52 weeks; and drug level between week 0 and week 52

(Table 3 continues on next page)

Trial title	Target size	Follow-up time	Patient characteristics	Treatment groups	Primary outcome(s)	Secondary outcome(s)
(Continued from previous page)						
Randomised, open-label, blinded-assessor study; NORD-STAR (NCT01491815 and NCT02466581)	Active conventional therapy compared to three different biologic treatments in early rheumatoid arthritis with subsequent dose reduction	800	56 weeks	Rheumatoid arthritis (ACR/EULAR 2010 criteria) treated with and achieving stable remission (at 24 weeks) on: csDMARD combination *vs* abatacept + methotrexate *vs* tocilizumab + methotrexate *vs* certolizumab pegol + methotrexate	De-escalate treatment at randomisation (early dose reduction) *vs* first continue and then de-escalate treatment 24 weeks after randomisation (late-dose reduction)	Difference in the proportion of patients who maintain LDA (CDAI) at 24 weeks after de-escalation initiation	Not applicable
Targeted synthetic DMARDs						
Observational study (Netherlands [Dutch] trial registry ID: 6698)	Biologicals and targeted synthetic DMARDs in inflammatory rheumatic diseases: The Reade Rheumatology Registry	Unknown	Unknown	Patients with Rheumatoid arthritis, psoriatic arthritis, or : ankylosing spondylitis	Not applicable	Disease activity, patient-reported outcomes, radiological progression, and functional capacity	Changes in biomarkers

ACR=American College of Rheumatology, bDMARD=biological disease-modifying antirheumatic drug. CDAI=Clinical disease activity index. csDMARD=conventional disease-modifying antirheumatic drug. CRP=C-reactive protein. DAS=disease activity score. DAS28=disease activity score for 28 joints. DMARD=disease-modifying antirheumatic drug. EQDS=EuroQol 5 dimension questionnaire. EULAR=European League Against Rheumatism. FACIT-F=functional assessment of chronic illness therapy-fatigue scale. HAQ=Health Assessment Questionnaire. LDA=low disease activity. RAID=rheumatoid arthritis impact of disease questionnaire . SDAI=simple disease activity index.

Table 3: **Ongoing studies on tapering (randomised controlled trials and observational studies)**

synthetic DMARDs will be effective again when restarting the treatment.[57] Physicians can tell their patients that various studies have reported that restarting discontinued biological DMARDs is rapidly successful in most cases (between 67% and 91% reported in the C-OPERA study, SURPRISE study, POET study, and the RA-BEYOND study).[31,33,28,59]

In general, conventional synthetic DMARDs are regarded as being well tolerated and, unlike biological DMARDs, these drugs are not associated with an increased risk of serious (infectious) adverse events.[60] However, many patients have, and apparently put up with, side-effects that are (medically) non-serious.[61,62] In the TARA study,[38] the side-effects of conventional synthetic DMARDs were reported to have a greater effect on patients' life compared with side-effects of biological DMARDs. In a qualitative study from Baker and colleagues,[63] patients appeared to desire tapering of medication because of concerns regarding potential long-term toxicity rather than because of specific side-effects. This finding might also explain, at least in part, reports on patient non-compliance, which indicate that a substantial proportion of patients have tapered or discontinued (or never took) prescribed DMARDs.[64,65]

However, in daily practice, tapering of conventional synthetic DMARDs appears to be rare and is independent of the current DAS score.[66] The costs of conventional synthetic DMARDs are certainly lower than those of biological and targeted synthetic DMARDs, although these costs are increased by the associated expenses of continued regular blood tests to monitor for asymptomatic laboratory abnormalities (recommended nationally and internationally), a circumstance not influenced by dose.[5]

Future considerations

After decades in which persistent disease activity required constant treatment intensifications in most patients with rheumatoid arthritis, treatment tapering and discontinuation can now be explored. Still, previous experiences and failed earlier attempts of stopping medication make patients and physicians cautious. Little information is available from clinical trials regarding the effects of tapering, and with the focus on the occurrence of flares or loss of remission after tapering, many studies appear to warn against attempting this. In placebo-controlled studies,[32,33] the differences in flare rates and other outcomes appear to be smaller compared with open-label studies, in which a nocebo effect of dose reduction might have a role.[30,31,59] A structured assessment of the risk of bias shows that most findings in the past 5 years on DMARD tapering are from open-label or single-blinded studies, which are (in part) not primarily focused on studying the option to taper or discontinue certain drugs. The potential benefit of lower drug exposure and thereby reduced risk of side-effects is not felt as immediately and objectively as the increase in

disease activity that can occur after tapering or discontinuation. We believe that placebo-controlled trials, with sufficiently large groups and long follow-up periods, are needed to provide unbiased information about the effects of tapering or stopping therapy, and to offer comparison of observed adverse events.

For glucocorticoids, historical knowledge and continued reports on the risk of complications associated with their continued use support the recommendation to discontinue, or at least optimally taper, glucocorticoids as soon as possible.[2,5,6,67] Many patients are wary of starting glucocorticoids,[68,69] yet, once proven effective in suppressing inflammation, glucocorticoids are often continued, particularly when the more expensive biological and targeted synthetic DMARDs are not available. As well as the optimal initial dose, the optimal tapering strategy for glucocorticoids is yet to be determined. The STAR trial (NCT02997605; table 3) is currently investigating two strategies of glucocorticoid tapering: reducing 1 mg per month versus replacement therapy with hydrocortisone. Early tapering and discontinuation of glucocorticoids might be facilitated if other effective therapies are available to be used as an alternative, as shown in protocolised treatment strategy studies.[8,19]

Tapering biological DMARDs was reported to not reduce the number and burden of adverse events.[40] However, this effect can be biased by small participant numbers, relatively short follow-up, or the reduction of the number of participants at risk in longer follow-up studies. Other than glucocorticoids and conventional synthetic DMARDs, tapering biological DMARDs (and targeted synthetic DMARDs) offers financial benefits. Studies show that tapering biological DMARDs puts patients at risk of a disease flare or radiographic progression, or both,[35,70–72] although not all radiological progression or functional score changes might constitute a clinically significant deterioration, and efficacy can be rapidly restored after restarting the original dose.[31,33,59,73] Additionally, not all patients have disease flares after tapering or discontinuation. Previous studies have suggested that patients who had the lowest levels of disease activity, and patients who are negative for anti-citrullinated protein antibodies and in early stages of the disease, had the lowest risk of flare after discontinuation.[41–43] However, in clinical practice it is still not possible to predict who can successfully stop treatment, nor who cannot stop treatment.[74,75]

It is unclear how much time a patient needs to be in stable remission or low disease activity before tapering the biological DMARDs, and it is unclear how fast and how far the dose can be reduced, or the dose interval for individual biological DMARDs can be stretched, before the treatment is effectively discontinued. Stretching the dose interval of biological DMARDs (guided by drug concentration or disease activity) is currently under investigation in several trials (table 3).

Little has been published about the possibility of dose reduction of conventional synthetic DMARDs as monotherapy. It might appear illogical to risk a flare by lowering the dose of a therapy that has proven to be effective. However, as current strategies are aimed at the suppression of disease activity as soon as possible, slow-acting conventional synthetic DMARDs, such as methotrexate, are now often rapidly escalated to a dose that might no longer be required once disease control is achieved. A randomised controlled trial should establish whether it is better to maintain or gradually taper the DMARD dose. If tapering is possible, further studies should elucidate the optimal timing and strategy for tapering (and maybe discontinuation) of conventional synthetic DMARDs. Following our experience with tapering conventional synthetic DMARDs in the BeSt and the IMPROVED studies,[20,53] at least some dose reduction is now offered to patients in the clinic who have persistent DAS remission (most often defined as at least 6 months), depending on the conventional synthetic DMARD used. In follow-up, DAS results as well as reported symptoms, radiological follow-up, and side-effects assist in the decision making with regard to tapering, stopping, or restarting treatment. Tapering and stopping medication, even for some time, might have a positive impact on how patients feel.[63] However, restarting or increasing the medication should always be anticipated and not considered as failure.

Conclusion

In summary, based on current knowledge, tapering and stopping strategies of antirheumatic treatments can now be part of daily practice, with different strategies and timings dependent on the specific circumstance. Patients starting on glucocorticoids should be aware that these

Search strategy and selection criteria

We searched PubMed, MEDLINE, Embase, and the Cochrane Library for trials published between June 1, 1997, and June 15, 2021. The principal search was done with five main themes: "rheumatoid arthritis", "tapering", "anti-rheumatic agents", "patient preference", and "clinical trial" (see appendix pp 1–2 for the complete search strategy). Relevant articles were selected based on title and abstract screening by LO and JMM using a prespecified decision rule. Only selected articles published in English were used. Articles without primary analysis or with insufficient relevance to the contents of this Review were excluded. After full-text reading, recent articles with available full-text and sufficient relevance to the topic of the current Review were included and reviewed for bias using the Cochrane Collaborations Risk of Bias tool for randomised controlled trials. The Risk of Bias assessment (appendix pp 1–2) was done by LO and JMM independently, and differences were discussed until consensus was reached.

See Online for appendix

drugs will be tapered and stopped as soon as clinically possible, with treatment alternatives at the ready in case of a flare. The option of discontinuation or at least dose reduction of biological DMARDs and targeted synthetic DMARDs should be discussed when these treatments are started, to be effectuated if the disease has been in remission for the past 6–12 months. If disease activity remains well suppressed, gradually reducing the dose is the safest option. Thus, close monitoring of disease activity should be in place to intensify treatment again as soon as this approach is needed. After glucocorticoids, biological DMARDs, targeted synthetic DMARDs, and eventually conventional synthetic DMARDs can be gradually tapered, to monotherapy, then to the lowest effective dose, and if remission is sustained after another 6 months, complete discontinuation can be considered. All these treatment changes should be strictly monitored in terms of disease activity, and close consultation with the patient is needed.

Contributors

All authors contributed equally regarding the concept and design, acquisition of data, analysis and interpretation, and drafting of the manuscript. All authors read and approved the final manuscript.

Declaration of interests

We declare no competing interests.

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