Concerns and opportunities related to discontinuation of treatment in rheumatoid arthritis

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PART I

How to taper drugs in case of remission?


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Tapering of disease modifying antirheumatic drugs, an overview for daily practice

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SUMMARY

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 (DMARDs). Including the background of international guidelines and recommendations and remaining uncertainties, in an overview of the recent literature. Per drug category, data on three strategy types of tapering, defined as de-escalating the dose and/or number of medications that have resulted in the patients being in a state of remission or at least low disease activity (LDA), are discussed: 1) tapering by discontinuation of one of the drugs in combination therapy, 2) tapering by reducing the dose of one of the drugs in combination therapy and 3) tapering by dose reduction of DMARD monotherapy. We discuss outcomes and robustness of evidence of trials and observational cohorts and give a trajectory for further research and drug tapering in daily practice.

Introduction

In the last decades, 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. This results in improved long-term outcomes with prevention of joint damage and maintenance of functional ability.(1) As a result, new challenges and opportunities arise. Long-term continuation of escalated treatment, once the disease is effectively suppressed, may result in overtreatment risking adverse events (AEs) and unnecessary costs. Therefore, concepts of tapering or even discontinuing treatment have been tested in trials and daily practice. Several methods of drug tapering are possible: 1) tapering by discontinuing one of the drugs in combination therapy, while maintaining the (dose of the) other(s). This approach is mostly applied to glucocorticoids, but sometimes to biological or targeted synthetic DMARDs or conventional synthetic DMARDs, that are stopped while other DMARD(s) are continued unchanged; 2) tapering by reduction of the dose of one of the drugs in combination therapy. This 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; 3) tapering by gradual dose reduction of a single DMARD in monotherapy until the lowest effective dose is reached, without discontinuation, 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 (DFR), which is only briefly discussed in this review if included in a trial investigating our tapering definition. Tapering or discontinuation of treatment because of adverse effects or lack of efficiency falls outside the scope of this review. We conducted a literature search, restricted to trials and cohorts, in patients with rheumatoid arthritis, including the terms stopping, tapering, discontinuation, reducing and focusing on oral glucocorticoids and any approved conventional, biological or targeted synthetic DMARD published in the last 5 years. We will discuss the design and the outcomes regarding success of the tapering strategy and the strength of evidence from these studies. Finally, we will suggests on future studies and steps to be made for implementation of tapering strategies in daily practice.

Glucocorticoid tapering and discontinuation

With the pendulum of 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 League against rheumatism (EULAR) recommendations, both recommend initial use of glucocorticoids, but in 2019 with more emphasis on short term use as bridging therapy and tapering as rapidly as clinically feasible, aiming at complete discontinuation (with or without continuation of other DMARDs) within 3 months.(2,3) The

American college of rheumatology (ACR) guidelines from 2015 recommended to consider using glucocorticoids in patients with moderate or high disease activity starting on a conventional synthetic DMARD, used at the lowest possible dose and the shortest possible duration. But the recently updated 2021 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 treatment of rheumatoid arthritis also recommend tapering of glucocorticoids timed 'once symptoms improve', postponing discontinuation until remission is achieved.(6) Thus, there appears to be little discussion about the efficacy of initial glucocorticoids (7,8), but more about how to weigh this against the risk of adverse effects, even of short term use. Continued reports show that even relatively low dosages, as low as 5mg/day, can increase the risk sleep disturbance, skin changes, or infection and that there is a (cumulative) dose-response effect for many AEs.(9-11) In this, glucocorticoids differ from most other DMARDs and in general patients and physicians appear to agree on minimizing the prolonged use of glucocorticoids.(12)

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 where glucocorticoids as well as other DMARDs were tapered and discontinued as part of the treatment strategy. This information was recently summarized by Wallace et al. (table 1).(13) Observational studies report the use of glucocorticoids for over 12 months from diagnosis in up to 60% of rheumatoid arthritis patients, suggesting complete discontinuation in daily practice to be difficult.(14, 15) However, in the protocolized setting of strategy studies, between 70% and 90% of patients discontinued glucocorticoids used as bridging therapy without the reported need to restart for disease flare.(16-18) In the SEMIRA trial, 259 patients with established rheumatoid arthritis treated with glucocorticoids and the anti-interleukin(IL)-6 receptor antagonist tocilizumab (with or without concomitant conventional synthetic DMARD) were randomized to blinded glucocorticoid continuation (prednisone 5mg/day, n=128) or glucocorticoid tapering (reducing the dose with 1mg every 4 weeks) to zero (n=131), while continuing the other DMARD(s). After 24 weeks, a significant greater increase in disease activity score ((DAS)28-ESR) was seen in the discontinuation arm (difference in ΔDAS28-ESR 0.61, 95% CI 0.35;0.88 p <0.001). Low disease activity was maintained in 77% of patients who continued compared to 65% who tapered (RR 0.83, 95% CI 0.71;0.97) (table 2).(19) During follow-up, limited to 24 weeks, no differences in adverse events was seen between the groups. No other randomized controlled studies comparing glucocorticoid continuation with tapering/discontinuation have

been published. Future studies should clarify which patients can discontinue and what is the best tapering strategy to achieve this. Or if discontinuation is failing, which is the lowest effective and long-term still safe dose and what is the best follow-up treatment step after glucocorticoid tapering.

Biological DMARD tapering and discontinuation

Although biological DMARDs, as much as glucocorticoids, 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 sufficiently respond to conventional synthetic DMARDs, the high treatment costs of biological DMARDs (20) 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 ACR, APLAR and EULAR recommendations suggest tapering can be tried and EULAR includes possibly discontinuation of biological DMARDs, when remission is achieved for sufficiently long time.(2,4,6) Continued treatment with (a) conventional synthetic DMARD(s) is 'preferred' (2,6), or required.(4) All recommendations caution that flares may occur, potentially causing radiographic damage.

Various trials have studied biological DMARD tapering by dose reduction, interval spacing and/or (eventually) discontinuation, recently summarized and evaluated in preparation for the 2019 update of the EULAR recommendations (table 1).(21) Tapering by discontinuation of the biological DMARD while continuing a conventional synthetic DMARD (tapering strategy 1) was studied mostly open-label studies. These studies found that discontinuation versus continuation resulted in around 30-33% more flares and loss of remission or LDA in up to 66% of patients.(22,23) The randomized placebo controlled trials (24,25), reported fewer flares overall, with a smaller differences (up to 10%) in flare rate between the discontinuation (placebo) and continuation arm than in the open label studies.

Tapering the biologic DMARD by dose reduction while continuing other DMARDs (strategy 2), was only studied in open-label studies. In the OPTTIRA trial, patients with DAS28≤3.2 that were randomized to 66% dose reduction (n=21) of either tumor necrosis factor inhibitor (TNFi) adalimumab or etanercept, had a higher risk of disease flare (defined as ≥0.6 DAS28 increase resulting in a DAS28 >3.2) (HR 5.10 95% CI 1.81-21.95) than patients randomized to 33% dose reduction (n=26).(26) However, in the DRESS study no significant difference was found in major flare incidence (defined as a >1.2 DAS28-CRP increase or ≥0.6 increase and current DAS28-CRP >3.2, persisting for >12 weeks) after lowering the dose of biological DMARDs (by 3-monthly interval increase) (n=115) or continuing it unchanged (n=57) in continued follow-up up to 3-years (10% vs. 12%).(27) l'Ami et al., reported non-inferiority in maintenance of disease control (ΔDAS28

<0.6) of interval increase from 2 to 3 weeks of adalimumab (n=27), compared to continuing at every 2 weeks (n=27).(28) The STRASS study an open-label non-inferiority trial in which patients were randomized to continue (n=73), or progressively space (n=64) etanercept or adalimumab dosages, reported similar DAS28 and radiographic damage progression over time, but an increased risk for disease relapse (defined as DAS28>2.6 and >0.6 DAS28 increase) was found in the spacing group (HR 2.37 95% CI 1.47-3.83).(29) In the TOZURA study, patients randomized to continue tocilizumab 162mg weekly (n=89) more often maintained DAS28 <2.6 than patients randomized to spacing to 162mg biweekly (n=90) (90% versus 73%, p<0.01), but most other efficacy measures were comparable.(30) The level of evidence of these studies was limited due to open-label design, small numbers and sometimes not achieving the needed 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).(31-33) In the double blind placebo controlled PREDICTRA study, in patients who were in remission for at least 6 months, a disease flare occurred in 36% of patients who tapered (by increasing the interval from 2 to 3 weeks) adalimumab (n=102) compared to 45% of patients who discontinued adalimumab (n=20).(32) The single blind TARA trial randomly assigned patients in remission on a combination of a biological DMARD and conventional synthetic DMARD(s) to either taper and stop the biological DMARD first (n=95) or the conventional synthetic DMARD first (n=94), while continuing the other, which was then tapered and stopped in the second year.(33) The proportion of patients with a disease flare (defined as DAS>2.4 or swollen joint count >1) (primary outcome), the mean DAS and Health Assessment Questionnaire (HAQ) scores were similar between the groups. After 2 years, DFR rates were 20% in the conventional synthetic DMARD first group vs. 11% in the biological DMARD first group (p-value=0.07).

In the EULAR 2019 updated guideline about safety it is reported that biological DMARDs carry a higher risk of serious infectious AEs compared to conventional synthetic DMARDs. This is based on two studies with moderate or high risk of bias.(34) A meta-analysis of Vinson et al. 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 to patients who continued treatment dose (risk difference (RD) 0.01 (95%CI 0.00 to 0.02)).(35) Also in the later conducted PREDICTRA, TARA and SEAM-RA studies tapering or stopping biological DMARDs did not appear to reduce the number and burden of AEs.(31-33) In light of the relative rareness of serious adverse events, however, the numbers of patients selected and the follow-up time (maximum of 2 years) of these studies may have been insufficient to find a benefit in tapering/stopping.

Prior assessment of flare risk when considering biological DMARD tapering or discontinuation would support treatment decisions. In general in patients with early rheumatoid arthritis and/or patients without autoantibodies and/or Shared Epitopes, tapering and stopping biological DMARDs is more likely to be successful.(36-38) 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 patient can safely taper or discontinue biological DMARDs.

Targeted synthetic DMARD tapering and discontinuation

In the double blinded RA-BEYOND study patients with stable Clinical Disease Activity Index (CDAI) ≤10 were randomized to continue full dose baricitinib (n=281) or reduce to half dose (n=278) while continuing conventional synthetic DMARD(s) and/or glucocorticoids (table 2).(39) More patients who continued full dose maintained LDA and remission compared to the half dose group (80% versus 67% LDA, $p<0.01$ and 40% versus 33% remission) and fewer full dose patients flared (and also flared later) (23% versus 37% respectively, $p=0.001$). After restoration to full dose, 67% of patients regained LDA or remission. More information on targeted synthetic DMARD tapering may emanate in the coming years, but currently there are no ongoing intervention trials evaluating tapering and/or discontinuation of targeted synthetic DMARDs.

Conventional synthetic DMARD tapering and discontinuation

The EULAR recommendations state that conventional synthetic DMARD in monotherapy, provided that they are tolerated, should not be discontinued but that dose reduction can be considered.(2) This is based on a double blind placebo controlled study from 1996 (40,41), where patients with longstanding, mostly erosive rheumatoid arthritis in stable LDA, were randomly assigned to continuation (n=142) or discontinuation (n=143) of the conventional synthetic DMARDs of the time. The cumulative incidence of flares was higher in the placebo group (38% vs. 22%). Rapid improvement occurred after restarting medication.(41) No similar discontinuation studies including treatment strategies reflecting current routine of care and other placebo controlled studies on stopping conventional synthetic DMARDs as monotherapy, have been done since. Several studies, summarized in 2020 by Kerschbaumer et al. (table 1) (21), have investigated the option to taper or stop conventional synthetic DMARD(s), while continuing biological DMARDs. The open label studies showed contradicting results in their non-inferiority designs.(42,43) The randomized placebo controlled trials all demonstrated noninferiority of discontinuing MTX while continuing the biological DMARD.(44-46) In the more recent double blind, placebo controlled SEAM-RA study patients in stable Simple Disease Activity Index (SDAI) remission on methotrexate in combination with etanercept, were randomized to either discontinuation of etanercept

(n=101), methotrexate (n=101) or neither (n=51).(31) Discontinuation of etanercept was associated with more loss of SDAI remission compared to discontinuation of methotrexate (71% vs. 50%, p<0.01). Also in the TARA study tapering a conventional synthetic DMARD first versus the biological DMARD first resulted in comparable efficacy outcomes.(33) An open-label randomized non-inferiority study compared stopping the conventional synthetic DMARD while continuing certolizumab pegol (n=45) with continuing both (n=43). For DAS28 <3.2 and change of DAS28 ≥1.2 at 18 months, the cut-off for non-inferiority was not met and comparisons on CDAI and HAQ-DI showed similar results in both groups.(43) More recently, the double blind phase of the non-inferiority ORAL shift study showed that in patients who achieved LDA on methotrexate with the Janus kinase inhibitor tofacitinib, discontinuation of methotrexate (n=267) was non-inferior to continuation (n=266) regarding change in DAS28 (table 2) (47), which was in line with previous studies.(44,45)

Recently the open-label ARCTIC REWIND trial randomly assigned patients with stable DAS remission to continuing on stable-dose (n=78) of one or more conventional synthetic DMARDs (66% on methotrexate monotherapy, baseline mean dose 19 mg/week), or on half-dose (n=77).(48) During the 12-months study period, 25% of patients in the half-dose group versus 6% in the stable-dose group flared (risk difference 18%, 95%CI 7-29, p-value <0.01). Dosages were restored after a flare. After 12 months follow-up 85% of patients in the half-dose group and 92% in the stable-dose group were in DAS remission, but over time, remission percentages, disease activity scores, functional ability and radiographic progression scores were similar in both groups. More (non-serious) adverse events were reported in the stable-dose group.(48)

Gradual tapering of conventional synthetic DMARDs in monotherapy (strategy 3), ultimately to zero, was introduced in several treat-to-target studies. In the first 5 years of the single blind BeSt study (n=508), where treatment was tapered as long as DAS <2.4 was maintained and then discontinued when remission was maintained, 23% of all patients achieved drug free remission. Although 46% of patients later lost remission, restart of the last discontinued conventional synthetic DMARD rapidly restored remission in 74% (or LDA in another 21%). (49) Tapering to DFR seemed more successful if the initial therapy had been with a combination of a conventional synthetic and biological DMARD (18% DFR vs. 8-14% DFR, results from the first 4 years).(37) In the open-label RETRO study, patients with established rheumatoid arthritis, in remission for at least 6 months on conventional synthetic and/or biological DMARDs, were randomized to DMARD continuation (n=38), to halving the dosages (n=36) and to first halving, then discontinuing all DMARDs (n=27). Over 12 months follow-up 16%, 39% and 52%, respectively, lost remission.(38) The results confirmed the possibility to taper or stop conventional synthetic DMARD therapy (mostly methotrexate) although flare rates were significantly lower if therapy was

continued (16% in continuing group vs. 44% overall in the two tapering groups). During 2 years in the open-label tREACH study in early arthritis patients, after protocolized tapering of (conventional synthetic) DMARDs, 34/159 patients (21%) had achieved drug free remission. Of these, 27 patients within 6 months subsequently lost remission and restarted treatment (50). In the single blind IMPROVED study (n=610), patients with early arthritis were treated-to-target DAS remission (DAS <1.6), which was achieved after 4 months by 63% of patients, who then tapered to drug free remission. During 5 years follow-up 26% of patients achieving sustained (>=1 year) DFR at least once (51,52), but independent predictors for long-term successful tapering to DFR could not be identified.

Patient perspectives

Based on a 2020 review about patient perspectives on treatment changes in rheumatoid arthritis (53), 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 earlier experience(s) with increased in rheumatoid symptoms in the past were observed and made patients more reluctant to treatment tapering. Fear of flaring is a significant reason to remain on a treatment scheme that has shown to be successful in achieving the desired treatment target. A 'safety net of continued monitoring of disease activity' and the possibility of rapid treatment escalation if necessary are conditions which should be guaranteed before tapering should be attempted. Patients declared that information provision and shared decision making are important to be convinced to taper their medication.(54-56) Patients want to know that the biological or targeted synthetic DMARD will be effective again when restarting it.(55) Physicians can point out that various studies showed that restarting the discontinued biological DMARD is rapidly successful in the large majority of cases (between 67% and 91% reported in the C-OPERA study, SURPRISE study, POET study and the RA-BEYOND study).(23,25,39,57)

In general, conventional synthetic DMARDs are regarded as being well tolerated and, unlike biological DMARDs, they are not associated with an increased risk of serious (infectious) AEs.(58) However, many patients experience, but apparently put up with side effects that are (medically) non-serious.(59,60) In the TARA study, the side effects of conventional synthetic DMARDs were found to have a greater impact on patients' life compared to side effects of biological DMARDs.(33) In a qualitative study from Baker et al. patients appeared to desire tapering of medication rather because of concerns regarding potential toxicity than because of experienced side effects.(61) This may also explain, at least in part, reports on patient non-compliance, which indicate that a significant proportion of our patients have tapered or discontinued (or never took) prescribed DMARDs.(62,63)

However, in daily practice, tapering of conventional synthetic DMARDs appears to be rare and independent of the current DAS.(64) The costs of conventional synthetic DMARDs are certainly lower than of biological DMARDs and targeted synthetic DMARDs , although increased by the costs of continued regular blood tests to monitor for asymptomatic laboratory abnormalities as (inter)nationally recommended and dose will not notably affect this.(5)

Future considerations

After decades where persistent disease activity required constant treatment intensifications in most patients with rheumatoid arthritis, we are now in the position where we can explore treatment tapering and discontinuation. Still, previous experiences and failed earlier attempts of stopping medication, make patients and also physicians, cautious. There is still limited information on the effects of tapering from clinical trials and with the focus on the occurrence of flares or loss of remission after tapering, many appear to warn against trying. In placebo controlled studies (24,25), the differences in flare rates and other outcomes appear to be smaller compared to open-label studies, where a nocebo effect of dose reduction may play a role.(22,23,57) A structured assessment of the risk of bias shows that most recent findings on DMARD tapering are from open-label or single blind studies, in part not primarily focused on studying the option to taper and/or discontinue certain drug(s). The potential benefit of lower drug exposure, reducing the risk of AEs, is not felt immediately and objectively as the increase in disease activity experienced after tapering/discontinuation. We conclude that, placebo controlled trials, with sufficiently large groups and long follow-up time, are needed to provide unbiased information about the effects of tapering or stopping and comparison of observed AEs.

For glucocorticoids, historical knowledge and continued study 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.(2,5,6,65) Many patients are wary of starting glucocorticoids (66,67), yet, once proven effective in suppressing inflammation, glucocorticoids are often continued, in particular when the more expensive biological and targeted synthetic DMARDs are not available. As well as the optimal initial dose, the optimal tapering strategy is yet to be determined. The STAR trial (table 3) is currently investigating two strategies of glucocorticoid, reducing 1mg/month versus replacement therapy with hydrocortisone. Early tapering and discontinuation of glucocorticoids may be facilitated if other effective therapies are available to be used as an alternative, as demonstrated in protocolized treatment strategy studies.(8,16)

Tapering biological DMARDs was not found to reduce the number and burden

of AEs. However, this effect can be biased by 'dilution of the susceptible' and can be due to relatively small numbers and relatively short follow-up. Other than glucocorticoids and conventional synthetic DMARDs, tapering biologic DMARDs (and targeted synthetic DMARDs) offers financial benefits. Studies show that it puts patients at risk of a disease flare and/or radiographic progression (27,68-70), although not all radiological progression or functional score changes may constitute a clinically significant deterioration and efficacy can be rapidly restored after restarting the original dose.(23,25,57,71) And not all patients experience disease flares after tapering or discontinuation. Previous studies have suggested that patients who had achieved the lowest levels of disease activity and patients who are ACPA negative and in early stages of the disease, had the lowest risk of flare after discontinuation.(36-38) Still, in clinical practice it is still not possible to predict who can successfully stop, nor who can definitely not.(72,73)

It remains unclear how much time a patient needs to be in stable remission or LDA before tapering the biological DMARD 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 may 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 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 may no longer be required once disease control is achieved. A randomized 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 study, depending on the conventional synthetic DMARD used, at least some dose reduction is now offered to our patients in the clinic who achieve persistent (which is mostly defined as at least 6 months) DAS remission. In follow-up, DAS results as well as radiologic follow-up, reported symptoms and adverse events, steer how far we taper, when we wait, or when the dose is again increased. Tapering and stopping medication, even for some time, may have a positive impact on how patients feel.(61) But restarting or increasing the medication should always be anticipated and not felt as failure.

Conclusion

In summary, based on current knowledge, tapering and stopping strategies of antirheumatic treatments can now be part of daily practice, for different treatments for different reasons and with different timings. Patients starting on glucocorticoids should be aware that these 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 they are started, to be effectuated if the disease has been in remission for the last 6-12 months. As long as disease activity remains well suppressed, gradually reducing the dose is the safest option. Thus, tight monitoring of disease activity should be in place to intensify treatment again as soon as needed. After glucocorticoids, biological DMARDs and/or targeted synthetic DMARDs, 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. This should all be under strict monitoring of disease activity and in tight consultation with the patient.

Search strategy and selection criteria

We searched PubMed, MEDLINE, Embase and the Cochrane Library for trials published between June 1997 and June 15, 2021. The principal search was performed with five main themes “rheumatoid arthritis”, “tapering”, “antirheumatic agents”, “patient preference” and “clinical trial” (see supplementary file for the complete search strategy). Relevant articles were selected based on title and abstract screening by LO and JMM using a prespecified decision rule. We only selected articles published in English. Articles without primary analysis or with lacking relevance to the contents of this review were excluded. After full-text reading articles 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 I for randomized controlled trials. The Risk of Bias assessment was done by LO and JMM independently and differences were discussed until consensus was reached.

Table 1. Overview articles on DMARD tapering and/or discontinuation in rheumatoid arthritis from the past five years

Review author	Title	Year of publication	Published between	Trials reviewed*	Results	Conclusion
Glucocorticoid tapering and/or discontinuation						
Wallace et al. (13) - letter	Evidence to support or guide glucocorticoid tapering in rheumatoid arthritis is lacking.	2019 (July)	August 1997 - June 2016	Number of studies included in review; 14 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=261), BeSt (n=508), CARDERA (n=467), Pincus et al. (n=31), Hickling et al. (n=128), Tengstrand et al. (n=58)	Eleven studies were found to evaluate oral GC tapering in RA patients since September 2008. An additional 5 studies were reviewed in a previous SLR. None of the studies directly compared GC tapering strategies.	Tapering of GCs is not sufficiently investigated to give guidance to clinicians.
Biological DMARD tapering and/or discontinuation						
Kerschbaumer et al. (21) – systematic literature review	Efficacy of pharmacological treatment in rheumatoid arthritis: a systematic literature research informing the 2019 update of the EULAR recommendations for management of rheumatoid arthritis	2020 (February)	January 2016 – March 2019	Number of studies included in review: 9 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), TARA (n=189)	Success rates of tapering measured with: - (major) flare rate: 25-80% - change in DAS28:-0.14;0.3 - change in mTSS 0.66-3.01 - bDMARD free rate: 21-67% - flare free rate: 39-53% - % of people with DAS28 <2.6: 33% - % 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 obtained again after re-initiation of therapy.
Schett et al. (74) - review	Tapering biologic and conventional DMARD therapy in rheumatoid arthritis: current evidence and future directions	2016 (June)	February 1996 - February 2015	Number of studies included in review: 29 Saleem et al.(n=47), Brocq et al. (n=21), Aguilar-Lonzano et al. (45), Naredo et al. (n=77), Iwamoto et al. (n=40), Alivernini et al. (n=42), van der Maas et al. (n=51), van Herwaarden et al. (n=22), ten Wolde et al. (n=285), Ahern et al. (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 (69), AVERT (n=222), RETRO (n=101), PRIZE (n=193), STRASS (n=137), PRESERVE (n=604), DOSERA (n=91), DRESS (n=180)	Preferable dose tapering phase followed by gradual withdrawal instead of immediate withdrawal.	The ideal patient characteristics for tapering remain unclear.

Table 1. *Continued*

Review author	Title	Year of publication	Published between	Trials reviewed*	Results	Conclusion
Conventional synthetic DMARD tapering and/or discontinuation						
Kerschbaumer et al. (21) – systematic literature review	Efficacy of pharmacological treatment in rheumatoid arthritis: a systematic literature research informing the 2019 update of the EULAR recommendations for management of rheumatoid arthritis	2020 (February)	April 2016 – June 2019	Number of studies included in review: 7 MUSICA (n=309), CAMEO (n=205), JUST-ACT (n=164), COMP-ACT (n=294), ACT-TAPER (n=272), CareRA (n=58), Pope et al. (81)	studies evaluate csDMARD continuing vs. stopping in patients treated with (bDMARD or csDMARD) combination therapy. Non-inferiority of MTX stopping vs. continuing was shown in 3 trials with tocilizumab. Non-inferiority was not shown for MTX dose reduction vs. full dose in patients initiating adalimumab.	Tapering of csDMARDs is mostly studied in the context of combination (bDMARD or csDMARD) therapy. Tapering and 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 et al. (75) – systematic literature review	Experts document on methotrexate use in combined therapy with biological or targeted synthetic disease modifying drugs in patients with rheumatoid arthritis	2020 (October)	until January 2019	Number studies included in review (regarding tapering): 8 PRESERVE (n=604) , OPTIMA (n=207), PRIZE (n=131), TARA (n=189), ACT-TAPER (n=272), JUST-ACT (n=164), SMART (58), AGREE (81)	For RA patients with sustained (at least 6 months) remission the panel recommends tapering of bDMARDs before csDMARDs.	Tapering should be considered individually for every patients.
Schett et al. (74)- review	Tapering biologic and conventional DMARD therapy in rheumatoid arthritis: current evidence and future directions	2016 (June)	February 1996- February 2015	Number of studies included in review: 5 BeSt (n=243), ten Wolde et al. (285), Ahern et al. (n=38), RETRO (n=101), PRIZE (n=193)	Preferable dose tapering phase followed by gradual withdrawal instead of immediate withdrawal.	The ideal patient characteristics for tapering remain unclear.

Abbreviations: bDMARD/csDMARD=biological/conventional synthetic disease-modifying antirheumatic drugs; DAS=disease activity score; EULAR=European league against rheumatism; GC=glucocorticoids; N/A=not applicable; mTSS=modified total Sharp score; MTX=methotrexate; SLR=systematic literature review.
* n= reported number of patients included in the trial as referred to in corresponding review

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

Clinical trial	Trial name	No. patients	Patient characteristics	Treatment groups	Primary outcome(s)	Secondary outcome(s)
Glucocorticoid tapering and/or discontinuation						
Burmester et al., *July 2020* (19)	SEMIRA	259	RA patients with stable LDA on tocilizumab and glucocorticoids (5-15mg)	1) Continue prednisone 5mg/day; 2) taper masked prednisone (decreased with 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<0.001)	Maintenance of DAS28 ≤3.2 without flare was lower in the tapered (65%) vs. the continuation (77%) group.
Conventional synthetic DMARD tapering and/or discontinuation						
Cohen et al., *November 2019* (47)	ORAL Shift	533	Moderate to severe RA with LDA on tofacitinib and MTX	1) tofacitinib + placebo; 2) tofacitinib + MTX	LSM change of DAS28(ESR) from week 24 to week 48 was greater in arm 1 (0.3, 95%CI 0.2-0.5) than in arm 2 (0.0, 95%CI -0.1;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 arm 1 from week 24 to 48. LSM changes HAQ and CRP were greater in arm 1 from week 24 to 36.
Lillegraven et al., *May 2021* (48)	ARCTIC REWIND	155	RA patients with stable 12-month remission on (a combination of) conventional synthetic DMARDs	1) half-dose of (all) csDMARD(s) 2) stable-dose of (all) csDMARD(s)	Percentage of patients with a DAS defined flare (DAS increase ≥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 and/or discontinuation						
Sanmarti et al. *April 2019* (30)	TOZURA	179	RA patients in remission on 162mg tocilizumab per week.	1) Continue tocilizumab 162mg/week 2) taper to tocilizumab 162mg every two weeks	Extension study week 24-48 had no primary reported outcomes.	Percentage of patients in maintained remission at week 48 (24 weeks after randomization) Mean change from baseline in DAS28, SDAI, CDAI, TJC, SJC, CRP, ESR, patient and physician global assessment of health, HAQ,
Emery et al. *May 2020* (32)	PREDICTRA phase IV	122	RA patients in stable remission on adalimumab 40mg every 2 weeks for ≥12 months	1) taper to 40mg adalimumab every 3 weeks; 2) discontinue adalimumab (placebo)	No association between baseline MRI and hand & wrist synovitis, osteitis and flare occurrence.	Time to flare longer in taper vs. withdrawal arm (NS). At week 40: 36% in the taper arm flared vs. 45% in the withdrawal arm.

Table 2. *Continued*

Clinical trial	Trial name	No. patients	Patient characteristics	Treatment groups	Primary outcome(s)	Secondary outcome(s)
Curtis et al., *November 2020* (31)	SEAM-RA	253	RA patients in maintained (24 weeks) SDAI remission on MTX + etanercept.	1) MTX monotherapy 2) etanercept monotherapy 3) MTX + etanercept combination therapy	SDAI remission at 48 weeks in significantly more patients in arm 2 (50%) compared to arm 1 (29%) and more in arm 3 (53%) vs arm 1 (29%).	Time to disease worsening significantly shorter for arm 1 (median 198 days) compared to arm 2 and arm 3 (medians not estimable). Restitution of SDAI remission with rescue therapy: 70-80% in each arm.
Targeted synthetic DMARD tapering and/or discontinuation						
Takeuchi et al. *September 2018* (39)	RA-BEYOND	559	RA patients in stable LDA or remission on 4mg baricitinib	1) Continue baricitinib 4mg/day ±csDMARDs; 2) taper to 2mg baricitinib ±csDMARDs	Maintained LDA and remission were higher in continuing group (88% LDA; 40% rem.) vs. taper group (67% LDA; 33% rem.)	Dose reduction resulted in increased disease activity and earlier and more frequent disease flares.

Abbreviations: ACR=American college of rheumatology; CDAI=clinical disease activity index; CI=Confidence Interval; DAS=disease activity score; (cs)DMARD=(conventional synthetic) disease-modifying antirheumatic drug; ESR=erythrocyte sedimentation rate; FACIT-F=functional assessment of chronic illness therapy-fatigue; HAQ=health assessment questionnaire; LDA=low disease activity; LSM=least squares mean; MTX=methotrexate; mono=monotherapy; NS=not significant; PtGA=patient global assessment of disease activity RA=rheumatoid arthritis; Rem.=remission; 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/or number of medications 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 3. Ongoing trials regarding tapering (RCTs and observational studies)

Contact person and study design	Trial name	Title	Target size	Follow-up time	Patient characteristics	Treatment groups	Primary outcome(s)	Secondary outcome(s)
Glucocorticoids								
A. Ruyssen-Witrand *NCT02997605 Double-blind parallel-group, controlled randomized clinical trial*	STAR	Comparison of two strategies of glucocorticoid withdrawal in rheumatoid arthritis patients	122	12 months	RA (ACR/EULAR 2010 criteria) on stable csDMARD/ bDMARD for and glucocorticoids for at least 6 months	1) prednisone tapering by 1mg dose reduction per month + placebo hydrocortisone 2) prednisone replacement with hydrocortisone (20mg/day) + prednisone placebo tapering	Proportion of patients who could withdraw from prednisone and hydrocortisone at one year	Difference 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, FACIT-F scores - proportion of SAEs
Biological DMARDs								
S. Atiqi *NCT04222920 Single blind, non-inferiority, randomized clinical trial*	ADDORA-low	Adalimumab dose reduction aiming low serum concentration with control of disease activity	89	24 weeks	RA (ACR 1987/ EULAR 2010 criteria) using adalimumab (serum concentration > 5mg/L)	1) dose reduction aiming at ADA serum concentration of 5 mg/l 2) dose reduction aiming at ADA serum concentration of 2 mg/l	Difference in mean time weighted DAS28-CRP after 24 weeks	Difference in; - mean time DAS28-CRP after 12 weeks - number of flares - direct medical costs - drug levels
S. Atiqi *NCT04194827 Open label, randomized controlled trial*	ADDORA	Adalimumab drug optimization in rheumatoid arthritis using therapeutic drug monitoring	267	80 weeks	RA (ACR 1987/ EULAR 2010 criteria) initiating adalimumab	1) concentration guided dose reduction 2) disease activity guided dose reduction	Direct medical costs associated with adalimumab dose reduction (52 weeks)	Difference in; - mean time weighted DAS28-CRP - direct medical cost - indirect medical costs - patients with DAS28-CRP <2.9 - number of flares - number of dose-interval shortenings - drug levels

Table 3. *Continued*

Contact person and study design	Trial name	Title	Target size	Follow-up time	Patient characteristics	Treatment groups	Primary outcome(s)	Secondary outcome(s)
L. Uhrenholt *Eudra CT 2017-001970-41* *Randomized controlled, open-label, parallel-group, equivalence study*	BIODOPT	Dose reduction and discontinuation of biological therapy in patients with rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis	180	18 months	RA, psoriatic arthritis or SpA treated with a bDMARD and in clinical remission/ LDA for 12 months	1) disease activity guided tapering (not further specified) 2) 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 remission in patients with reduced dose bDMARDs and discontinued bDMARDs - changes in DAS28, CDAI, SDAI for RA. - changes in PROMs- changes in PGA
R. Westhovens *Eudra CT 2012-004631-22* *Open label, randomized controlled trial*	TapERA	TapERA: maintaining remission in RA while tapering Etanercept.	120	12 months	Established RA treated with Etanercept and in DAS remission for at least 6 months	1) decreasing dose Etanercept to 50mg every 2 weeks 2) continuation of Etanercept dose 50mg weekly	Difference in proportion of patients remaining in remission at 6 months	Differences in: - proportion remission 6 months, 1 year according to Boolean definition, to SDAI definition - proportion regaining remission when retreated in case of flare - safety (AE) - evaluating usefulness FLARE questionnaire - exploring predictors for maintenance of remission
F. Hooijberg *NCT03895879* *Open label, randomized non-inferiority trial*	TODORA	Use of tocilizumab drug levels to optimize treatment in RA	98	52 weeks	RA (ACR 1987 or 2010 criteria) using tocilizumab 162mg/ wk for at least 6 months	1) increasing tocilizumab dosing interval to every two weeks 2) continuation of tocilizumab weekly All patients with concentration <15mg/L will continue tocilizumab weekly	Difference in mean time DAS28 after 28 weeks (between arm 1 and 2)	Differences in ; - mean time DAS28-ESR at 52 weeks and - CDAI, SDAI, HAW, direct medical costs, number of flares, number and severity of adverse events, after 28 and 52 weeks - drug level between week 0 and 52

R. van Vollenhoven *NCT01491815/ NCT02466581 Randomized, open-label, blinded-assessor study*	NORD-STAR	Active Conventional Therapy Compared to Three Different Biologic Treatments in Early Rheumatoid Arthritis With Subsequent Dose Reduction	800	56 weeks	RA (ACR/EULAR 2010 criteria) Treated with and achieving stable remission (24wk) on: 1) conventional synthetic DMARD combination 2) abatacept + MTX 3) tocilizumab + MTX 4) certolizumab Pegol + MTX	1) De-escalate treatment at randomization (early dose reduction) 2) First continue and then de-escalate treatment 24 weeks after randomization (late dose reduction)	Difference in the proportion of patients who maintain LDA (CDAI) at 24 weeks after de-escalation initiation.	N/A
Targeted synthetic DMARDs								
M.T. Nurmohamed *observational study NTR ID: 6868*	N/A	Biologicals and tsDMARDs in inflammatory rheumatic diseases: The Reade Rheumatology Registry	unknown		patients with RA, psoriatic arthritis or SpA	N/A	disease activity, patient reported outcomes, radiological progression and functional capacity.	changes in biomarkers

Abbreviations: ACR=American college of rheumatology; ADA=adalimumab; bDMARD/csDMARDs/tsDMARD=biological/conventional/targeted synthetic disease-modifying antirheumatic drugs; CDAI=Clinical disease activity index; CRP=C-reactive protein; DAS=disease activity score; EULAR=European league against rheumatism; HAQ=health assessment questionnaire; LDA=low disease activity; N/A=not applicable; NTR ID=Dutch trial identification number; PROM=patient reported outcome; RA=rheumatoid arthritis, RCT=Randomized Controlled Trial; SDAI=simple disease activity index; SpA=ankylosing spondylitis; Tx=treatment

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