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Tapering biologic and conventional DMARD therapy in rheumatoid arthritis - Current evidence and future directions

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Abstract

Improvements in the control of inflammation in rheumatoid arthritis (RA) by conventional synthetic and biologic disease modifying anti-rheumatic drugs (DMARDs) have led to a substantial change in the clinical outcomes of patients during the last 30 years. Current treatment can lead to sustained remission in some patients raising questions about the optimal management strategies in this subgroup of patients. Today, tapering of DMARDs and even their discontinuation appears as an interesting concept for achieving a more tailored and dynamic treatment approach of RA, especially in patients, who achieved full disease control by DMARD treatment. In this review article, current developments of DMARD tapering are discussed. The article provides an overview of existing studies on this topic and addresses new strategies to reach drug-free remission. Furthermore, concepts for defining patients eligible for DMARD tapering are described and potential future strategies in using biomarkers in predicting the risk for disease relapse after initiation of DMARD tapering are addressed. These findings are finally considered in light of the vision to achieve cure as an ultimate goal in patients with RA achieving full control of inflammation.

Introduction

The clinical picture of rheumatoid arthritis (RA) has changed dramatically during the past decades (1). Thirty years ago, inflammation in RA was often difficult to control with available agents, leading to significant joint damage, loss of joint function and frequently crippling in a large number of patients. Today, inflammation in RA can be controlled much more decisively and effectively because of the advent of new therapies, including biological agents, as well as the application of the treat-to-target strategy based on a wide array of conventional synthetic and biologic disease modifying anti-rheumatic drugs (csDMARDs and bDMARDs), used alone or in combination (2). As a result, patients can achieve less severe disease in terms of signs and symptoms and a proportion can achieve remission. Hence, RA has become a "controllable" disease in a proportion of patients, where the disease is tightly monitored and anti-rheumatic drug therapy is continuously administered and adjusted on the basis of objective measures of disease activity.

RA is traditionally regarded as a life-long disease that cannot be cured and patients require life-long immune modulation to control the inflammatory process effectively and prevent damage. Such a concept of disease control, but not cure, is well established in other fields of medicine for conditions such as diabetes, hypertension, human immunodeficiency virus infection and certain forms of cancer. Under these circumstances, control of disease is possible as long as medication is given. However, despite improvements in disease control, cure still appears out of reach. In the same way, the improvement in RA treatment may represent a similar situation as unprecedented levels of disease control are routinely achieved. Whether sustained control signifies cure or at least a new specific disease state from a pathogenic view is unknown unless there is willingness to reduce or even withdraw

medication entirely. This development raises a major challenge concerning the management of RA patients who experience stable disease remission over a period of 6 months or even longer. Benefits of being in remission have to be weighed against potential over-treatment, safety considerations and treatment costs. Such considerations of safety and cost effectiveness are different in patients with long-standing remission as compared to patients who still have evidence of active disease. On the other hand, the indication for tapering and stopping of DMARD need to be rather strict and its procedures should be well- controlled in order to prevent under- and/or- *laissez affair* treatment in patients with residual inflammatory disease activity.

The conceptualization of disease has changed

Remission in the treatment of RA occurs more frequently now than ever before. Registry data support the common clinical observation that RA patients show much better responses than in previous years, especially in countries with easy access to an armamentarium of synthetic and biologic disease modifying anti-rheumatic drugs (DMARDs). In the Norwegian (NOR)-DMARD registry, for instance, remission rates doubled in the last decade: hence, about 40% of RA patients in Norway achieve remission of RA defined as disease activity score (DAS) 28 of less than 2.6 (3). Other registries/observational studies come to similar conclusions (4,5). For example, in the ESPOIR cohort, 50% of the patients with early RA were in DAS28 remission 5 years after disease onset and 65% in low disease activity (LDA).

Of course, these improvements in overall outcomes in RA treatment by no means imply that our current treatment tools for inducing remission in RA patients are already optimal, since a subset of patients is still resistant to treatments and approximately half of the patients fail to achieve a state of remission especially if the more stringent remission criteria are applied.

Also, “low disease activity” as defined by DAS28 scores allows substantial residual inflammation and may therefore not anymore be considered as an ideal treatment target and even remission based on DAS28 criteria often reflects only minimal disease activity rather than true remission. Nonetheless, the aforementioned changes towards an increasing number of RA patients with excellent disease control suggest that managing RA patients in sustained remission is an increasing issue and concepts need to be developed to guide optimal treatment strategies for this group of patients.

Improvements in the management of RA

The reasons for a growing population of RA patients in remission can be attributed to several different factors, related in part to the more appropriate use of DMARDs, early treatment as well as the treat-to-target approach with tight control and appropriate adjustment of treatment (2). Thus, RA patients are diagnosed earlier and treatment is initiated at an early stage, when RA has not progressed to severe joint damage associated with irreversible functional decline. Another important factor in the improvement of RA outcomes is the rapid expansion of our treatment armamentarium, particularly the introduction of biological DMARDs that address different targets and allow more effective treatment of resistant disease manifestations. In addition to the utilization of the new agents, the current treatment paradigms permit more appropriate use of synthetic DMARDs regarding dosing or combination of synthetic DMARDs and glucocorticoids (6,7). Finally, better monitoring of the disease state („tight control“) as well as the definition of commonly accepted treatment goals („remission“) have contributed to substantially improved outcomes (8). In the future, the availability of biosimilars with lower costs may also allow patients´ access to potent drugs at earlier time points in the course of disease and thereby prevent damage.

The concept of DMARD tapering

The question of de-escalation or even stopping DMARD therapy emerges when patients have reached long-standing remission. This question is of major importance for patients, physicians and payers for several reasons: (i) taking chronic medication for a symptom-free disease state requests the highest-level safety of therapy and the demonstration of continuous benefit from taking such medication. In the absence of clinical evidence of significant inflammation continuous, if not life-long, DMARD therapy in full dose may provide more harms than benefits in certain individuals. Therefore, patients as well as physicians have to see the advantages of continued drug therapy, which may be difficult to demonstrate, especially when weighing it against the risks of therapy. (ii) The costs of DMARDs, especially biological DMARDs (bDMARDs) are high and health care resources are under growing economic pressure. Hence, potential over-treatment of patients with expensive drugs needs to be avoided. In this regard, de-escalation of drugs in remission patients could liberate resources in health care systems for applying potent - particularly, biologic DMARDs - much earlier in cases of severe disease; and (iii) Finally and, most importantly, only de-escalation of therapy will allow distinction between mere suppression of inflammation by DMARDs from real cure of the disease.

Therefore, if we in the future want to investigate the possibility of curing RA and to develop treatment strategies to reach cure, we will need to consider structured DMARD tapering to address this concept.

Patients eligible for DMARD tapering

At present there is no standardized way to determine the patient for whom de-escalation of

DMARD therapy is appropriate. Beyond demonstration of clinical remission by a standard measure, the ideal patient profile has yet to be defined. Nonetheless, clinical experience, data from de-escalation studies and results from registries suggest that RA patients in sustained remission are the best target population to study drug-tapering regimens (9-12). In contrast, LDA, which allows substantial residual inflammatory disease activity should not anymore be considered as an indication for DMARD de-escalation. Remission can be defined by various clinical measures, but most commonly a DAS28-ESR score of <2.6 has been used as a treatment goal for remission (13). In early RA studies, the DAS44 remission definition (<1.6 units) has also been used. Notably, current DAS remission cut-offs "accept" a certain level of residual clinical disease activity. Hence, not all the patients in DAS "remission" show complete absence of clinical symptoms; as such, their condition may reflect a state of minimal disease activity rather than a "true" clinical remission defined as complete absence of signs and symptoms of RA. Lower thresholds may better disentangle patients with a specific disease state where pathogenic pathways have been deeply altered or even erased from patients with only suppressed pathogenic pathways. ACR/EULAR remission criteria have therefore been defined; these criteria consist of the same items as in DAS remission criteria but have stricter cut-offs and are therefore considered as an important treatment target in RA patients (14). Whether the utilization of a stricter cut-off is necessary to define patient populations eligible for DMARD tapering remains open at the moment, as a recent randomized controlled trial has shown no benefit to the use of ACR/EULAR remission criteria in this setting (15). Furthermore, virtually all information on treatment tapering currently available is based on using DAS remission or low disease activity as inclusion criteria, suggesting a need for more data on the impact of using stricter clinical or even imaging remission criteria in DMARD tapering.

Next to remission state *per se*, other factors appear to be important to consider when considering tapering of DMARDs (Table 1). Thus, duration of remission is a decisive factor for starting de-escalation of treatment. While patients can come into remission at one time point, they can subsequently lose their remission status, even if continuing on DMARDs (16,17). In support of this notion, studies aiming to define RA flare have evidenced this instability in disease activity, also called "bad days," during which remission is lost (18). Hence, remission needs to be stable and sustained over time, ideally over a period of at least 6 months and documented at three sequential visits prior to starting the DMARD taper. Furthermore, DMARD treatment itself needs to be stable and GC withdrawn. An exception concerning the use of the glucocorticoids may be stable doses of low-dose glucocorticoids (equal to or less than 5 milligram prednisolone per day), which are sometimes included in the long-term DMARD therapy and which can be included into the tapering regimens. Finally, it should be mentioned that the possibility of tapering DMARDs appears applicable to patients receiving either conventional synthetic DMARDs or biological DMARDs, given that the aforementioned conditions are fulfilled.

Tapering and stopping of DMARDs is now also included in the treatment guidelines of RA by major organizations. EULAR guidelines, for instance, recommend stopping glucocorticoids first, even those administered at low doses, before DMARD tapering is envisioned (19). Then, biological DMARDS should be tapered and stopped before synthetic DMARDs are de-escalated. Although such a sequence appears reasonable from a clinical and economic perspective, no strategy trials have yet compared different modes of tapering DMARDs. The guidelines of the ACR also include the possibility of tapering DMARDs as part of the new treatment recommendations (20). The ACR guidelines, similar to the EULAR recommendations, note that sustained remission should be present before starting DMARD tapering; low disease activity status is not considered as being of sufficient quality to justify

the withdrawal of DMARDs. ACR also highlight the role of a shared decision process that incorporates patients' values and preferences in the context of DMARD tapering (20).

Knowledge on tapering DMARDs has increased over the past years and several studies have either included de-escalation in their protocols or were entirely dedicated to de-escalation of DMARD treatment (Table 2). In principle, these studies represent either observational studies or post-hoc analyses of data from randomized controlled trials or randomized controlled trials entirely dedicated to DMARD tapering. Most of these studies addressed the role of biological DMARD tapering, while only few studied tapering and withdrawal of conventional DMARDs. Exceptions are two studies conducted more than 20 ago (21,22); these studies addressed the withdrawal of synthetic DMARDs and showed an increased risk for the recurrence of RA. In addition, a few studies that are more recent included tapering and withdrawal of conventional DMARDs, which are addressed below.

Evidence from prospective uncontrolled studies

Stopping tumour necrosis factor inhibitors was studied in two observational studies by Tanaka and colleagues. Although the *RRR study* included patients in DAS28(ESR) remission as well as LDA over 6 months, the study helped to advance the concept that stopping bDMARD treatment can be feasible in some RA patients (23). In fact, most (78%) of the patients were in DAS28(ESR) remission when stopping infliximab treatment without or with minimal dose of glucocorticoids. Interestingly, 55% of the patients remained in the low disease activity/remission status for at least one year despite stopping TNF inhibitor treatment.

Similar results were obtained in the *HONOR study* where stopping adalimumab was

compared with continuation of adalimumab (24). In this study, only patients in stable DAS28(ESR) remission over 6 months without glucocorticoids were included. While more than 80% of those patients continuing TNF inhibitor remained in remission, still about half (48%) of the patients stopping adalimumab maintained their remission state over one year without glucocorticoids. In a very small number of patients (N=6), who relapsed and developed DAS28(ESR) scores over 3.2, adalimumab was reintroduced reaching LDA in 5 and remission in 2 patients.

Three additional small studies also investigated the stopping of TNF inhibitor therapy in patients with RA. The Leeds group of Saleem et al. discontinued TNF inhibitors in 47 patients in sustained DAS28(ESR) remission over 6 months and found that disease relapses occurred more often in patients starting TNF inhibitors late in their disease course. In contrast, the majority of patients starting bDMARDs early in their course of disease remained in remission over one year (25). The second study by Brocq and colleagues involved a very similar setting, removing TNF inhibitors in patients with stable DAS28(ESR) remission over 6 months. These investigators reported a rather high relapse rate of 75% in their population; however, the sample size was rather small, with only 21 patients studied (26). Van der Maas and colleagues gradually tapered infliximab treatment in RA patients in DAS28(ESR) LDA over 6 months and were able to successfully taper treatment in 45% and stop it in 16% of the patients (27). However, it should be mentioned at this point that a state of mere LDA without remission would not be anymore considered to be an indication for tapering DMARDs.

Regarding non-TNF biologic DMARDs, Aguilar-Lozano and colleagues showed that a substantial proportion (44%) of tocilizumab-treated RA patients remained in remission after treatment was stopped (28). The authors included 45 patients in DAS28(ESR) remission with no duration specified and followed them for one year. Relapses were high in the *DREAM*

study performed by Nishimoto and colleagues (29). Only 13% of the 187 RA patients maintained LDA over one year if tocilizumab was stopped. The high relapse rate in this study may have resulted, however, from the fact that patients included in this study were in DAS28(ESR) LDA rather than remission, had no specific duration of remission required and were not treated with concomitant methotrexate. Finally, van Herwaarden and colleagues studied 22 patients on tocilizumab who reached DAS28(ESR) LDA on standard dose of tocilizumab (8mg/kg) demonstrating that more than half of the patients could successfully maintain their low disease activity state after reducing their dose to 4mg/kg tocilizumab (30).

These prospective uncontrolled studies have provided valuable evidence that de-escalation of DMARDs is feasible in a subset of patients with RA. However, for exclusion of bias also randomized controlled studies are needed to address this topic. In the following two chapters the evidence on de-escalation of DMARDs obtained in such studies is summarized.

Subanalyses of withdrawal of DMARDs in randomized controlled trials

Several studies on the effects of biological DMARDs in RA analysed treatment withdrawal in the subset of patients reaching remission. These studies did not *a priori* include RA patients in remission, but those with active disease with the primary aim to induce remission. Patients who achieved remission, which was not necessarily sustained remission, subsequently underwent de-escalation following an induction-maintenance treatment approach.

Quinn and colleagues studied 20 early RA patients in a randomised, controlled double-blind study (*20TNF study*) and showed that treatment with methotrexate plus infliximab produced fast improvements in disease activity, physical function and MRI inflammation compared to methotrexate alone (31). Since most of the patients in the combination treatment arm reached remission (not specifically defined but most in DAS28-ESR remission) after one year,

treatment with infliximab but not methotrexate was stopped and patients were observed for another year. In the majority of the patients, improvement was maintained for another year despite discontinuation of infliximab. Moreover, recent follow-up analyses of the study of Quinn et al have shown that this remission induction regimen followed by bDMARD tapering led to sustained benefits of function and quality of life over 8 years (32).

Data for DMARD tapering are also available from the *BeSt study*, where four dynamic treatment strategies were compared for inducing remission in early RA patients (33,34). In patients with sustained remission defined by a DAS44 score of less than 1.6 over 6 months, DMARDs were tapered and finally stopped, with bDMARDs first followed by csDMARDs. About half (48%) of the BeSt study patients reached remission of RA in the entire study population. Rates for complete drug-free remission were 21% in arm 1 (sequential monotherapy), 17% in arm 2 (step-up to combination therapy), 16% in arm 3 (initial combination therapy) and 27% in arm 4 (initial combination with MTX and infliximab). The majority (74%) of the patients relapsing regained remission when introducing the last therapeutic regimen. Moreover, the *BeSt study* also produced valuable insights about the consequences of DMARD tapering by demonstrating that re-initiation of the last DMARD regimen prior to tapering can restore remission in case of disease relapse. Also, data from this study demonstrated that the presence of anti-citrullinated protein antibodies (ACPA) influenced the risk of disease relapse after drug tapering.

In the *OPTIMA study*, patients with active RA were randomized to receive methotrexate or methotrexate plus adalimumab (35). Patients treated with combination therapy, who experienced low disease activity status (DAS28-CRP, no minimal duration required) were then randomized to stopping or continuing adalimumab; they were then followed over one year. Although significant differences were observed between the two groups in maintaining

low disease activity status (stop: 81%; continuation: 91%) or remission status (stop: 66%; continuation: 86%), the majority of patients were able to maintain a state of low disease activity or even remission even after stopping the TNF inhibitor. On the other hand 18% of OPTIMA study patients had radiographic progression, which may indicate that some patients had not achieved full disease control by using a DAS28-CRP LDA cut-off for entering deescalation.

Adalimumab stop was also performed in the *HIT HARD trial*, in which patients with very early RA were treated with the combination of methotrexate and adalimumab versus methotrexate plus placebo for the first 6 months of therapy followed by an open period applying methotrexate only for subsequent 6 months. About half of the patients (48%) receiving the active combination achieved DAS28(ESR) remission after the first 6 months. After another 6 months, when adalimumab had been withdrawn still 89% of the withdrawers maintained their remission status (36). Likewise, in the *GUEPARD study*, initial treatment with methotrexate plus adalimumab was superior to adalimumab alone. Those patients who started on the combination and reached DAS28(ESR) LDA discontinued adalimumab. Only about one third of them remained in LDA, which may be based on the use of LDA as entry for discontinuing adalimumab and the fact that no minimal duration of LDA was required (37). Also, the *IDEA study* followed the concept of remission induction followed by stopping TNF inhibitors, if remission is reached. Hence, patients having achieved sustained remission, defined as DAS44 score of less than 1.6 over 6 months, using combination treatment with methotrexate and infliximab had discontinuation of infliximab (38). In this study, remission was maintained in a somewhat lower proportion (25%) of the patients after withdrawing the TNF inhibitor; however, patient numbers withdrawing treatment (N=14) were small in this study.

Additional supportive data for treatment tapering in randomized settings come from the *EMPIRE trial*, which included patients with early arthritis although not necessarily early RA. Patients were randomized to receive methotrexate or methotrexate plus etanercept. After reaching sustained remission (TJC0/SJC0, no minimal duration required), etanercept was stopped successfully in a small number of the patients (N=9), who maintained their remission status as defined by no swollen or tender joint (39).

Concerning non-anti-TNF biologic DMARDs, patients reaching remission with either abatacept monotherapy or a combination of abatacept with methotrexate discontinued abatacept treatment in the *AVERT trial*. While 61% of the patients reached remission (DAS28-CRP; no minimal duration required) with abatacept plus methotrexate, only 15% of the patients maintained remission for 12 months after discontinuing abatacept. The high relapse rate in this study may be attributed to the fact that methotrexate was concomitantly stopped and even more importantly that a sustained remission was not ensured before abatacept was stopped; hence, stopping of abatacept may have been initiated too early (40). These findings are in accordance with data from the *ACT-RAY study*, in which tocilizumab was discontinued after a rather short phase of remission (DAS28-ESR for < 6 months). Only 14% of the patients stopping tocilizumab maintained remission over one year (41).

Randomized controlled trials on drug tapering/withdrawal in remission

Two classical RCTs in the 80s and 90s addressed the possibility of tapering conventional DMARDs in RA (21,22): Ten Wolde and colleagues (21) stopped or continued csDMARDs in 285 RA patients achieving ACR remission over a period of 6 months. Remission was maintained in 62% of the patients over one year. Ahern and colleagues (22) tapered or

continued D-penicillamin in 38 RA patients in remission (TJC0/SJC0 over 6 months). Only a minority (21%) of the patients remained in remission (no swelling) over a period of 6 months. More recently, several RCTs have addressed the possibility of tapering DMARDs in patients in sustained remission.

The RETRO study is a randomized controlled study to compare treatment strategies in established RA patients in sustained DAS28(ESR) remission over 3 sequential visits over at least 6 months (15). Tapering and withdrawal of both synthetic and biological DMARDs was investigated. In this study, patients were randomized to continue synthetic and biological DMARDs, tapering them by 50% or stopping them after a 6-month tapering phase. This real-life study includes RA patients, who had achieved remission independent of the type of DMARD regimen, including conventional synthetic as well as biologic DMARDs in mono- and combination treatment setting. In the RETRO study, 66.3% of the patients remained in remission over a period of 12 months and 33.7% relapsed. Relapse rates were low in the continuation arm (16%) and significantly higher in the tapering (38.9%) and stopping arms (52%). Still more than half of the patients were able to maintain their remission state despite the de-escalation of treatment. Relapse rates were not different between patients, who did fulfil ACR-EULAR remission criteria and those who did not fulfil them. Moreover, relapses could be successfully treated and remission could be reintroduced in all patients when the original DMARD regimen was restarted again. The authors concluded that tapering and even stopping of DMARDs is feasible in a subset of patients if long-term remission was achieved.

In the *PRIZE study,* the potential of methotrexate plus etanercept to achieve remission was addressed in early RA (42). In this study, more than 60% of the patients achieved remission. Those patients achieving remission (DAS28-ESR; no minimal duration required) were then

randomized into three strategy arms, which involved tapering of etanercept, stopping it or stopping both methotrexate and etanercept. Remission rates after 1 year were 62%, 40% and 23%, respectively, showing that the level of reduction of treatment reduction was associated with the relapse rate in the patients. While more than half of the patients maintained remission while tapering, withdrawal of etanercept was possible in less than half of the patients and complete withdrawal of DMARDs only in one quarter of the patients.

In the *STRASS study,* the possibility of DAS-driven spacing out the time intervals between TNF inhibitor injections was studied according to the treat-to-target paradigm (43). Fautrel and colleagues included patients in sustained DAS28(ESR) remission over 6 months. All patients were taking etanercept or adalimumab. 137 patients were randomized to either continuing full-dose TNF inhibitor or tapering it by spacing the injection interval. If remission was lost, the last dosing regimen was reintroduced. The study showed that 39% of the patients could stop the TNF inhibitor in the tapering arm while maintaining the remission status. Another 35% of patients could successfully taper but not stop the treatment, while the other patients had to resume full-dose treatment.

Furthermore, preliminary data from the *ADMIRE study* in which 31 patients in DAS28(ESR) remission (>6 months) on methotrexate plus adalimumab were randomized to either continue or discontinue adalimumab. An 80% relapse rate upon discontinuation was noted, but the rate in the continuation group (50%) was also much higher than in other studies and clinical practice observations, suggesting that these patients may indeed not have been in stable remission.

Three RCTs using DAS28-ESR LDA (>6 months) as an inclusion criterion for treatment

tapering were published. At present, however LDA would not qualify for DMARD tapering anymore as substantial residual disease activity can be present. In the *PRESERVE study,* patients receiving etanercept were randomized into stopping, tapering or continuing the agent on background methotrexate treatment. After stopping etanercept, 43% of the patients remained in low disease activity over one year (44). In the *DOSERA trial* (45), patients on methotrexate plus etanercept were randomized to either continue full-dose treatment or reduce to half the usual dose or stop etanercept. After one year, 52% of patients on full-dose and 44% of patients on half-dose etanercept, but only 13% of patients on etanercept stop maintained a low disease activity state. The authors concluded that discontinuation of the anti-TNF agents in this previously highly-active patients population is generally not possible, but that dose reductions may be feasible in a meaningful subset of patients. In the *DRESS trial,* 180 patients with RA who had achieved DAS28-ESR LDA (no minimal duration required) on methotrexate plus either adalimumab or etanercept were assigned 2:1 to a gradual taper of the biologic by increasing the interval between injections versus continued unchanged treatment (46). After 18 months, the tapering strategy was shown to be non-inferior to continued treatment with respect to major flares (DAS28-ESR change > 1.2, or DAS28-ESR increase of 0.6 and current DAS28ESR ≥ 3.2), the primary outcome. The authors felt that these data strongly support the strategy of gradually widening the dosing interval of these two subcutaneous biologics in patients who are in stable low disease activity. Currently, another RCT (named *POET*) aiming for TNF inhibitor discontinuation is underway in the Netherlands. This study searches for predictors for treatment tapering in patients in sustained low disease activity status, who taper their TNF inhibitor. So far, only preliminary data have been published (47).

Predictors of flares

To improve the implementation of DMARD tapering in real-life, it will be critical to define predictors for disease relapses. All studies on DMARD tapering so far have shown that tapering is feasible in a subset of patients in sustained remission. Hence, decision-making and appropriate information about the risk for flare will be facilitated when clinical predictors or biomarkers, which determine the likelihood to relapse or remain in remission, will be available. In principle, clinical, imaging and serum biomarker can be envisioned for predicting relapse risk and which are also feasible in their application.

Specific clinical features have been associated with the risk for relapse. In the *RRR study* and the *HONOR study*, cut-off points for a successful discontinuation of TNF inhibitors were a baseline DAS28 value of 2.22 and 1.98, respectively, suggesting that "deep" remission may be required to keep the biological-free remission and that residual inflammation in patients in DAS28 remission could be associated with a higher likelihood to flare (23,24). Other studies such as *RETRO* have investigated the influence of baseline disease activity on relapse rates (15). Thus, *RETRO* tested whether patients fulfilling ACR-EULAR remission criteria at baseline had a lower risk of relapse than those not fulfilling them. However, no difference was found suggesting that ACR-EULAR remission is not necessarily required to start tapering DMARDs. On the other hand also ACR-EULAR remission allows some residual disease activity to be present.

In the *HONOR study,* another baseline factor affecting adalimumab-free remission was disease duration, indicating that patients with early RA have better chance to stop TNF inhibitors. Preliminary analyses in the *POET study* and earlier data from Van der Woude and colleagues also suggest that longer disease duration is associated with higher relapse risk

(47,48), while other studies did not find such association (15). The reasons for these discrepancies in the use of clinical parameters in relapse prediction are not yet fully understood yet but may reflect the different patient populations in the studies and challenges in the discrimination properties of disease activity instruments at the very low range. For instance, high-level sustainability of remission may compensate for overall disease duration. In accordance, observations from the *CORRONA registry* suggest that rapid response to DMARDs is associated with better maintenance of remission when the agents are tapered later on (49).

The concept that residual, mostly subclinical inflammation can be associated with enhanced relapse risk has prompted investigators to test whether imaging can help predict flare risk. This concept is also stimulated by observations that a substantial proportion of RA patients in remission can show signs of synovitis by ultrasound or MRI. In fact, three studies found that synovitis detected by ultrasound, mainly Doppler-detected synovitis, is a strong predictor of failure of successful tapering of biologic DMARD. Naredo and colleagues investigated RA patients in sustained remission (DAS28 less than 2.6 over 6 months) who tapered TNF inhibitors (50). Patients with Power Doppler positive synovitis had a significantly higher risk of relapse than those without residual inflammation. If combined with baseline DAS28 scores, predictive value of ultrasound for relapse risk was especially high. Iwamoto and colleagues reached similar conclusions about the likelihood of relapse when stopping TNF inhibitors in 42 RA patients in sustained remission (51). In addition, a recent study by Alivernini and colleagues showed that synovial hypertrophy is associated with higher risk of flares after tapering and withdrawing TNF inhibitors (52). Of particular interest, the authors also showed that absence of ultrasound hypertrophy is associated with only minimal synovial changes in the histology, supporting the accuracy of ultrasound examination to detect residual

disease activity. Also, preliminary data from the *POET study* support the concept that the presence of synovitis by ultrasound enhances the risk for flare during DMARD tapering (47). Hence, both presence of grey scale synovitis and Power Doppler synovitis can be associated with a higher flare risk. A combination of clinical and imaging remission could, therefore, represent a potentially attractive starting point for successful DMARD tapering. Whether a time- consuming comprehensive assessment of many joints by ultrasound or a more focussed approach through a few index joints is sufficient, however, remains to be determined.

With respect to serum biomarkers the best-studied predictor of relapse to date is ACPA positivity. In the *RETRO study*, ACPA status clearly indicated higher relapse risk with lower chances to maintain remission when ACPAs are present (15). Data from other studies, like *BeSt and HIT-HARD,* as well as preliminary data from the *POET study* support this concept (33,34,49). The hypothesis that underlying autoimmunity may indeed act as a driving force for inflammation in RA promoting a higher likelihood for relapse is additionally supported by observations from Tanaka and colleagues, who found that continuous presence of rheumatoid factor lowers the likelihood for successful withdrawal of TNF inhibitors (53).

To evaluate remission more objectively, attempts have been made to assess immune activity in RA using serum tests. While C-reactive protein level is widely measured to assess inflammation in RA, it may not provide an adequate picture of inflammation and related processes in the joint (e.g., tissue destruction). Hence, new serum biomarkers, which address processes other than the acute phase response may be helpful in better predicting the risk of relapse in RA patients deescalating DMARDs. Based on the heterogeneity of the patient population, however, several of such biomarkers may be needed to allow accurate prediction of relapses. Recently, composite biomarker testing including acute phase reactants, cytokines

and metalloproteinases has shown to improve prediction of relapse risk in patients tapering DMARDs in the RETRO study (53). Thus, the presence of elevated serum markers of inflammation increases the one-year relapse risk from 13% to 32% in ACPA negative patients and from 33% to 76% in ACPA positive patients. These findings indicate that the assessment of subclinical inflammation by laboratory testing may provide a useful tool to determine a patient's risk of flare and to define high-risk groups in whom DMARD tapering should be postponed.

Research agenda and unanswered questions

Tapering and stopping DMARDs provide the opportunity to develop new insights into the pathogenesis and clinical course of RA, re-conceptualizing RA from a life-long chronic inflammatory disease into a more acute or subacute process, which can erupt but then also resolve under certain circumstances, especially if appropriate treatment is given. While efforts in the treatment of RA so far have been primarily directed towards controlling inflammation and related immune cell dysfunctions, the future challenge in RA treatment will be to understand how remission is maintained over time, how subclinical disease can be detected and evaluated and how to distinguish a cure of disease from effective but incomplete suppression of inflammation (Figure 1).

It will be important to define an operating definition of remission in the perspective of DMARD tapering, with respect to quality and duration. At present, remission in RA is predominantly defined by clinical instruments detecting signs and symptoms of inflammation, such as joint tenderness and swelling, rather than the extent of synovial inflammation itself. Moreover, even clinical remission definitions based on DAS scores are rather loose and allow

presence of residual clinical disease activity. In fact, "remission" likely resembles different conditions varying in their risk to relapse to the original disease state – in this case, active RA (Figures 1 and 2). DMARDs usually reduce the inflammatory burden of RA and ideally bring patients from one of the three clinical activity states (low, moderate, high) into "remission". In this context, immediate recognition and treatment of early RA is of paramount importance to achieve disease control, before extensive synovitis and joint destruction have occurred. Despite a virtual absence of signs and symptoms of disease, RA patients considered to be in clinical remission may nevertheless have subclinical inflammation and/or the autoimmune changes related to RA (Figure 1). Therefore, a more cautious approach with tapering existing DMARDs rather than abruptly discontinuing them is generally recommended. Apart from mere clinical remission in terms of joint manifestations, imaging/serologic remission may have to be considered, where also synovitis has completely ceased. The lower relapse rates observed in patients with normal ultrasound examination and in those with negative serum biomarkers of inflammation score support the biological relevance of this concept. Finally, and probably most rarely, a reset of autoimmunity in RA may occur ("immunological remission"), which is clearly still the most challenging treatment goal (Figures 2). Taken together, these concepts suggest that studies using a stricter definition of "remission" based on (i) the true absence of clinical signs of inflammation, (ii) the normalization of serum and imaging marker of inflammation and potentially also (iii) the disappearance of autoantibodies (seroconversion) are needed as they could allow to achieve even higher rates of drug-free remission and even cure of disease.

Tapering and stopping DMARDs will also allow better understanding of the pathways and markers that indicate resolution of inflammation in RA. Little is now known about these processes, which counteract pro-inflammatory cytokines and allow reestablishment of

homeostasis in the joint. Tapering studies have taught us that, in some patients with RA, homeostasis appears to be restored since such patients do not relapse if drugs are withdrawn. Hence, the whole concept of cure of RA will benefit from data from tapering studies. Many issues require resolution: For instance, little is known about progression, arrest or regression of structural bone damage during tapering of DMARDs. Conceptually, suboptimal control of disease could result in progression of damage. Currently, no data support such a scenario but information on structural progression in tapering studies is limited. In this context, it is reassuring that some data suggest that tapering of drugs does not lead to enhanced damage, especially if appropriate monitoring occurs and treatment adjusted. Hence, Tanaka and colleagues showed no progression of radiographic damage when patients stopped TNF inhibitors in their HONOR study (24). Re-initiation of therapy, if relapse occurs, seems important in this context. As treatment is usually initiated promptly after relapse, patients are not exposed to significant periods of high disease activity which may be required to trigger damage. In addition, data several studies such as DOSERA, DRESS, RETRO and STRASS suggest that reintroduction of the original treatment regimen allows successful re-induction of remission in virtually all patients with relapses. Future analysis of imaging data including ultrasound, MRI and CT are warranted to finally answer these questions.

Other questions concern the concept that even patients in remission may benefit from ongoing therapy due to „extraarticular“ actions of drugs, such as methotrexate on the cardiovascular system potentially leading to less mortality. Hence, tapering may require true remission of inflammation rather than absence of symptomatic joint disease. In consequence, biomarkers need to be developed that allow distinguishing true absence of inflammation from the absence of symptoms. These considerations are also important in light of the rather short follow-up periods of current tapering studies, which are usually confined to one year. For long-term

drug-free remission, however, true absence of inflammation may become increasingly important. Finally, it remains unclear whether patients who have already experienced a relapse and in whom DMARD treatment has been reintroduced should undergo another tapering attempt.

Conclusion

In summary, evidence from a series of clinical studies suggests that tapering and stopping DMARDs is a feasible strategy in a subset of RA patients who have entered clinical remission. Present data are astonishingly consistent in showing that some remission patients are able to successfully taper and/or withdraw treatment without experiencing flare, as a loss of complete control of disease activity, in the subsequent observation period. However, the ideal profile of the patient who profits most from de-escalation of DMARD treatment remains to be defined. Complete withdrawal of DMARDs may only be possible in the presence of full remission. The search for biomarkers for assessing persistent subclinical disease activity and predicting flare risk is on-going and substantial progress has been achieved by using imaging and serum markers to identify patients with low or high relapse risk. Still, more efforts are needed in studying this growing population of remission patients in order to facilitate the decision making for patients and physicians when and how to taper and stop their treatment. At the moment, it is at least reassuring that reintroduction of DMARDs usually allows rapid regain of the remission status and hence can be pursued without substantial concern if appropriate monitoring is ascertained (15).

Key research points

- Finding biomarkers, which allow better prediction of relapse risk in patients tapering DMARDs

- Defining the characteristics of patients entering long-term drug-free remission
- Disentangling the biological relevance of clinical, imaging/serologic and imunnological remission in rheumatoid arthritis patients
- Defining the impact of tapering and stopping of DMARDs on the structural progression
- Improving knowledge that reintroduction of original DMARD regimen is effective to rapidly regain remission after relapse

Competing interests

GS has received speakers and consultancy fees from Abbvie, Bristol-Myers, Celgene, Chugai, Crescendo, GlaxoSmithKline, Eli Lilly, Novartis, Roche and UCB. PE has received speakers and consultancy fees from Abbvie, Bristol-Myers, Eli Lilly, MSD, Novartis, Pfizer, Roche, Samsung, Sandoz and UCB. YS has received speakers and consultancy fees from Abbvie, Chugai, Daiichi-Sankyo, Bristol-Myers, Mitsubishi-Tanabe, Astellas, Takeda, Pfizer, Teijin, Asahi-kasei, YL Biologics, Sanofi, Janssen, Eli Lilly, GlaxoSmithKline and research grants from Mitsubishi-Tanabe, Takeda, Daiichi-Sankyo, Chugai, Bristol-Myers, MSD, Astellas, Abbvie and Eisai. GB has received speakers and consultancy fees from AbbVie, BMS, MSD, Pfizer, UCB and Roche. EN has received speaker fees from Abbvie, Roche, BMS, Pfizer, UCB and Novartis. DP has received speakers and consultancy fees from Biorad Laboratories, Biogen Idec, Crescendo and Pfizer. BF has received speakers and consultancy fees from AbbVie, BMS, Celgene, Hospira, MSD, Nordic Pharma, Novartis, Pfizer, Roche, Sanofi, SOBI, UCB and research grants from Pfizer, MSD and Roche. RVV has received speakers and consultancy fees from Abbvie, Biotest, Bristol-Myers, Celgene, Crescendo, GlaxoSmithKline Eli Lilly, Janssen, Merck, Novartis, Pfizer, Roche, UCB and Vertex as well as research grants by Abbvie, Amgen, BMS, GlaxoSmithKline, Pfizer, Roche and UCB.

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Figure Legend

Figure 1. From active disease to cure

Disease modifying anti-rheumatic drugs (DMARDs) debulk inflammation in patients with rheumatoid arthritis, ideally shifting them from high (HDA), moderate (MDA) or low (LDA) activity to remission. Remission can resemble different states: Immunological remission (IMUR) characterized by an immunological reset and seroconversion with respect to autoantibodies, which is rare; imaging/serologic remission (I/SR) resembling true absence of inflammation (synovitis) measured by either imaging or serum biomarkers; and simple clinical remission (CR) indicating the virtual absence of signs and symptoms in the joints. These states may differ considerably in their likelihood to relapse, with IMUR having the highest chance for cure, followed by I/SR and CR. Thickness of arrows indicate the respective likelihoods to move to cure or disease relapse.

Figure 2. Shell model of remission states in rheumatoid arthritis

Remission (green) can have different qualities. The common denominator of remission is the absence (or at least reduction to very low levels) of symptoms related to arthritis. This state is usually assessed by composite clinical scores such as disease activity scores (DAS) 28 and 44, simplified disease activity index (SDAI) or fulfilment of the American Colleague of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) remission criteria. In addition, deeper remission states such as (i) imaging/serological remission defined by the additional absence of synovitis and osteitis in imaging and/or serological inflammation markers such multi-biomarker disease activity (MBDA) or on top of that (ii) immunological remission characterized by seroconversion from positive into negative rheumatoid factor (RF) and/or antic-citrullinated protein antibody (ACPA) testing can be distinguished.

Table 1. Key messages for the practice

1. Eligible patients

DMARD tapering should be considered if patients (a) fulfil standardized clinical criteria for remission state (DAS28 <2.6; DAS44 <1.6; SDAI <3.3; CDAI <2.8;ACR/EULAR remission) (b) show sustained remission for at least 6 months documented by appropriate disease activity instruments at three sequential visits and (c) use stable DMARD treatment with respect to type and dose of DMARDs over the last 6 months and (d) do not use glucocorticoids to maintain their remission state

2. Risk and predictors for relapse

Some RA patients can successfully taper or even stop DMARD treatment. Anti-citrullinated autoantibody negativity and presence of "deep" remission such as absence of ultrasound synovitis and/or normal serum markers of inflammation are associated with higher chances to achieve drug-free remission.

3. Mode of DMARD tapering/withdrawal

Both direct DMARD withdrawal and dose tapering protocols were studied. Patient need to be informed about the mode, how to taper their DMARD. For practical reasons gradual withdrawal with an initial dose tapering phase may be preferable over immediate withdrawal. This concept applies to both biological and synthetic DMARDs.

4. Monitoring and relapse management

Particularly when starting DMARD tapering and/or withdrawal regular monitoring needs to be scheduled in order to early detect relapses. Patients need to be instructed about the risks of relapse as well as the way to manage them. Re-introduction of the former DMARD regimen has shown to re-capture remission in virtually all patients relapsing.

Table 2. DMARD tapering/withdrawal studies

Author	Acronym	Type	Arms*	N+	ERA/RA	DMARDs	MODE	IC	Type	SUS	REM#	FO	Ref
Tanaka et al	HONOR	UC	2	75	RA	ADA	STOP	REM	DAS28<2.6	>6m	48%	1	24
Saleem et al	-	UC	1	47	ERA/RA	TNFi	STOP	REM	DAS28<2.6	>6m	15-59%	2	25
Brocq et al	-	UC	1	21	RA	TNFi	STOP	REM	DAS28<2.6	>6m	25%	1	26
Aguilar-Lonzano et al	-	UC	1	45	RA	TOC	STOP	REM	DAS28<2.6	-	44%	1	28
Naredo et al.	-	UC	1	77	RA	TNFi	TAP	REM	DAS28<2.6	>6m	55%	1	50
Iwamoto et al.	-	UC	1	40	RA	TNFi,TOC	STOP	REM	DAS28<2.6	-	60%	0.5	51
Alivernini et al	-	UC	1	42	RA	TNFi	TAP/STOP	REM	DAS44<1.6	>6m	61%	0.5	52
Tanaka et al	RRR	UC	1	102	RA	IFX	STOP	LDA	DAS28≤ 3.2	>6m	55%	1	23
Van der Maas et al.	-	UC	1	51	RA	IFX	TAP	LDA	DAS28≤3.2	>6m	16-45%	1	27
Nishimoto et al	DREAM	UC	1	187	RA	TOC	STOP	LDA	DAS28≤3.2	-	13%	1	29
Van Herwaarden et al	-	UC	1	22	RA	TOC	TAP	LDA	DAS28≤3.2	-	55%	0.5	30
Quinn et al.	20TNF	SA	2	20	ERA	IFX	STOP	REM	-**	-	70%	1	31
Klarenbeek et al.	BEST	SA	1	243	ERA	SD/IFX	TAP	REM	DAS44<1.6	>6m	23%	2	34
Nam et al.	IDEA	SA	1	14	ERA	ETA	STOP	REM	DAS44<1.6	>6m	42%	0.5	38
Nam et al.	EMPIRE	SA	1	9	EA/ERA	IFX	STOP	REM	TJC0/SJC0	-	25%	1	39
Huinzinga et al.	ACT-RAY	SA	1	238	RA	TOC	STOP	REM	DAS28<2.6	-	14%	1	41
Detert et al.	HIT-HARD	SA	1	155	ERA	ADA	STOP	-++	-++	-	89%	1	36
Smolen et al.	OPTIMA	SA	2	207	ERA	ADA	STOP	LDA	DAS28≤3.2***	-	66-81%	1	35
Soubrier et al.	GUÉPARD	SA	1	69	ERA	ADA	STOP	LDA	DAS28≤3.2	-	33%	<1	37
Emery et al	AVERT	SA	1	222	ERA	ABA	STOP	LDA	DAS28≤3.2***	-	15%	1	40
Ten Wolde et al.	-	RCT	2	285	RA	SD	STOP	REM	ACR	>6m	62%	1	21
Ahern et al.	-	RCT	2	38	RA	SD	TAP	REM	TJC0/SJC0	>6m	21%	0.5	22
Haschka et al.	RETRO	RCT	3	101	RA	All##	TAP/STOP	REM	DAS28<2.6	>6m	48-61%	1	15
Emery et al.	PRIZE	RCT	3	193	ERA	MTX/ETA	STOP	REM	DAS28<2.6	-	24-63%	0.5	42
Fautrel et al.	STRASS	RCT	1	137	RA	TNFi	TAP	REM	DAS28<2.6	>6m	74%	1.5	43
Smolen et al.	PRESERVE	RCT	3	604	RA	ETA	TAP/STOP	LDA	DAS28≤3.2	>6m	43-79%	1	44
Van Vollenhoven et al	DOSERA	RCT	3	91	RA	ETA	TAP/STOP	LDA	DAS28≤3.2	>6m	52%	1	45
Van Herwaarden et al.	DRESS	RCT	2	180	RA	ADA, ETA	TAP	LDA	DAS28≤3.2	-	88%	1.5	46

UC, uncontrolled study; SA, subanalysis of randomized controlled trial; RCT, randomized controlled trial; ERA, early rheumatoid arthritis; EA, early arthritis; RA, established rheumatoid arthritis; DMARDs, disease modifying anti-rheumatic drugs; ABA, abatacept; ADA, adalimumab; ETA, etanercept; IFX, infliximab; SD, synthetic DMARDs; TOC, tocilizumab;STOP, withdrawal of DMARD; TAP, dose tapering of DMARD; IC, inclusion criterion; LDA, low disease activity; REM, remission; DAS 28, disease activity score 28 (based on erythrocyte sedimentation rate if not stated otherwise); TJC, tender joint count; SJC, swollen joint count; ARA, American Rheumatism Association criteria from 1981; SUS,

sustained remission of at least 6 months (6m) before tapering/stopping of DMARDs, FO, follow up time after tapering/stopping in years; (-) means not defined or less than 6 months; *number of treatment arms during the tapering phase; [+]number of patients subjected to tapering; [#]% of patients with successful tapering; **not defined but most in DAS2.6 remission; [++]no specific definition; [##] all conventional DMARDs as well as TNFi and TOC; [***]DAS28 based on C-reactive protein