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Review

Predicting successful tapering of biologic therapy for patients with rheumatoid arthritis in remission – Why are we still using clinical remission criteria to inform decisions?

Hanna L Gul, Leticia Garcia-Montoya, Laurence M Duquenne, Peta E Pentony, Luiz E Oliviera and Paul Emery*

Leeds Institute for Rheumatic and Musculoskeletal Medicine, Chapel Allerton Hospital, Leeds, UK

****Corresponding author***
Paul Emery, MA, MD, FMed.Sci
Leeds Institute for Rheumatic and Musculoskeletal Medicine
Chapel Allerton Hospital
Leeds, UK
E-mail: p.emery@leeds.ac.uk

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ABSTRACT

Remission is the optimum treatment target for patients with rheumatoid arthritis. With the advent of biologic therapies, and the use of treat to target strategies, many more patients are achieving remission. Once a patient has achieved a period of sustained remission, there is little to guide subsequent management and patients usually continue treatment long-term. This may be inappropriate. Recent evidence suggests that some patients may be able to reduce or even stop therapy however, the ideal patient profile is yet to be determined. Potential predictors have been identified, however have not entered routine clinical practice. There is a need for robust biomarkers to facilitate the prediction of successful tapering.

KEY WORDS: Rheumatoid arthritis (RA); Remission; Tapering.

ABBREVIATIONS: RA: Rheumatoid Arthritis; DAS: Disease Activity Score; T2T: Treat to Target; LDA: Low Disease Activity; ACPA: Anti-Citrullinated Protein Antibody; EULAR: European League Against Rheumatism; TNFi: Tumour Necrosis Factor inhibitors; RCTs: Randomised Controlled Trials.

BACKGROUND

Rheumatoid arthritis (RA) affects up to 2% of individuals worldwide and is a chronic, immune-mediated systemic disease, characterised by a symmetrical inflammatory polyarthropathy.[1] The primary pathology is synovitis, which results in joint destruction.[2] This occurs as a result of immune system dysfunction, in which loss of self-tolerance triggers antibody production and cytokine-mediated synovial proliferation.[3]

Sub-optimal treatment of RA results in substantial joint pain, disability, adverse social consequences and increased mortality compared to the general population.[2] Furthermore, RA is a disease of considerable socioeconomic burden.[4,5] Since there is no cure, the optimum treatment target is remission,[6] classically defined as a disease activity score (DAS28) of ≤2.6 (failing this, a state of low disease activity (LDA, DAS28≤3.2)).[7] This involves the rapid control of inflammation to prevent structural damage and maintain function. In clinical practice this is usually achieved through treat to target (T2T) strategies, which employ strict monitoring of disease activity using composite measures e.g., DAS28 and focus on successive escalation of immunosuppressive agents (conventional synthetic and biologic disease modifying drugs (csDMARDs and bDMARDs respectively), used alone or in combination).[6,8,9]

Although, T2T strategies have led to significant improvements in patient outcomes,[10-12] there is little to guide clinical practice on how to manage remission once it has been achieved. Ap-

proximately 20-40% of patients achieve sustained remission (6 months or longer) following treatment.[13] Typically these patients continue their immune-modulatory treatment long-term, which may be inappropriate. For those who achieve sustained DAS28 remission, clinical experience, combined with data from de-escalation and registry studies suggest that treatment may be optimised through either dose tapering (de-intensifying treatment) or discontinuation, whilst maintaining the same treatment goals.[13-15] However, it is unclear whether successful drug cessation is a consequence of the natural disease course or is influenced by treatment regime. Pathogenetic and environmental factors e.g. shared epitope status, anti-citrullinated protein antibody (ACPA) positivity and smoking status may also be significant contributors to the outcome.[16]

Both the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) recommend tapering of treatment after the achievement of remission not LDA due to the presence of residual inflammation. They advise a specific sequence of reduction, based on cost and effectiveness (starting with corticosteroids, bDMARDs then csDMARDs). They also highlight that the basis of this decision should be a combination of patient preference and physician judgement. However, there is a lack of consensus on how to deliver this approach.[8,17] To be able to offer tapering or discontinuation of bDMARDs, clinicians need to be able to identify the ideal patient profile, using robust biomarkers which can predict successful tapering.[18]

In addition to describing the rationale for tapering and providing a summary of existing studies, this review aims to present evidence for the use of more objective biomarkers to predict successful tapering and potentially discontinuation of bDMARDs (with a focus on tumour necrosis factor inhibitors, TNFi) for RA patients in stable remission.

WHY TAPER?

The concept of dose tapering (towards discontinuation), for bDMARDs is appealing for several reasons. First, maintaining full doses of treatment in patients who are well could be regarded as over-treatment, potentially subjecting them to an unnecessary risk of toxicity. Although the adverse effects of bDMARDs reported in clinical trials is generally low, they can pose a significant safety risk of adverse reactions particularly infection and malignancy (dose-dependent) plus neurological and cardiovascular morbidity.[19,20] This is particularly relevant for inhibitors TNFis. bDMARDs are also associated with high costs, being more expensive than csDMARDs.[21,22] From a patient's perspective, patients who are well frequently express the desire to reduce their treatment or have a 'drug-holiday' due to the burden of taking tablets/self-injecting and concerns regarding long-term side-effects.[23,24] This frequently leads to poor adherence to therapy, with patients self-discontinuing treatment in 15% of cases.[25] This poses the risk of increased morbidity through subsequent loss of disease control when not based on predictive criteria.

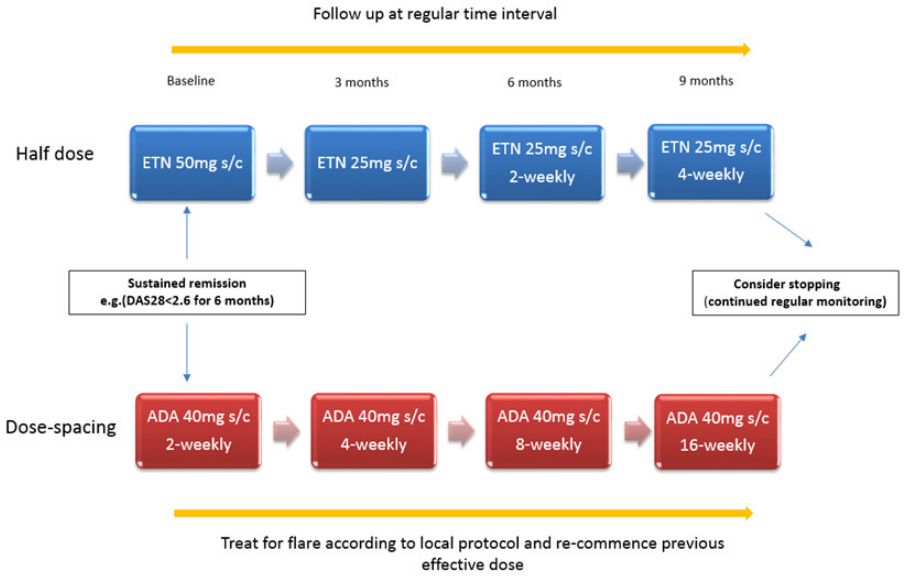
There is also a separate pharmacodynamic rationale supporting targeted dose-tapering of bDMARDs in a proportion of patients. bDMARDs classically manifest their action after achieving a minimal serum drug concentration, which is maintained over a specific time interval between two consecutive administrations. The half-life and volume of distribution of the drug may vary between patients, therefore the dose required to achieve the minimum serum drug concentration can also vary.[26] Therefore, patients should be able to taper down until a minimum effective concentration is reached. The minimum serum drug concentration can also vary between patients; thus each patient is thought to have their own 'dose-response curve'. Several variations may be possible, as described by Fautrel et al. Conceptually, some patients have an average response curve, meaning that they could consider tapering as the clinical effect is not related to treatment. Others may have a good response to a lower dose (left-shift), therefore may be subject to over-treatment using current treatment strategies or a good response to a higher dose only (right-shift). To complicate matters, some patients may achieve only a partial response, or no response at all, therefore potentially subjecting patients to an increased risk of morbidity due to lack of response. In this case, it may be plausible to consider switching to an alternative drug.[18,26] A potential issue to consider when tapering is the 'nocebo' effect, in which a reduced dose is perceived as inferior, thus resulting in a perceived deterioration of disease control. There is also a risk of attribution, when a disease flare following dose-tapering is attributed to the lower dose when, in fact it may be a result of the natural disease course.[21]

Conversely, there is the danger that tapering of therapy leads to more frequent disease flares, with impact on a patient's quality of life and function. There is also the concern that disease control may not be re-captured with the re-commencement of prior therapy, thus accelerating disease progression.[21] Reassuringly, however, evidence suggests that control is re-captured in approximately 80-100% of patients within 3-6 months[18] and is not associated with more adverse events or higher immunogenicity.[27,28]

Overall, it is felt that tapering, especially when evidence based, should represent a better risk-benefit profile, maintaining clinical response with more targeted and a shorter duration of therapy, whilst reducing the risk of medication-induced side-effects and adverse outcomes, whilst being cost-effective.

HOW TO TAPER?

Dose-tapering/discontinuation of bDMARDs has been tested in RA patients in both observational studies and randomised controlled trials (RCTs). Several possible strategies have been employed including drug withdrawal upon achievement of treatment target and fixed-dose reduction by either halving the dose or increasing the time interval between doses (dose-spacing) (Figure 1). Dose spacing is generally more favourable and practical, since half-doses are not always available. This is true for pre-filled syringes. A half-dose strategy may be more feasible for



*ETN=Etanercept; ADA=Adalimumab; S/c=Subcutaneous; DAS28=Disease Activity Score.

Figure 1: An Example of Tapering for Clinical Practice by Fixed-Dose Reduction, by Half Dosing or Dose-Spacing.

IV therapy or where half doses are available (e.g., Etanercept/ Enbrel). Another possible strategy is a step-wise dose-reduction of treatment until the drug is discontinued or a disease flare occurs (disease activity guided).[18] Fixed-dose reduction and open-label disease activity guided dose optimisation have largely been found to be non-inferior to continuation.[29-32] Disease activity guided tapering is considered to be the best strategy for clinical practice. In general, direct withdrawal is considered inferior to other methods.[18]

Drug Withdrawal/Stopping

Several studies have analysed the effects of bDMARD withdrawal in RA patients, the majority of which involve TNFis. They predominantly include patients with early RA and active disease who underwent remission induction with a bDMARD in order to achieve remission or LDA, followed by treatment withdrawal.[6] In the majority, direct discontinuation of a bDMARD leads to disease flare in many patients[30,33-35] however; a small proportion (3.6-22%)may achieve drug-free remission.[16]

The first bDMARD withdrawal study by Quinn et al studied 20 early RA patients in a double-blind RCT. They demonstrated that treatment with methotrexate (MTX) plus infliximab (IFX) produced rapid improvements in disease activity, physical function and MRI synovitis scores compared to MTX alone. IFX was stopped after 1 year. 70% of patients had sustained clinical response and maintenance of quality of life and function at 12 months.[36] Similarly, the RRR study aimed to investigate whether IFX (concomitant MTX) could be stopped in patients with persistent LDA (DAS28<3.2 for >24 weeks). Out of 102 patients, 56% discontinued IFX and 43% reached DAS28 remission within 1 year.[37]

The IDEA study, a 78 week, double-blind RCT, compared remission induction with MTX plus IFX versus MTX plus high-dose IV methylprednisolone for early RA patients**.** Those in DAS44 (<1.6) remission at 26 weeks stopped IFX. MTX plus IFX was not statistically superior to MTX plus IV steroid in a T2T approach. 76% of patients that discontinued IFX remained in remission until the end of the study.[38]

In the Hit Hard study, a double-blind RCT, very early RA patients were randomized 1:1 to receive MTX plus placebo versus MTX plus adalimumab (ADA) for 24 weeks, followed by ADA discontinuation, irrespective of disease activity. MTX was continued for 6 months. Remission rates at week 48 were significantly higher in the ADA group (43%, p=0.009). MTX maintenance therapy was effective in a significant proportion of patients for sustaining remission following cessation of ADA. Radiographic progression (assessed by the Sharp-van der Heijde score) was slightly higher in the MTX group.[39] A similar study (OPTIMA), investigating the withdrawal of ADA for patients in stable LDA (DAS28CRP<3.2) at 26weeks found that patients were more likely to be in LDA (91 *vs*. 81%) and remission (86 *vs*. 66%) at 52 weeks if they continued ADA (compared to stopping).[40] These results are supported by an observational study of ADA discontinuation for established RA patients (following open-label MTX plus ADA for 52 weeks). 85% were in LDA and 75% in remission according to DAS28 at entry. At 1 year, patients were more likely to be in LDA (91 *vs*. 74%) and remission (76 *vs*. 60%) if ADA was continued. Increase radiographic progression was noted for the MTX monotherapy group, during the initial RCT.[41]

In the EMPIRE study, the efficacy of ETN plus MTX versus MTX monotherapy (plus placebo) was compared for patients with early inflammatory arthritis. Patients continued treatment until they had no tender or swollen joints for 26 weeks and at 52 weeks, all patients stopped ETN and placebo. MTX was discontinued if patients were in DAS28 remission for 12 weeks. Early treatment with ETN did not increase the chance for drug-free

remission.[42]

For non-TNFis, the CERTAIN study was a small observational study involving 23 patients initially treated with certolizumab pegol (CZP) and MTX. CZP was discontinued in patients who achieved remission according to the clinical disease activity index score (CDAI ≤2.8). Only 18% remained in remission at 7 months.[43] The DREAM study was a single-arm study in which 187 patients with established RA were initially treated with tocilizumab (TCZ) monotherapy. TCZ was discontinued at enrollment if patients were in DAS28 remission/LDA. At 1 year follow up only 9% were in remission and 13% LDA.[44] In the AVERT study, 186 early RA patients (initially treated 1:1:1 with subcutaneous abatacept (ABA) plus MTX, ABA monotherapy or MTX monotherapy for 12 months) discontinued ABA once LDA was achieved. At 6 months, more patients were in remission in the ABA groups compared to the MTX group (25-28 versus 17%).[45]

Dose Reduction or Spacing

The PRIZE study is a double blind RCT of ETN versus standard of care in early RA patients. Patients received ETN 50 mg/week plus MTX to induce remission (DAS28ESR) over 52 weeks. Over 60% achieved remission. Patients were subsequently randomized to receive either half dose ETN plus MTX, placebo plus MTX or placebo alone for 39 weeks. Remission rates were 62%, 40% and 23% respectively, demonstrating that the level of treatment reduction was associated with loss of remission in this cohort. Withdrawal of ETN was possible in less than half of patients and drug-free remission in a quarter of patients only.[46]

In the PRESERVE study, established RA (n=604) patients receiving ETN 50 mg/week (with MTX) were randomized to either stop, taper (25 mg/week) or continue treatment based, on the achievement of LDA (DAS28). After stopping ETN, 43% of patients remained in LDA at 1 year (83% and 79% for the continuing and tapering groups respectively). Radiographic progression was reduced in the ETN groups. It was found that stopping ETN was associated with significant progression of joint damage.[30]

DOSERA is a double-blind RCT in which established RA patients receiving either ETN + MTX were randomized to either continue full dose treatment or reduce to half the dose or stop. After 1 year, 52% of patients on full dose and 44% on half dose maintained LDA. Only 13% of those who stopped maintained LDA.[33]

In the DRESS study,180 patients with established RA who achieved LDA (DAS28ESR)> 6 months on MTX plus either ETN or ADA were randomized 2:1 to gradually taper the bDMARD by increasing the time interval versus continuing treatment. After 18 months, the tapering strategy was shown to be non-inferior with respect to increase in flare (DAS28ESR change>1.2, or DAS28ESR increase of 0.6 and current DAS-28ESR ≥3.2).[32]

The STRASS study investigated the possibility of DAS-driven dose-spacing of TNFi injections, according to the T2T strategy. Patients with established RA in DAS28ESR remission (<2.6) over 6 months were treated with either ADA or ETN (alone or in combination with csDMARD). 137 patients were randomized to continue full dose TNFi or spacing of the dosing interval. In the case of loss of remission, the last dosing regimen was re-introduced. 39% of patients were able to stop the TNFi in the tapering arm, whilst maintaining remission. 35% could taper, however not discontinue treatment. The others resumed full treatment.[31]

In the BeSt study, four dynamic treatment strategies were compared for the induction of remission for patients with sustained remission (DAS44 <1.6 over 6 months). DMARDs were tapered and stopped, with bDMARDs stopped first, followed by csDMARDs: arm 1, sequential monotherapy (n=126); arm 2, step up combination therapy (n=121); arm 3, initial combination therapy with prednisolone (n=133) and arm 4, initial combination therapy with MTX and IFX. Approximately half (48%) of patients reached remission. Drug-free remission was achieved in 21% in arm 1, 17% in arm 2, 16% in arm 3 and 27% arm 4.74% relapsed, the majority of which regained remission when introducing the last therapeutic regimen.[47,48]

The RETRO study is an RCT comparing treatment strategies in established RA patients in DAS28ESR remission over 6 months. Patients were randomized to either continue csDMARDs and bDMARDs, taper by 50% or stop after a 6 month tapering phase. Relapse rates were low in the continuation arm (16%) and higher in the tapering (38.9%) and stopping (52%) arms. More than half of patients maintained their remission state.[49]

In the AGREE study, 108 patients with early RA in DAS28 remission were randomized 1:1 to standard versus half dose IV ABA. They initially received treatment in combination with MTX for 1 year. Remission rates were slightly higher in the full dose arm (47 versus 36%).[50]

Although, general conclusions can be drawn from these studies, it is important to recognize that several limitations exist, contributing to variability in outcomes. Considerable heterogeneity exists in terms of the methods used, criteria used for patient selection and definitions of flare/sustained remission. In addition, most studies have used the 1987 ACR classification criteria[51] for RA which consequently may have led to misclassification of some patients.[16]

WHO AND WHEN TO TAPER?

Despite the recognised benefits of bDMARD tapering and the evidence to support its implementation in a proportion of patients, there is a paucity of evidence to guide clinicians on such a change in treatment focus.[52]

Logically, tapering should only be applied in patients who have achieved their target treatment goal.[18] As demonstrated by the existing studies, the best target population for tapering are pa-

tients in a sustained stable state, ideally remission, defined clinically (based on clinical experience and data from clinical trials).[31-33,49] The majority of clinical trials exploring bDMARD discontinuation or tapering have done so based on patients achieving sustained DAS28 LDA or remission over a period of 6 months.[18] Current evidence suggests that patients in DAS28 remission are heterogeneous in terms of clinical, immunological and imaging characteristics, with a proportion of patients still displaying clinical signs and symptoms of inflammation and sub-clinical synovitis on US.[53] Furthermore, radiographic progression has been demonstrated in some patients.[54] It has therefore been suggested that DAS28 may actually represent minimal disease activity rather than a true state of remission and is not the best selection criteria for tapering.[6] Most studies of bDMARD tapering were conducted prior to the development of the ACR/Boolean remission criteria however, the RETRO study did not find any additional benefit in using this stricter definition to identify patients suitable for csDMARD/bDMARD tapering,[49] whereas PRIZE did.[46]

Consequently, there is a need to define remission more precisely to reflect inflammation at the site of pathology. There is an abundance of literature proposing both imaging and immunological biomarkers, either alone or in combination to characterize a true remission state however, none have entered routine clinical practice. The notion of 'deep' remission, defined clinically as a DAS28<2.2 has been suggested and thought to reflect the absence of biological inflammation[55] (not routinely used in practice). More specifically, the notion of molecular/immunological remission (RF or ACPA negativity or evidence of seroconversion) has been proposed. Recently, the concept of deep remission has been introduced to more closely define a true state of remission of inflammation, which involves the combined achievement of clinical, imaging, serological (normal inflammatory markers) and negative autoantibodies i.e., a state where synovitis has been completely suppressed.[6]

Further work is needed to develop a uniform set of remission criteria using validated measures/biomarkers, to help identify the best target population for tapering. One must also keep in mind the transferability of such measures to clinical practice.

PREDICTORS OF SUCCESSFUL TAPERING/DISCONTINUATION

In order to define the remission state more objectively, it is critical to identify independent predictors of disease relapse to help inform tapering decisions. Response prediction is well established in other medical specialties e.g., Oncology, where Her2 receptor expression is used to assess response to trastuzamab in breast cancer.[56] Although several potential biomarkers have been proposed, to date, no single clinically useful baseline marker has been identified to predict successful tapering of bDMARDs.[57]

Clinical and Demographic Predictors

A number of clinical predictors have been identified which may aid the decision making process. Longer disease duration has been shown to be a crucial risk factor for progressive disease.[52] Specifically, the HONOR study demonstrated that shorter disease duration was a baseline predictor for ADA free remission.[41] This is supported by the preliminary analyses from the POET study.[58]

These findings support the 'window of opportunity' hypothesis[59,60] that aggressive therapy in the early stage of disease can lead to improved outcomes and sustained benefit,the likely reason being that there is potential reversibility of autoimmunity in the early stages of disease. It is therefore regarded that remission induction during this phase increases the chance of successful tapering of bDMARDs to maintenance therapy. This reversibility of autoimmunity decreases over time, contributing to chronic synovitis, lasting cytokine abnormalities and structural progression. To this end, the efficacy of therapies may be less for patients with chronic disease, providing only moderate benefit and less of a chance of drug free remission.[16] This concept is supported by the observation that therapeutic response in the first 3 months of treatment can predict the potential for achieving remission later.[61]

Baseline disease activity and the quality of clinical remission has also been shown to be predictive of successful discontinuation of TNFis.[55] Specifically, the cut-off points in the RRR and HONOR studies was a baseline DAS28 score of 2.22 and 1.98 respectively, supporting the notion that 'deep remission' i.e. no residual inflammation, is necessary for successful discontinuation.[37,41] In the OPTIMA study, good baseline functional status at discontinuation of ADA, as assessed by standardized patient reported outcome measures, was found to predict sustained low disease activity.[40] El Miedany et al also found that worsening functional disability is associated with disease flare.[55] Similar findings were found in the AVERT study.[45] In addition, longer remission duration, longer duration of TNFi therapy, non-smoking status, negative shared epitope, younger age and female gender have been shown to be predictive of successful discontinuation of TNFis.[37,47,62] Barral et al recently conducted a study to develop a predictive score for successful TNFi tapering, based on clinical assessments. They found that baseline HAQ and CRP were independent predictors. They have developed a composite score with an AUC of 0.829 and 100% specificity however, this needs validation.[63]

The type of bDMARD used may also influence the ability to successfully taper. No great differences have been identified between TNFis however; the DREAM study demonstrated high relapse rates for patients treated with tocilizumab. It has been suggested that standardised treatment regimens may in fact over treat a proportion of patients by using the maximum effective dose at group level.[18,44]

Imaging Predictors

Physical examination is known to have a low sensitivity for the detection of mild synovitis, such as that found in clinical remission, however,[64] musculoskeletal (US) has proven to be an excel-

lent tool to identify subclinical inflammation.[53]

The role of imaging in Rheumatology has gained significant interest since several studies found an association between residual synovitis, the risk of relapse and structural damage. One meta-analysis[65] describes that 44% of patients considered to be in clinical remission had synovial hypertrophy with PD signal when assessed with US. In accordance with other studies, these finding appear to be the reason why radiographic progression occurs in many cases.[66]

Since US has demonstrated to be a reliable method of predicting relapse in patients in clinical remission,[67] there is interest in using this tool to identify patients who may taper biologic therapy. A prospective study from Italy demonstrated that PD synovitis was a good predictor of relapse within six months. They also discovered that the absence of PD signal was associated with a more stable remission state in over 90% of cases.[68]

Five main studies have assessed the value of musculoskeletal US during tapering of bDMARDs in RA. Iwamoto et al followed 42 patients with established RA in DAS28 remission after discontinuation of bDMARD. They confirmed the superiority of PD US over DAS28 concerning relapse prediction and also found that grey scale synovial hypertrophy has a predictive value for flare.[69] Naredo et al shared similar findings.[70] They reported that PD synovitis was able to predict failure of bDMARD tapering for RA patients in remission. They also highlight that the risk of relapse is increased with a higher baseline DAS28 score. Alivernini et al affirmed that PD synovitis correlated with the histological characteristics of synovial tissue in long standing RA patients in clinical remission. Furthermore, they suggest that US, could be used in combination with ACR/EULAR remission criteria to identify patients likely to achieve drug-free remission.[71]

El Miedany et al concluded that assessment with musculoskeletal US was superior to DAS28 in predicting relapse for RA patients in remission. Both PD synovitis and synovial hypertrophy, assessed by grey scale changes were independent predictors of relapse. In addition, ACPA positivity and worsening functional disability were helpful when combined with US.[55] In contrast to the previous studies, preliminary analyses from the POET study have demonstrated that US was only a modest predictor of flare in the individual patient when combined with clinical measures; however it was a better predictor at the group level.[72] Ultrasonography is not the only imaging technique capable of assessing subclinical activity; several studies have confirmed that bone marrow oedema on magnetic resonance imaging (MRI) is predictive of structural damage in the joint.[73,74] Brown et al were the first to demonstrate that subclinical inflammation on MRI and ultrasound could predict poor radiographic outcomes.[54] Krabben et al[75] had similar findings and Ostergaard et al found an association between synovial membrane volume (determined by MRI) and the rate of progression with bone destruction.[76] In contrast, a prospective study by Foltz et al did not support the finding that MRI can predict disease progression (only PD could). Nevertheless, they believe that the use of low-field MRI and short delay between radiographic assessments could have biased the results.[77] In spite of promising outcomes, MRI has not entered routine practice due to its elevated cost.

Concerning other imaging techniques, computed tomography (CT) has generally been discarded as a tool to monitor disease activity as it requires high doses of radiation. On the other hand, X-rays generally do not seem to be useful for predicting progression as they give information of past inflammation. By the time erosions are seen on X-ray, structural damage has already occurred.[76] Interestingly, a recent systematic reviewby Tweehuysen et al[78] found that radiographic erosions, as assessed by the Sharp Van der Heijde score was weakly predictive of progression probably by identifying more severe or longer duration disease.

In light of these findings, the use of sensitive imaging assessments particularly US, either alone or in combination with clinical assessments could assess remission more objectively and represent a starting point to identify the best candidate for bDMARD tapering.[79,80] This strategy is yet to enter routine practice, perhaps due to cost and resource allocation.

Immunological Predictors

In addition to imaging assessments it has been attempted to evaluate immune activity using serological tests for a more objective assessment of remission. The best studied predictor of relapse to date is ACPA positivity. This has been studied in several bDMARD tapering studies. ACPA positivity clearly indicated higher risk of relapse following dose reduction and lower chances of maintaining remission status in the RETRO study.[49] Other studies including BeST,[48] Hit-Hard[39] and preliminary results from the POET[72] study support these findings. In contrast, a small study by Saleem et al did not find this association.[79] Van der Woude, et al conducted a DAS-driven versus a non-DAS-driven dose reduction trial with a cohort of more than 500 patients. As well as identifying the absence of ACPA, RF and shared epitope alleles were found to be independent predictors for sustained remission. They highlighted that ACPA positive patients in the DAS-driven cohort had a slightly higher probability of achieving drug-free remission, suggesting that DAS-driven therapy could compensate the disadvantage of being ACPA positive.[81]

Tanaka et al also found that the presence of RF was associated with lower chance of successful withdrawal of TNFis.[82] This finding is also supported by the RETRO, DREAM and STRASS studies.[31,44,49] In a study by El Miedany et al 172 patients received either a bDMARD (TNFi, TCZ or ABA) or csDMARD which was subsequently tapered or discontinued. After 1 year of follow-up, 8.3% of patients showed seroconversion (disappearance of previously positive ACPA, RF or both) and all of them kept their remission status.[55]

There has been recent interest in measuring T-cell subsets to assess immune activity in RA patients.[83,84] In a study comparing the characteristics of 47 patients undergoing TNFi tapering,

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sustained remission was associated with low levels of immunological abnormalities.[79] More precisely, patients who sustained remission for 24 months presented a higher frequency (%) of naïve T-cells and lower frequency of Inflammation-related Cells (IRC). In addition, the frequency of T-regulatory (Treg) cells was higher in the sustained remission group, particularly for the $CD62L^{+}$ subgroup. Interestingly, these proportions were different for the patients receiving early, aggressive treatment compared to those whose treatment was delayed, for whom Treg frequency was higher.

Studies of imaging and immunological biomarkers need to be replicated in larger cohorts with a predefined tapering protocol before they can be considered predictors.[78] Several studies are underway (STARA,[85] BioStop-RA,[86] BioRRA[87]), with the aim of investigating this.

Other Serum Biomarkers

On the theoretical basis that low inflammatory markers or tissue inflammation markers might suggest better control of inflammatory disease, serum markers of inflammation have also been studied as predictors of drug-free remission in RA. Although measures of CRP and ESR are widely used to assess inflammation in RA, these are non-specific and do not assess the localised inflammatory activity/related processes such as structural degradation at the joint level.[6] Acomposite multi-biomarker disease activity (MBDA) score has been established to better define remission. It involves a total of 12 inflammation parameters, including markers linked to the acute phase response [CRP, Interleukin 6 (IL-6) and serum amyloid (SAA)], local tissue inflammation markers [Tumour necrosis factor receptor-1 (TNFRI), epidermal growth factor (EGF),vascular endothelial growth factor-A (VEGF-A) and vascular cell adhesion molecule-1 (VCAM-1) expressed by activated synovial fibroblasts], local tissue remodelling markers[Matrix metalloproteinase-1 and 3 (MMP-1&3)and human cartilage glycoprotein 39 (YKL-40) and adipokines (resistin and leptin).[88] It was initially developed and validated to correlate with the DAS28CRP score.[89,90] Several studies have shown an association with high MBDA and radiographic progression,[91,92] two have demonstrated the score to be a better predictor for radiological progression than the DAS28CRP score.[91,93]

Two major bDMARD tapering studies have utilised the MBDA score. The RETRO study showed that the MBDA score didn't differ according to ACPA positivity. Nevertheless, if combined with ACPA testing, it could predict the relapse of more than 80% of the patients if both were positive. Only double positive or double negative results for ACPA and MBDA were predictive of respective relapse or sustained remission. Strikingly, while MBDA scores were higher at baseline and during a relapse in the tapering groups, in the non-tapering group, it did not differ between relapsing and sustained remission patients. The RETRO study also showed that ACPA and MBDA contributed independently to the risk of relapse during dose reduction, and in a recent study by Hagen et al[94] the combination of MDBA score and ACPA status allowed for successful DMARD tapering in patients enrolled on the RETRO study, suggesting that both autoimmunity and inflammation are involved in the risk of relapse of in RA patients undergoing bDMARD tapering. Interestingly, no difference was revealed when MBDA was replaced by CRP, ESR, CDAI or SDAI.[49] On the other hand, the DRESS study contradicts these results. They showed that neither baseline MBDA nor ACPA were predictive of flare in the tapering group, but they were in the usual care group. The design of this study was different from the others discussed, where patients were in LDA rather than remission, with long standing RA.[88]

Additional evidence to support the use of serological biomarkers to predict success of tapering is demonstrated in a study of tocilizumab discontinuation for patients with established RA and sustained DAS28 remission. Nishomoto et al found that serum IL-6 and MMP-3 levels were good predictors of flare following discontinuation of therapy.[44]

These findings indicate that the assessment of subclinical inflammation by laboratory testing may be a useful tool to determine risk of flare/high risk candidates in whom tapering should not be initiated. Further work is needed to validate these biomarkers. A prospective trial currently in progress (VECTRA-DA) will analyse the MBDA score to evaluate rigorously its potential use in patients' management.[95]

Serum Drug/anti-Drug Antibody Levels

A study in 2008 monitored infliximab trough level antibodies during tapering according to DAS28CRP measures. It revealed considerable variations between patients. Trough levels tended to decrease with the reduction of the medication dose and a lower level of infliximab was found in the patients with anti-infliximab antibodies. Even though the DAS28 remained relatively constant for most of the patients before and after dose reduction, infliximab levels were highly variable from one to another. Moreover, the one patient that flared at the first visit had high infliximab levels and no anti-drug antibodies. Analysis of trough levels were retrospective. And a prospective study should be interesting for the prediction of tapering success.[96]

In 2016, another study involving 64 patients receiving ADA as their first biologic underwent a 50% reduction in treatment dose and were followed-up for 24 weeks. Medication trough level, ADA antibodies and change of DAS28CRP were measured. It showed that ADA levels correlated with the DAS28CRP before and after the medication reduction. They also witnessed that patients with ADA antibodies had significantly lower trough levels, and also had worse methotrexate compliance. All of them relapsed during the study.[97] A more recent study evaluated baseline ADA, ETN and IFX drug levels and their antibodies during dose reduction. It revealed that they were not predictive of success for reduction or discontinuation of treatment. One possible exception could be the high ADA trough levels.[98] The predictive value of measuring ADA drug levels was not confirmed in the STRASS study.[31]

Other Predictors

In relation toTNFi treatments, it has been suggested that TNF gene polymorphisms and variability of TNFi response may predict better drug responsiveness and better chance for tapering.[57] As previously mentioned, Schett et al suggest that the attainment of deep remission requires the achievement of remission at multiple levels. This includes remission defined by clinical assessments, imaging assessments (US+/-MRI), serological absence of inflammation (normal inflammatory markers) and negative autoantibodies for RF and ACPA). This could potentially form the basis of offering tapering in the future however, there are currently no studies assessing the predictive value of deepremission for successful tapering of bDMARDs.

CONCLUSION

Evidence supports that tapering or discontinuation of bDMARDs is feasible in a sub-set of patients who have achieved clinical remission; however, the ideal patient profile is yet to be defined. Biomarker based prediction is not yet ready for clinical practice, therefore we are obliged to continue to use clinical remission criteria, in-line with national guidance. It is therefore critical to identify more robust biomarkers and validate existing biomarkers, towards providing targeted treatment. This would be better than current disease activity guided tapering methods, which are based on trial and error. Achieving a state of deep remission, followed by gradual tapering of bDMARD appears to be the most logical approach, followed by csDMARD tapering.

In clinical practice, a pragmatic approach should be taken when tapering bDMARDs, with the benefits of being in stable remission weighed against the potential risk of overtreatment, safety concerns and costs. It is recommended that strict disease activity monitoring and patient education on recognising flare should also be employed. Future tapering studies may provide new insights into disease pathogenesis and disease course. Further work is needed to explore the role of genetic and environmental factors that allow re-establishment of immune tolerance. We should also consider the presence extra-articular inflammation in patients who are in clinical remission, since patients may benefit from ongoing therapy to prevent cardiovascular mortality. Therefore, biomarkers of systemic inflammation may provide added value, when assessing the remission status of RA patients.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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