Autoimmunity Reviews 18 (2019) 102399

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Can we wean patients with inflammatory arthritis from biological therapies?

Christopher J. Edwards[a,*], Mauro Galeazzi[b], Salvatore Bellinvia[a,c,*], Ariana Ringer[d], Theodoros Dimitroulas[e], George Kitas[f,g]

[a] Department of Rheumatology and NIHR Clinical Research Facility, University Hospital Southampton NHS Foundation Trust, Southampton, UK
[b] Research Center of Systemic Autoinflammatory Diseases, Department of Medical Sciences, Surgery and Neurosciences, University of Siena, Italy
[c] Department of Rheumatology, Salisbury NHS Foundation Trust, Salisbury, UK
[d] Department of Rheumatology, Centenario Hospital, Rosario National University, Argentina
[e] Fourth Department of Internal Medicine, Hippokration University Hospital, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece
[f] Arthritis Research UK Epidemiology Unit, University of Manchester, Oxford Road, Manchester, UK
[g] Department of Rheumatology, Dudley Group NHS Foundation Trust, Russells Hall Hospital, Dudley, West Midlands, UK

ARTICLE INFO

Keywords:
Inflammatory arthritis
Biological therapies
Tapering
Pros
Cons

ABSTRACT

Biological therapies have represented a cornerstone in the treatment of immune-mediated inflammatory diseases. Their advent combined with implementation of a treat-to-target approach has meant that remission or low disease activity are now realistic targets for treatment achieved by a significant number of patients. However, biologicals are not risk free and their elevated costs continue to present an important economic burden to national healthcare services.

"Can we wean patients with inflammatory arthritis from biological therapies?"

Over the last decade this question has become increasingly important as to define the best management strategies in terms of efficacy, safety and economic outcomes. Not surprisingly this has generated an interesting debate as to whether reasons to taper biologics outweigh reasons not to taper and evidence in support of either of these schools of thought is persistently growing.

Aim: In this article we reviewed the contents of the relevant session from the 2019 Controversies in Rheumatology and Autoimmunity meeting in Florence.

1. Introduction

Biological Disease Modifying Antirheumatic Drugs (bDMARDs) have brought about dramatic improvements in changing the natural history of immune-mediated inflammatory diseases (IMIDs) such as rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondylarthritis (SpA). Due to the effectiveness of these drugs and implementation of treat-to-target strategies, low disease activity (LDA) and remission are goals now reached by a significant number of patients [1]. However, biologicals are not risk free: infections and malignancies have been described after long term immunosuppression and their elevated costs still represent an important economic burden despite the increasing availability of biosimilars.

Over the last decade questions about long term treatment with biologics for individuals in remission or LDA have arisen. Is it possible to down titrate or withdraw biologicals? Is it better to reduce the dose or space it? Which treatments and patients are suitable for tapering and is there any difference amongst rheumatic conditions? How long would the effect last? What about immunogenicity? What is the next step in case of flare or relapse of disease? Answers to these and many other enquiries are current hot topics and present clinicians with difficult challenges. Different dose tapering and discontinuation strategies have been analyzed, such as dose reduction, dose spacing, progressive stepwise dose/frequency reduction and disease activity driven tapering. Withdrawal regimens can also be different according to the biological drug and the rheumatic disease considered.

In patients with RA, Disease Activity Score 28C-reactive protein (DAS28-CRP) remission or LDA normally have to be stable for over six months prior to considering biological tapering, with a steady dose of conventional disease modifying antirheumatic drugs (csDMARDs) and no concomitant use of steroids. In some studies, the absence of power doppler ultrasound activity and radiographic progression were also necessary [2,3]. The American and European recommendations suggest biologic tapering for patients in remission and, in selected patients who

* Corresponding authors at: Department of Rheumatology and NIHR Clinical Research Facility, University Hospital Southampton NHS Foundation Trust, Southampton, UK.
E-mail addresses: cedwards@soton.ac.uk (C.J. Edwards), salvatore.bellinvia@uhs.nhs.uk (S. Bellinvia).

https://doi.org/10.1016/j.autrev.2019.102399
Received 26 May 2019; Accepted 30 May 2019
Available online 19 October 2019

continue to be in sustained remission, discontinuation may also be considered [4,5]. Flare is mainly described as an increment in DAS28 ≥ 1.2 consistent with relapse or loss of remission/LDA.

Many studies have shown how drug discontinuation is associated with high incidence of flares, worse radiographic and functional outcomes [1,8]. On the contrary, dose down titration seems to be a more feasible approach, with less risk of relapse or radiographic progression in comparison with discontinuation, although losing remission and minimal radiographic progression may be possible eventually. Initial high disease activity, established RA, positive rheumatoid factor or anti-citrullinated peptide and synovial hypertrophy were negative predictive factors for tapering. In case of relapse, biologic reintroduction achieved LDA/remission again in a variable percentage of patients according to published studies [1,2,6–11].

Evidence in SpA is more limited than in RA and disease activity is evaluated with the BASDAI score (Bath Ankylosing Spondylitis Disease Activity Index) and more recently with the ASDAS (Ankylosing Spondylitis Disease Activity Score). In some studies, biologic tapering in patients in remission for more than six months (with or without NSAIDs) had better outcomes than discontinuation. If relapse occurred, patients returned to initial dose and regained acceptable disease activity in most cases [2,12–15]. For individuals with PsA, tapering has been considered for those with minimal disease activity, with LDA or remission by different scores depending on the author. Similar approaches to RA, such as dose down titrating, interval widening and discontinuation, were evaluated [16–21].

Despite the controversial results found in literature, evidence is persistently growing as to define the best management strategies in terms of efficacy, safety and economic outcomes in both the shorter and longer periods. Nevertheless, the importance of shared-decision making between the rheumatologist and the patient should be always emphasized.

1.1. Reasons to taper

The treatment of inflammatory arthritis is directed toward the goal of achieving clinical remission or LDA [22]. Biologicals may have different mechanisms of action including selectively blocking the effects of individual cytokines, inhibiting lymphocyte activation or depleting B-cells. Using biological therapies in clinical practice and the consolidation of a treat-to-target approach have greatly increased the likelihood of remission or LDA in a number of inflammatory rheumatic diseases [22,23]. However, the cost of this treatment is significantly higher than csDMARDs and there are dose-related side-effects associated with their use. Therefore, once a treatment target has been successfully reached and maintained for a period of time, dose adjustment should be considered. There are many reasons to engage in withdrawal treatment strategies which are underpinned by a need for personalized care, an increasing body of evidence, adherence to national and international guidelines and safety issues related to dose-dependent adverse advents with the use of biologicals. The multitude of reasons behind the idea of tapering the dose of biologicals certainly finds a common thread in reducing the significant cost and burden of these medications on national healthcare systems and rheumatology department budgets.

1.1.1. Personalized care

Patients' perspectives and preferences regarding weaning biologicals and its various aspects are core questions to be answered with a view to implementing personalized medicine in clinical practice [24]. In general terms, the reduction in dose or frequency and ultimately the discontinuation of biologicals in patients who achieve remission or LDA is a valuable strategy. However, there is a need to identify those patients who are most likely to benefit or in other terms less likely to relapse as a result of a tapering strategy [25,26]. Some data suggest that the relapse rate can vary in different chronic inflammatory diseases with significantly higher relapse rate in patients with RA than in AS [2,12]. A degree of variation can also be seen within the same disease group. In RA patients on TNF inhibitors for instance, evidence to date has revealed that completely stopping anti-TNFs in established disease leads to higher relapse rates [27].

A systematic review focusing also on the clinicians' perspective has confirmed different rates of relapse and flare across early RA, established RA, axial spondyloarthritis and PsA in patients who reduced therapy. However, in many cases LDA or remission could be regained promptly upon retreatment [2]. Patient and disease characteristics are important in deciding a tapering strategy and the overarching principle of defining a minimum acceptable duration of clinical remission or LDA based on composite scores (DAS28 or BASDAI etc) in order to allow consideration of treatment withdrawal strategies. No clear monitoring approach has been suggested and therefore a personalized line of action, tailored to each individual's disease state and characteristics, is important.

The concept of a window of opportunity in treating inflammatory rheumatic diseases is widely accepted and supported by large clinical data but yet this system does not treat the individual. As a result patients' views and preferences regarding tapering strategies of biologicals remain important but are often not considered fully. This aspect has been further detailed in a recent study designed to explore patients' perspective and concerns about dose reduction of biologicals through a validated questionnaire developed in collaboration with patient partners [28]. Loss of LDA and remission were amongst the most common concerns and patients seemed to be also fearful of the consequences of a flare and how quickly they could get back on treatment. However, patients agreed that they would be keen to try a reduced dose were overall more than patients in disagreement with this statement and a lower risk of adverse events was a perceived benefit.

1.1.2. The evidence

The interest in the feasibility of tapering biologicals is increasing as well as evidence coming from randomised controlled trials, disease-activity guided strategy trials and real-world observational studies. A systematic literature review of published studies evaluating tapering of biologicals in RA and including three RCTs (two for TNF inhibitors and one for Rituxumab) has suggested that dosing down is a feasible option in many patients who have achieved remission or LDA [29]. Different strategies have been adopted in the tapering of biologics but the most common are dose reduction, either through decreasing the dose or increasing the spacing between individual doses, and discontinuation of therapy. Some clinical or laboratory variables associated with the successful tapering of TNF inhibitors have been identified such as anti-citrullinated peptide antibody(anti-CCP) negativity, absence of ultrasound synovitis and normal serum inflammatory markers but the ideal profile of the subgroup of patients who are more likely to achieve drug-free remission remains to be defined [11]. Across all studies investigating dosing down strategies in IMIDs, RA has been the most studied inflammatory disease model since patients with RA represent one of the largest populations receiving the widest spectrum of current available biologics. However, descriptions of the current evidence on tapering and discontinuation of biologic therapy in well-controlled psoriatic arthritis have also been encouraging [30].

The majority of clinical trials have investigated optimizing treatment with TNF inhibitors in good responders. The length of time in clinical remission before inclusion was variable but usually at least 6 months [31]. In one study, tapering etanercept or adalimumab by one third had no impact on disease activity or frequency of flares and was practical in patients with sustained remission (OPTTIRA study). Interestingly, the flare rate for patients receiving adalimumab (33%) was lower than for patients receiving etanercept (53%). The effect of reduced dose or withdrawal of etanercept in patients with moderately active disease was assessed in the PRESERVE study [27]. All patients received conventional dose of etanercept in an open-label period of 36 weeks prior to entering the double-blind phase. This well-designed

controlled trial addressed a number of novel aspects in the treatment of RA because of the target population and the patients' randomization for investigation of response maintenance. The PRESERVE study showed that conventional or reduced doses of etanercept plus methotrexate in patients with moderately active RA maintain LDA more effectively than does methotrexate alone after withdrawal of etanercept. But equally interesting, although the study was not conceived to show differences between the two etanercept arms, findings with both regimens were similar without much loss of response on the reduced dose. The effects of tapering strategies in a selected cohort of patients with early active RA who had achieved remission on etanercept-plus-methotrexate therapy have been assessed in a three-phase study conducted at 57 centres in Europe and Asia (PRIZE study) [32]. Findings from this study suggest that dose reduction or withdrawal of biologicals is feasible in some patients after induction of remission or LDA with early treatment.

Further disease-activity guided strategy trials have aimed at demonstrating the non-inferiority of progressively spacing injections of TNF inhibitors adalimumab and etanercept to maintaining therapy at the usual dose [33,34]. What makes these studies important is the fact that their design and outcomes come closer to decisions clinicians are take in real life clinical practice. In the STRASS study, patients with established RA (~9 years) and DAS28 remission ≤2.6 for 18 months were randomised into the two arms of either maintenance or injection spacing by 50% every three months until complete discontinuation. DAS28 was assessed at 3-monthly follow-up visits and treatment adjusted accordingly [33]. The study enrolled fewer patients than planned because of lack of funding. As a matter of fact, the non-inferiority of the spacing strategy could not be disproven due to insufficient recruitment and the tapering strategy resulted in higher chances of relapses compared to maintenance strategy. However, 75% of patients in the spacing arm were able to successfully space injections and equally important there was no impact on radiographic structural damage progression. Over a longer time period, an observational extended follow-up study of the STRASS trial showed that a sustained de-escalation or withdrawal was achievable in 41% of patients who had data available up to 3 years [10]. A similar study design with a DAS-steered progressive spacing of adalimumab or etanercept injection was conceived in another main disease-activity guided strategy trial (DRESS study) [34]. In this randomised controlled non-inferiority trial study, the injection interval could successfully be increased in 43% of patients in the dose reduction group and what is more 20% were able to successfully stop TNF inhibitors. Of most importance to clinical practice, this study revealed that a disease activity-driven dose reduction strategy is non-inferior to usual care in maintaining disease control [35].

Interesting data is already emerging from real-world studies evaluating sustained dose reduction strategies of anti-TNF therapies in patients with established rheumatoid arthritis. Interestingly, the first real-world description of a pragmatic tapering approach in patients with longstanding and severe disease has investigated the possible use of combined clinical and ultrasound assessments to identify individuals in clinical remission who are more suitable for dose reduction as well as to enhance prompt detection of sub-clinical disease flares [26]. In this UK study patients receiving TNF inhibitors per standard care within the National Health Service (NHS) were reviewed in a dedicated biologics clinic and those not taking oral corticosteroids with both DAS28 score remission and absence of synovitis on power Doppler US for at least six months were invited to reduce the dose by one third. Combined DAS28 and ultrasound remission were maintained by 34% of 70 patients who underwent TNF inhibitor dose reduction. Furthermore, inclusion of US follow-up assessments allowed early identification of about 25% of flares at a sub-clinical stage.

Overall the current evidence shows how careful and controlled dose reduction is achievable even in established severe RA and virtually all patients relapsing respond well upon reintroduction of treatment with no loss of efficacy of biological therapy [2,11]. However, a relatively small number of RCTs have been published and additional evidence is needed, in RA as well as in other immune-mediated inflammatory diseases, in order to provide further guidance on this treatment strategy.

1.1.3. The guidelines

The effectiveness of biologic therapies now means that remission or LDA are attainable targets. In recognition of this trend international guidelines now envisage tapering of biologicals and Janus kinase inhibitors in patients with RA who have achieved remission. Item 11 of the EULAR recommendations for the management of rheumatoid arthritis with conventional synthetic and biological DMARDs (2016 update) deals with the tapering of biologicals stating this can be considered if a patient is in persistent remission after having tapered glucocorticoids and especially if the treatment is combined with a conventional synthetic disease-modifying antirheumatic drug (csDMARD). This item remained unchanged compared with the 2013 publication and it is still not perfectly clear how treatment should be discontinued in patients who are in remission [36]. However, it was advised that biologic agents could be tapered by reducing the dose or expanding the interval between doses. The 2015 American College of Rheumatology (ACR) Guideline for the Treatment of Rheumatoid Arthritis has also contemplated downward tapering of csDMARD therapy, TNF inhibitors, non-TNF biologics and tofacitinib (as the only representative of JAK inhibitors included when the guidelines were released) in patients who have achieved sustained remission although it was not clearly outlined how long patients need to be in remission prior to dose reduction [37]. Guideline from the Asia Pacific League of Associations for Rheumatology (APLAR) also includes references to tapering of biological therapy for patients in extended remission (> 12 months) and as opposed to the ACR guideline the grade of evidence is regarded as moderate [38].

1.1.4. Safety

The safety profile of biologic therapies is generally reassuring but some concerns remain regarding dose-dependent safety issues associated with their long-term use, particularly the increased risk of malignancy and serious adverse effects (SAEs), in addition to the well-known increased rate of infection [6,39]. A systematic review and meta-analysis of registries and prospective observational studies has shown that although TNF inhibitor treatments in clinical practice do not appear to increase the risk of malignancy there does appear to be an increase in some skin cancer [40]. More recent studies have been using novel hierarchical network meta-analysis and synthesis methods in order to estimate the impact of dose level on the risk of adverse events from a medical intervention. Interestingly, one of the studies has focused on the effect on malignancy of three TNF inhibitors as a motivating example. Higher doses of infliximab, adalimumab and etanercept were associated with higher odds ratio (OR) for malignancy [41]. In terms of dose-dependent SAEs, it is relevant to mention a recent systematic review including data from 117 randomised trials of ten different biological and targeted-synthetic DMARDs approved for RA. Despite the low degree of confidence in the estimates, the analysis found differences in rates of SAEs and in particular there was a potential dose response for certolizumab, adalimumab and etanercept in conjunction with csDMARDs when compared to patients on csDMARDs alone [42]. Overall these data support proactive tapering of biologicals to minimise dose-dependent adverse effects once sustained remission is achieved [43].

1.1.5. Economic outcomes

It is a reality that the availability of high cost therapies is restricted in many countries. In the case of biologicals the pursuit of optimal dosing is of crucial importance in view of their high costs and the increased likelihood of low cost-effectiveness [6,43]. The decrease in cost with biological tapering is easily predictable and supported by robust economic data reported in a systematic literature review for a variety of

biologic drugs comprising different mechanisms of action [29] and in a well-designed cost-effectiveness analysis based on the tapering strategies used in controlled trials [44]. The challenge of rational use of biologicals in treatment sequences in RA and for improving identification of patient groups in which biologicals can be successfully discontinued has been raised for some time now [45] but should however continue with equal efforts despite the introduction of biosimilars.

1.2. Reasons not to taper

The question asked in this debate is whether we "can WEAN PATIENTS with INFLAMMATORY ARTHRITIS from BIOLOGICAL THERAPIES". In medicine, as in science, the clearer we are about what we are asking and the more accurate and specific we are about the evidence we utilize, the more likely we are to get to the correct answer. There are several important words in the question posed and we should seek to find and evaluate the relevant evidence to be able to address each and every one of them. "Wean" means "accustom", i.e. taper in order to stop – so we should be seeking evidence for both dose reduction and discontinuation. The question refers to "patientS", not "a patient", so it implies a blanket approach to a population of patients rather than an individual patient once a certain target has been reached – so we should be looking for evidence that a universal target is appropriate and reachable in a population that we can define clearly. Although it is not explicitly stated in the question, presumably it refers only to patients with inflammatory arthritis (IA) that have achieved a state of sustained remission or at least low disease activity – so we should also be able to define these disease states clearly. "Inflammatory arthritis" implies at least all of the common forms, that is not only rheumatoid arthritis (RA) but also psoriatic arthritis (PsA) and spondyloarthritis (SpA) – so we should look for evidence in all three of these clinical conditions. The same applies to "Biological therapies", i.e. all of them, not only a single class of bDMARDs, such as the anti-TNFs.

There is no doubt that the landscape has changed significantly in the last couple of decades and we do now see many more patients than in the past who achieve an acceptable level of disease activity, accumulate little joint damage and maintain good function in the long term. However, this is not only due to the (thus far mostly continuous) utilization of new treatments, e.g. bDMARDs, but also better overall management strategies (including early identification and treatment initiation, better ways of using "old" treatments, e.g. methotrexate, treatment to a specific target and tight control). This does therefore provide us with the opportunity to consider treatment modification in the form of tapering or discontinuation for entire groups of patients rather than individuals – but we should have good reasons for doing this and good evidence to underpin the practice. There is only a limited number of reasons for which we should consider such a systematic approach as part of our routine clinical practice: (1) because an appropriate, important therapeutic target is achievable in a sizeable proportion of patients; (2) in order to have a proven health benefit for the patients including maintenance of a good health state with less treatment, reduced chances for side-effects, improved adherence to (remaining) treatment, improved quality of life in the wider sense, amongst others; (3) cost reductions to the patient and/or the health system. Let us consider each of them in turn.

1.2.1. The target in the context of personalized medicine and the patient population

Personalized medicine is currently a buzz word but is not new. Throughout the history of medicine, from the times of Hippocrates through to Alfred Garrod and William Osler amongst many others, the emphasis has always been on treating the individual patient rather than the disease. "Clinical knowledge may have been changing, but clinical practice – in its most basic incarnation of treating the right patient at the right time in the right way – has not"; with the notion of "right" being within the context of the knowledge of the time [46]. Treatment modification, including tapering or stopping medication, is something that we all do as managing physicians on a daily basis. It may be due to absolute need (e.g. pregnancy, infection, surgery), due to patient preference (irrespective of our preference) [47], due to our mentors' wisdom or our own experience. It is based on a continuous re-evaluation of the risk/benefit ratio that we assess as good managing physicians for the individual patient we have in front of us and which the patient assesses for him/herself according to his/her personal values and circumstances at the time [48]. It is absolutely clear to any practising rheumatologist that personalized medicine cannot (and should not) be encapsulated into a single outcome (disease activity) however this is assessed. This may well be a reasonable target for clinical trials, for the rheumatology community and for regulatory authorities – but it is not a personalized target for the individual patient or his/her rheumatologist. So, the question posed in this debate, if anything, steers us away from personalized medicine: it is about whether we can SYSTEMATICALLY wean bDMARDs off patients who have achieved remission or LDA in a blanket approach. Translated into clinical practice this would mean that we should attempt to wean off bDMARDs every single patient with RA we see who has been in DAS28 remission or LDA for > 6 months, irrespective of the patient's own goals or our judgement based on other factors (e.g. comorbidity, psychology, amongst many others). This is definitely not personalized medicine!

Virtually all of the studies that have addressed whether tapering or stopping biologics is feasible in RA patients have utilized the DAS28 to define remission or LDA [11]. Whereas DAS28 may well be (one of) the best tools to use for these definitions it is far from actually being sufficient for the purpose. It is probably the least strict of all current clinical tools used to define remission or LDA [49]; it does not encapsulate many other important outcomes [50,51]: for example most patients who reach DAS28 remission continue to report significant fatigue [52], while low-grade sub-clinical local or systemic inflammation may still be present with negative consequences for continuing joint damage [53] or some comorbidities such as cardiovascular disease [54]. It is also not the easiest to use in many routine clinical settings. The definition of "sustained" remission or LDA is also open to question. Again, virtually all studies have used a threshold of > 6 months, which is rather short for any chronic life-long condition. Even utilizing such a "loose" outcome measure, remission or LDA remain uncommon in real-world practice: about 1 in every 4 patients treated with biologics will be in these disease states for > 6 months at any given point but they are not the same patients, the majority go in and out of "sustained remission" all the time and there continues to be an unmet need requiring continues rethinking of our treatments and strategies [55–57]. The definitions of remission or LDA in PsA and AS are even grayer than those in RA and data on what proportion of patients with these conditions enter these states and for how long is scant. The same applies to bDMARDs other than the anti-TNFs.

It would appear therefore that reason no 1 for attempting systematic weaning of biologic therapy cannot be substantiated on current evidence because the only target that has been assessed is not sufficiently robust, it does not reflect various significant disease dimensions, it is hardly important to the individual patient and is not even frequently achieved in the entire population of patients.

1.2.2. Health benefits in the context of current evidence

In order to support a systematic change in practice such as weaning off biologics all patients in remission or LDA for at least 6 months, we should consider: (a) whether there is any evidence at all to underpin such a practice, in which patient groups and what is the overall quality of current evidence; (b) whether the existing evidence address important health outcomes which as a minimum should include: (I) sustained maintenance of a good arthritis state following treatment change; (II) improved adherence to treatment; (III) reduced incidence and severity of side-effects; (IV) similar or reduced incidence and severity of comorbidities; (V) rare and easy to control relapses in the

overwhelming majority of patients without long-term treatment escalation; (c) whether there are any supporting guidelines and whether current evidence can be easily translated into routine clinical practice. Again, let us consider these points.

(a)There is a continuously increasing number of studies that have addressed this question, several of which have already been mentioned. There is a Cochrane review from 2014 [6] which concluded that evidence at the time were at best of moderate quality due to limited data, high heterogeneity of available studies, superiority (rather than the more appropriate for the question non-inferiority) designs, and limited outcomes assessed (particularly no outcomes other than disease activity, lack of long-term safety or radiological progression data, no cost analyses). A subsequent authoritative review in 2017 [11] included many more studies but the overall picture has not improved much. Most of the evidence derives from uncontrolled studies or sub-analyses of randomised controlled trials (RCTs) not designed to answer the specific question; there are only a few RCTs that were designed specifically for the purpose and they involve small numbers of patients (mostly < 200). There is a good mix of studies looking at early and at established disease but there is no further discrimination of clinical populations: this is much needed information if we are to apply systematic treatment changes to routine clinical practice. A general profile of patients more likely to enter remission appears to be younger, male, seronegative, non-smokers with late-onset disease of short duration and low baseline activity and severity [58] – it is unknown whether they are more likely to stay in remission once bDMARD treatment has been reduced or stopped. The overwhelming majority of studies have been done in RA, with PsA and AS just starting to get in the picture. They have addressed almost exclusively the anti-TNFs with very little data available on other bDMARDs and virtually none on tsDMARDs. They have assessed mostly stopping rather than tapering strategies (and again various different ways of tapering). Finally the majority of studies assessed patients in remission (rather than in remission or LDA) and as previously mentioned "sustained" was defined as > 6 months and follow-up was mostly 6–12 months. So, although there is an increasing body of evidence to support the practice, the overall quality remains modest at best in RA, poor/absent in AS and PsA, limited to anti-TNFs and not applicable either to the entire patient population or to particular subgroups.

(b-I)The only outcome that has been addressed is this of disease activity (maintenance of remission or LDA) roughly for up to 1 year post treatment change. There is no sufficient evidence to support such a practice in terms of many other important arthritis outcomes (including longer term (> 1 year) remission, many important patient reported outcomes, functional or radiographic data, amongst others) [50,51]. Indeed only 8% of RA patients feel that all of their disease-related symptoms are completely controlled at any time [59] while the patient perspective clearly indicated that pharmacological interventions alone are inadequate to address their needs [60].

(b-II)Several lines of evidence indicate that adherence to therapy is important for optimal health outcomes [47]. There are many factors that affect adherence: in people with IA, adherence appears to depend more on treatment beliefs than the actual disease state, it appears to be better in people receiving anti-TNFs compared with other treatments and in people with shorter disease duration [61,62]. The question whether weaning off or stopping bDMARD therapy associates with improved adherence to the (remaining) medication and improved longer-term health benefits mediated by this has not been addressed.

(b-III)The issue of side-effects is important but remains unanswered in the context discussed here. The general profile of patients more likely to have side-effects are older, seropositive smokers with high disease activity and severity, long disease duration, comorbidities and polypharmacy [63]. This is the exact opposite end of the spectrum of patients likely to enter remission, in whom we would be able to consider treatment reduction. Interestingly, data from the BSRBR suggest that the risk of infection from anti-TNF therapy was higher in the first 6 months of treatment (i.e. before we can even start considering to reduce treatment), whereas mortality within 30 days of serious infection was 50% lower in those receiving anti-TNFs compared to non-bDMARD-treated patients [64]. So, the overall risk of infection (or other potential treatment side-effects, including malignancy) needs to be counterbalanced with the risk of inadequate disease control or of other treatments [65,66]. To date, we do not have sufficient evidence to be able to claim that tapering or stopping bDMARD therapy reduces any side-effect risk and for how long and whether a stop-restart (in case of flare) strategy is better or worse in this respect.

(b-IV)Exactly the same, i.e. lack of any evidence, applies with regards to the incidence or severity of comorbidities. For some comorbidities, e.g. cardiovascular disease resulting from accelerated atheromatosis, even subclinical (in the rheumatology context) inflammation may be sufficient to promote the comorbidity [54].

(b-V)Current evidence suggests that relapses are relatively easy to control with re-introduction of the bDMARD in the majority (around 80%) certainly not in all patients [67]. However, virtually all studies suggest that loss of control of disease activity requiring treatment escalation will occur in at least half of the patients in whom bDMARDs were tapered or stopped with some studies showing that only 10% of patients will still be in remission (without steroids or a biologic) 2 years after stopping their bDMARD [68]. So within a very short time-frame for a life-long condition, relapses are virtually universal and not always easy to control.

(c) Is the practice of systematic bDMARD tapering or stopping supported by current recommendations and are they easy to translate in routine clinical practice? Let us use the latest EULAR recommendations for RA as an example [36]. Careful scrutiny clearly suggests that a systematic approach is not supported. We should not only look at the relevant box in the relevant figure. Overarching principle number 2 clearly states that "treatment decisions are based on disease activity AND other patient factors, such as progression of structural damage, comorbidities, and safety issues". The specific recommendation (No11) is very carefully and wisely worded: only "persistent remission" is mentioned, not LDA, and neither the word persistent nor the word remission are defined exactly; tapering (by dose reduction or spacing) can be "considered" but stopping "may lead to a recurrence of disease in a majority of patients"; there is a clear attempt to limit the approach to particular patients (early RA, not on steroids, continuing to take a csDMARD, in deep remission for a long time) and only those that agree to it (as per overarching principle No1) once they have been informed accordingly. This is very useful guidance for a clinician, guidance that very clearly sides with the practice of personalized medicine and moves us away from a blanket approach. Indeed, even closer scrutiny demonstrates how large the knowledge gap still is in this area: the level of evidence supporting recommendation 11 is one of the lowest at 2b, as is the level of agreement, while about half of all items listed in the research agenda are related to this issue.

So, let's take a best case clinical scenario that we may encounter in routine clinical practice: 43 year old practising solicitor, mother of two young children with seropositive RA and 2 small erosions on presentation. It took about 6 months to work her way through the health system, get a definite diagnosis and start treatment (initially methotrexate, hydroxychloroquine and steroids). Four months after treatment initiation, etanercept was added because of incomplete disease control and inability to taper steroids. This was followed by excellent clinical and laboratory control. Another 6 months later she has stopped steroids completely and 6 months after that she remains well on methotrexate, hydroxychloroquine and Etanercept, which she tolerates extremely well. She has her personal, family and professional confidence back and is by her own assessment "…back in control of her life, 100% in all areas…". So, following the rheumatology unit's protocol for systematic tapering / stopping bDMARD therapy once remission has been achieved, she attends an outpatient appointment to discuss this possibility. In a combination of pre-prepared information and answering

direct questions from her, she is informed that based on current evidence: she has at best a 50/50 chance to flare within the next year and up to 90% to flare within the next 2 years; if this happens, she has 1/5 chance not to respond to the same treatment; we cannot guarantee that we will be able to control her disease again immediately (particularly without using steroids, which she did not like at all) or that things will not be as bad as before, to the extent that she may again not be able to go to work for a few days or weeks; we cannot be sure whether she will have any benefit in terms of the risk of short or long-term side-effects; the clinical and laboratory monitoring she will require will remain exactly the same; we cannot be sure whether she will have any benefit or detriment in terms of comorbidities or long-term joint damage (about which she has read a lot). What do you think would be her preference and what would be ours if we were in her place?

1.2.3. The economic argument

It is intuitive to assume that by down-titrating or stopping bDMARDs may provide cost benefits and there is some evidence to suggest this. However, even this evidence is not strong. Firstly it is not clear what costs we are talking about: to the individual, to the health system, to society? Secondly, a lot of the evidence arises from extrapolating data from clinical trials [29,44], which hardly reflects everyday practice. Thirdly, the health care delivery systems and pricing structures are grossly different in different countries: for example the most commonly used anti-TNF worldwide currently has almost a 20-fold difference in retail price between the UK or the Netherlands and the USA. Fourthly, existing evidence is not unidirectional. For example, it is very interesting that despite the afore mentioned differences, a retrospective study in the USA demonstrated that patients who stayed on their standard maintenance dose of infliximab had significantly less admissions, physician visits, tests and prescriptions and significantly lower costs per year than those who reduced the dose, irrespective of whether they had commercial or government insurance [69]. Finally, there are no long-term, prospective studies to assess the upfront costs for systematically instituting the change (e.g. physician visits and consultation / education / information time), together with costs such as the above related to management of flares plus personal, family and societal costs that may counterbalance the direct drug-related costs. So, although it is likely that at current market prices there may well be some cost savings, the evidence even for this remains weak.

2. Conclusions

Rheumatologists should continue to practise “personalized medicine” within the limits of current knowledge in all contexts, including the best use of biological therapies for an individual patient. However, the practice of systematically tapering bDMARDs in all patients who have reached a certain disease activity target may not be supported on the basis of current evidence. As medical practitioners and as a community we should continue to do efforts for making the best treatments accessible by the largest possible number of patients. This should be achieved not by a rationing exercise but through appropriate use supported by good quality evidence, in turn generated through continuous good quality research.

Take home messages

- The likelihood of remission or low disease activity in patients with inflammatory arthritis has greatly increased with the introduction of biologicals and treat-to-target strategies.
- Despite therapeutic advances key domains in RA management such as pain, fatigue, physical and mental function remain suboptimally assessed and controlled.
- A multidimensional approach on an individualized basis may be applicable for biological tapering once a treatment target has been successfully reached and maintained for a period of time.
- The current level of evidence supports careful and controlled dose reduction even in established severe RA but additional evidence is needed in order to underpin the widespread implementation of tapering and discontinuation strategies in the whole population.

References

[1] Alperi-López M, Alonso-Castro S, Morante-Bolado I, Queiro-Silva R, Riestra-Noriega JL, Arboleya L, et al. Biological dose tapering in daily clinical practice: a 10 year follow-up study. Reumatol Clin. 2018 Oct 11. https://doi.org/10.1016/j.reuma.2018.08.002. pii: S1699-258X(18)30182-7.

[2] Edwards CJ, Fautrel B, Schulze-Koops H, Huizinga TWJ, Kruger K. Dosing down with biologic therapies: a systematic review and clinicians' perspective. Rheumatology 2017;56(11):1847–56.

[3] Lenert A, Lenert P. Tapering biologics in rheumatoid arthritis: a pragmatic approach for clinical practice. Clin Rheumatol 2017 Jan;36(1):1–8. https://doi.org/10.1007/s10067-016-3490-8.

[4] Singh JA, Saag KG, Bridges SL, Akl EA, Bannuru RR, Sullivan MC, et al. American college of rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol 2016;2015:1–2.

[5] Gossec L, Smolen JS. Treatment of psoriatic arthritis: management recommendations. Clin Exp Rheumatol 2015 Sep-Oct;33(5 Suppl 93):S73–7. [Epub 2015 Oct 15].

[6] van Herwaarden N, den Broeder AA, Jacobs W, van der Maas A, Bijlsma JW, van Vollenhoven RF, et al. Down-titration and discontinuation strategies of tumor necrosis factor blocking agents for rheumatoid arthritis in patients with low disease activity. Cochrane Database Syst Rev 2014;9:CD010455.

[7] Henaux S, Ruyssen-Witrand A, Cantagrel A, Barnetche T, Fautrel B, Filippi N, et al. Risk of losing remission, low disease activity or radiographic progression in case of bDMARD discontinuation or tapering in rheumatoid arthritis: systematic analysis of the literature and meta-analysis. Ann Rheum Dis 2018 Apr;77(4):515–22.

[8] Brocq O, Millasseau E, Albert C, Grisot C, Flory P, Roux CH, et al. Effect of discontinuing TNFa antagonist therapy in patients with remission of rheumatoid arthritis. Joint Bone Spine 2009;76:350–5.

[9] De Stefano R, Frati E, De Quattro D, Menza L, Manganelli S. Low doses of etanercept can be effective to maintain remission in ankylosing spondylitis patients. Clin Rheumatol 2014;33:707–11.

[10] Sigaux J, Bailly F, Hajage D, Mariette X, Morel J, Gandjbakhch F, et al. Sustainability of TNF-blocker tapering in rheumatoid arthritis over 3 years: long-term follow-up of the STRASS (Spacing of TNFblocker injections in Rheumatoid ArthritiS Study) randomised controlled trial. RMD Open 2017;3:e000474https://doi.org/10.1136/rmdopen-2017-000474.

[11] Schett G, Emery P, Tanaka Y, Burmester G, Pisetsky DS, Naredo E, et al. Tapering biologic and conventional DMARD therapy in rheumatoid arthritis: current evidence and future directions. Ann Rheum Dis 2016;75:1428–37.

[12] Arends S, van der Veer E, Kamps FB, Houtman PM, Bos R, Bootsma H, et al. Patient-tailored dose reduction of TNF-a blocking agents in ankylosing spondylitis patients with stable low disease activity in daily clinical practice. Clin Exp Rheumatol 2015;33:174–80.

[13] Zavada J, Uher M, Sisol K, Forejtová Š, Jarošová K, Mann H, et al. A tailored approach to reduce dose of anti-TNF drugs may be equally effective, but substantially less costly than standard dosing in patients with ankylosing spondylitis over 1 year: a propensity score-matched cohort study. Ann Rheum Dis 2016;75:96–102.

[14] Baraliakos X, Listing J, Brandt J, Zink A, Alten R, Burmester G, et al. Clinical response to discontinuation of anti-TNF therapy in patients with ankylosing spondylitis after 3 years of continuous treatment with infliximab. Arthritis Res Ther 2005;7:439–44.

[15] Brandt J, Khariouzov A, Listing J, Haibel H, Sörensen H, Grassnickel L, et al. Six-month results of a double-blind, placebo-controlled trial of etanercept treatment in patients with active ankylosing spondylitis. Arthritis Rheum 2003;48(6):1667–75.

[16] Cantini F, Niccoli L, Nannini C, Cassarà E, Pasquetti P, Olivieri I, et al. Frequency and duration of clinical remission in patients with peripheral psoriatic arthritis requiring second-line drugs. Rheumatology (Oxford) 2008;47:872–6.

[17] Ye W, Tucker LJ, Coates LC. Tapering and discontinuation of biologics in patients with psoriatic arthritis with low disease activity. Drugs 2018;78:1705.

[18] Lorenzin M, Ortolan A, de Hooge M, Frallonardo P, Piccoli A, Cozzi F, et al. Lengthening the time intervals between doses of biological agents in psoriatic arthritis patients: a single-center retrospective study. Int J Immunopathol Pharmacol 2015;28(4):479–87.

[19] Janta I, Martínez-Estupiñán L, Valor L, Montoro M, Baniandres Rodriguez O, Hernández Aragüés I, et al. Comparison between full and tapered dosages of biologic therapies in psoriatic arthritis patients: clinical and ultrasound assessment. Clin Rheumatol 2015;34(5):935–42.

[20] Gossec L, Smolen JS, Ramiro S, de Wit M, Cutolo M, Dougados M, et al. European league Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. Ann Rheum Dis 2016;75(3):499–510.

[21] Huynh DH, Boyd TA, Etzel CJ, Cox V, Kremer J, Mease P, et al. Persistence of low disease activity after tumor necrosis factor inhibitor (TNFi) discontinuation in patients with psoriatic arthritis. RMD Open 2017;3(1):e000395.

[22] Smolen JS, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas D, Burmester G, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis 2010 Apr;69(4):631–7. https://doi.org/10.1136/ard.2009.123919.

[23] Smolen JS, Braun J, Dougados M, Emery P, Fitzgerald O, Helliwell P, et al. Treating

spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis, to target: recommendations of an international task force. Ann Rheum Dis 2014 Jan;73(1):6–16. https://doi.org/10.1136/annrheumdis-2013-203419.
[24] Hamburg MA, Collins FS. The path to personalized medicine. N Engl J Med 2010 Jul 22;363(4):301–4. https://doi.org/10.1056/NEJMp1006304.
[25] van der Ven M, Kuijper TM, Gerards AH, Tchetverikov I, Weel AEAM, van Zeben D, et al. Can We Use Ultrasound to Identify Rheumatoid Arthritis Patients in Remission Who Cannot Taper Their Medication? Presented at EULAR. 2014. p. OP0123.
[26] Marks JL, Holroyd CR, Dimitrov BD, Armstrong RD, Calogeras A, Cooper C, et al. Does combined clinical and ultrasound assessment allow selection of individuals with rheumatoid arthritis for sustained reduction of anti-tumor necrosis factor therapy? Arthritis Care Res (Hoboken) 2015 May;67(6):746–53. https://doi.org/10.1002/acr.22552.
[27] Smolen JS, Nash P, Durez P, Hall S, Ilivanova E, Irazoque-Palazuelos F, et al. Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): a randomised controlled trial. Lancet. 2013 Mar 16;381(9870):918–29. https://doi.org/10.1016/S0140-6736(12)61811-X.
[28] Wallis D, Holmes C, Holroyd C, Sonpal K, Zarroug J, Adams J, et al. Dose reduction of biological therapies for inflammatory rheumatic diseases: what do patients think? Scand J Rheumatol 2019 May;48(3):251–2. https://doi.org/10.1080/03009742.2018.1533034.
[29] Lau CS, Gibofsky A, Damjanov N, Lula S, Marshall L, Jones H, et al. Down-titration of biologics for the treatment of rheumatoid arthritis: a systematic literature review. Rheumatol Int 2017 Nov;37(11):1789–98. https://doi.org/10.1007/s00296-017-3780-8.
[30] Ye W, Tucker LJ, Coates LC. Tapering and discontinuation of biologics in patients with psoriatic arthritis with Low disease activity. Drugs. 2018 Nov;78(16):1705–15. https://doi.org/10.1007/s40265-018-0994-3.
[31] Ibrahim F, Lorente-Cánovas B, Doré CJ, Bosworth A, Ma MH, Galloway JB, et al. Optimizing treatment with tumour necrosis factor inhibitors in rheumatoid arthritis-a proof of principle and exploratory trial: is dose tapering practical in good responders? Rheumatology (Oxford) 2017 Nov 1;56(11):2004–14. https://doi.org/10.1093/rheumatology/kex315.
[32] Emery P, Hammoudeh M, FitzGerald O, Combe B, Martin-Mola E, Buch MH, et al. Sustained remission with etanercept tapering in early rheumatoid arthritis. N Engl J Med 2014 Nov 6;371(19):1781–92. https://doi.org/10.1056/NEJMoa1316133.
[33] Fautrel B, Pham T, Alfaiate T, Gandjbakhch F, Foltz V, Morel J, et al. Step-down strategy of spacing TNF-blocker injections for established rheumatoid arthritis in remission: results of the multicentre non-inferiority randomised open-label controlled trial (STRASS: Spacing of TNF-blocker injections in Rheumatoid ArthritiS Study). Ann Rheum Dis 2016 Jan;75(1):59–67. https://doi.org/10.1136/annrheumdis-2014-206696.
[34] den Broeder AA, van Herwaarden N, van der Maas A, van den Hoogen FH, Bijlsma JW, van Vollenhoven RF, et al. Dose REduction strategy of subcutaneous TNF inhibitors in rheumatoid arthritis: design of a pragmatic randomised non inferiority trial, the DRESS study. BMC Musculoskelet Disord 2013 Oct 24;14:299. https://doi.org/10.1186/1471-2474-14-299.
[35] van Herwaarden N, van der Maas A, Minten MJ, van den Hoogen FH, Kievit W, van Vollenhoven RF, et al. Disease activity guided dose reduction and withdrawal of adalimumab or etanercept comparedwith usual care in rheumatoid arthritis: open label, randomised controlled, non-inferiority trial. BMJ. 2015 Apr 9;350:h1389. https://doi.org/10.1136/bmj.h1389.
[36] Smolen JS, Landewé R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017 Jun;76(6):960–77. https://doi.org/10.1136/annrheumdis-2016-210715.
[37] Singh JA, Saag KG, Bridges Jr SL, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American college of rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol 2016 Jan;68(1):1–26. https://doi.org/10.1002/art.39480.
[38] Lau CS, Chia F, Dans L, Harrison A, Hsieh TY, Jain R, et al. 2018 update of the APLAR recommendations for treatment of rheumatoid arthritis. Int J Rheum Dis 2019 Mar;22(3):357–75. https://doi.org/10.1111/1756-185X.13513.
[39] Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA. 2006 May 17;295(19):2275–85.
[40] Mariette X, Matucci-Cerinic M, Pavelka K, Taylor P, van Vollenhoven R, Heatley R, et al. Malignancies associated with tumour necrosis factor inhibitors in registries and prospective observational studies: a systematic review and meta-analysis. Ann Rheum Dis 2011 Nov;70(11):1895–904. https://doi.org/10.1136/ard.2010.149419.
[41] Warren FC, Abrams KR, Sutton AJ. Hierarchical network meta-analysis models to address sparsity of events and differing treatment classifications with regard to adverse outcomes. Stat Med 2014 Jun 30;33(14):2449–66. https://doi.org/10.1002/sim.6131.
[42] Tarp S, Eric Furst D, Boers M, Luta G, Bliddal H, Tarp U, et al. Risk of serious adverse effects of biological and targeted drugs in patients with rheumatoid arthritis: a systematic review meta-analysis. Rheumatology (Oxford) 2017 Mar 1;56(3):417–25. https://doi.org/10.1093/rheumatology/kew442.
[43] den Broeder AA, van der Maas A, van den Bemt BJ. Dose de-escalation strategies and role of therapeutic drug monitoring of biologics in RA. Rheumatology (Oxford) 2010 Oct;49(10):1801–3. https://doi.org/10.1093/rheumatology/keq060.
[44] Kobelt G. Treating to target with etanercept in rheumatoid arthritis: cost-effectiveness of dose reductions when remission is achieved. Value Health 2014 Jul;17(5):537–44. https://doi.org/10.1016/j.jval.2014.04.005.
[45] Fautrel B, Verstappen SM, Boonen A. Economic consequences and potential benefits. Best Pract Res Clin Rheumatol 2011 Aug;25(4):607–24. https://doi.org/10.1016/j.berh.2011.10.001.
[46] Steele FR. Personalized medicine: something old, something new. Pers Med 2009;6(1):1–5. https://doi.org/10.2217/17410541.6.1.1.
[47] Treharne GJ, Lyons AC, Hale ED, Douglas KM, Kitas GD. “Compliance” is futile but is “concordance” between rheumatology patients and health professionals attainable? Rheumatology (Oxford) 2006 Jan;45(1):1–5. https://doi.org/10.1093/rheumatology/kei223.
[48] Berry D, Bradlow A, Bersellini E. Perceptions of the risks and benefits of medicines in patients with rheumatoid arthritis and other painful musculoskeletal conditions. Rheumatology (Oxford) 2004 Jul;43(7):901–5. https://doi.org/10.1093/rheumatology/keh196.
[49] Sokka T, Hetland ML, Mäkinen H, Kautiainen H, Hørslev-Petersen K, Luukkainen RK, et al. Questionnaires in standard monitoring of patients with rheumatoid arthritis group. Remission and rheumatoid arthritis: data on patients receiving usual care in twenty-four countries. Arthritis Rheum 2008 Sep;58(9):2642–51. https://doi.org/10.1002/art.23794.
[50] Cutolo M, Kitas GD, van Riel PL. Burden of disease in treated rheumatoid arthritis patients: going beyond the joint. Semin Arthritis Rheum 2014 Feb;43(4):479–88. https://doi.org/10.1016/j.semarthrit.2013.08.004.
[51] Taylor PC, Moore A, Vasilescu R, Alvir J, Tarallo M. A structured literature review of the burden of illness and unmet needs in patients with rheumatoid arthritis: a current perspective. Rheumatol Int 2016 May;36(5):685–95. https://doi.org/10.1007/s00296-015-3415-x.
[52] Druce KL, Bhattacharya Y, Jones GT, Macfarlane GJ, Basu N. Most patients who reach disease remission following anti-TNF therapy continue to report fatigue: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Rheumatology (Oxford) 2016 Oct;55(10):1786–90. https://doi.org/10.1093/rheumatology/kew241.
[53] Zhang H, Xu H, Chen S, Mao X. The application value of MRI in the diagnosis of subclinical inflammation in patients with rheumatoid arthritis in remission. J Orthop Surg Res 2018 Jul 3;13(1):164. https://doi.org/10.1186/s13018-018-0866-2.
[54] Nurmohamed MT, Heslinga M, Kitas GD. Cardiovascular comorbidity in rheumatic diseases. Nat Rev Rheumatol 2015 Dec;11(12):693–704. https://doi.org/10.1038/nrrheum.2015.112.
[55] Hamann PDH, Pauling JD, McHugh N, Shaddick G, Hyrich K; BSRBR-RA Contributors Group. Predictors, demographics and frequency of sustained remission and low disease activity in anti-tumour necrosis factor-treated rheumatoid arthritis patients. Rheumatology (Oxford)doi: https://doi.org/10.1093/rheumatology/kez188. [Epub ahead of print].
[56] de Punder YM, Fransen J, Kievit W, Houtman PM, Visser H, van de Laar MA, et al. The prevalence of clinical remission in RA patients treated with anti-TNF: results from the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry. Rheumatology (Oxford) 2012 Sep;51(9):1610–7. https://doi.org/10.1093/rheumatology/kes078.
[57] Olsen IC, Lie E, Vasilescu R, Wallenstein G, Strengholt S, Kvien TK. Assessments of the unmet need in the management of patients with rheumatoid arthritis: analyses from the NOR-DMARD registry. Rheumatology (Oxford) 2019 Mar 1;58(3):481–91. https://doi.org/10.1093/rheumatology/key338.
[58] Katchamart W, Johnson S, Lin HJ, Phumethum V, Salliot C, Bombardier C. Predictors for remission in rheumatoid arthritis patients: a systematic review. Arthritis Care Res (Hoboken). 2010 Aug;62(8):1128–43. https://doi.org/10.1002/acr.20188.
[59] Rheumatoid Patient Foundation. Unmasking rheumatoid disease: the patient experience of rheumatoid arthritis. http://rheum4us.org/wp-content/uploads/2013/04/Unmasking-Rheumatoid-Disease-The-Patient-Experience-of-rheumatoid-Arthritis-White-Paper.pdf; 2013.
[60] Coenen M, Cieza A, Stamm TA, Amann E, Kollerits B, Stucki G. Validation of the International Classification of Functioning, Disability and Health (ICF) Core Set for rheumatoid arthritis from the patient perspective using focus groups. Arthritis Res Ther 2006;8(4):R84. https://doi.org/10.1186/ar1956.
[61] Hope HF, Bluett J, Barton A, Hyrich KL, Cordingley L, Verstappen SM. Psychological factors predict adherence to methotrexate in rheumatoid arthritis; findings from a systematic review of rates, predictors and associations with patient-reported and clinical outcomes. RMD Open 2016 Jan 20;2(1):e000171https://doi.org/10.1136/rmdopen-2015-000171.
[62] Smolen JS, Gladman D, McNeil HP, Mease PJ, Sieper J, Hojnik M, et al. Predicting adherence to therapy in rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis: a large cross-sectional study. RMD Open 2019 Jan 11;5(1):e000585https://doi.org/10.1136/rmdopen-2017-000585.
[63] Bechman K, Clarke BD, Rutherford AI, Yates M, Nikiphorou E, Molokhia M, et al. Polypharmacy is associated with treatment response and serious adverse events: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Rheumatology (Oxford) 2019 Apr 14. https://doi.org/10.1093/rheumatology/kez037.
[64] Galloway JB, Hyrich KL, Mercer LK, Dixon WG, Fu B, Ustianowski AP, et al. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. Rheumatology (Oxford) 2011 Jan;50(1):124–31. https://doi.org/10.1093/rheumatology/keq242.
[65] Mercer LK, Davies R, Galloway JB, Low A, Lunt M, Dixon WG, et al. Risk of cancer in patients receiving non-biologic disease-modifying therapy for rheumatoid

arthritis compared with the UK general population. Rheumatology (Oxford) 2013 Jan;52(1):91–8. https://doi.org/10.1093/rheumatology/kes350.

[66] Pincus T, Kavanaugh A, Sokka T. Benefit/risk of therapies for rheumatoid arthritis: underestimation of the "side effects" or risks of RA leads to underestimation of the benefit/risk of therapies. Clin Exp Rheumatol 2004 Sep-Oct;22(5 Suppl 35):S2–11.

[67] Smolen JS, Emery P, Ferraccioli GF, Samborski W, Berenbaum F, Davies OR, et al. Certolizumab pegol in rheumatoid arthritis patients with low to moderate activity: the CERTAIN double-blind, randomised, placebo-controlled trial. Ann Rheum Dis 2015 May;74(5):843–50. https://doi.org/10.1136/annrheumdis-2013-204632.

[68] Hashimoto M, Furu M, Yamamoto W, Fujimura T, Hara R, Katayama M, et al. Factors associated with the achievement of biological disease-modifying antirheumatic drug-free remission in rheumatoid arthritis: the ANSWER cohort study. Arthritis Res Ther 2018 Aug 3;20(1):165. https://doi.org/10.1186/s13075-018-1673-1.

[69] Nair KV, Tang B, Van Den Bos J, Zhang V, Saseen JJ, Naim A, et al. Categorization of infliximab dose changes and healthcare utilization and expenditures for patients with rheumatoid arthritis in commercially insured and Medicare-eligible populations. Curr Med Res Opin 2009 Feb;25(2):303–14. https://doi.org/10.1185/03007990802598736.