
The when and how of biologic agent withdrawal in rheumatoid arthritis: learning from large randomised controlled trials

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ABSTRACT

There has been great interest lately concerning the possibility that in the treatment of rheumatoid arthritis, biologic agents might be withdrawn for patients who achieve desirable targets, such as low disease activity or remission. While there are a number of reasons why such a treatment paradigm might be desirable, there is a paucity of relevant data at present to guide clinicians about embarking on such a treatment change. Data is starting to emerge, much of it from controlled trials, that can provide some guidance as to which patients might be the best candidates for such an approach. These data will provide answers to the key questions that remain concerning this important potential paradigm shift in the treatment of rheumatoid arthritis as well as other systemic inflammatory autoimmune diseases.

Introduction

Recent years have witnessed dramatic changes in the approach to treatment of rheumatoid arthritis (RA). After learning how to optimise the use of the anchor drug methotrexate (MTX) (1), the introduction of biologic agents, in particular TNF inhibitors, resulted in improved outcomes for many patients. Indeed, the efficacy seen with TNF inhibitors plus MTX highlighted the need for more rigorous consideration of describing better outcomes in RA, such as the debate concerning the optimal definition of 'remission' – remission became a realistic and frequently reachable goal (2). Moreover, the success achieved by newer agents renewed the impetus for changes in the approach to treatment that had first arisen some years prior: namely the earlier and more intensive use of traditional DMARDs, especially MTX. In addition, it helped with the codification of novel treatment paradigms such as "Treat-to-Target."

In this dynamic atmosphere, another novel potential treatment paradigm has emerged: namely, whether it is possible to discontinue biologic agents among RA patients who achieve a goal of remission or low disease activity, and maintain the clinical response.

This type of approach resembles treatment paradigms used in other disciplines, such as the "induction-consolidation" treatment approach used for certain malignancies. Such an approach has also been tried in RA patients several times over the years with traditional DMARDs (3). Alas, disease flares after stopping traditional DMARDs and significant difficulties in regaining remission were commonly seen with these drugs. However, with the more effective therapies and therapeutic strategies currently employed, this concept has gained increasing interest.

A number of reasons explain the appeal of potential successful withdrawal of therapy with biologic agents in RA. First, the safety profile of biologic agents appears acceptable, especially in the case of TNF inhibitors that have been studied for more than two decades. However, if a clinical response induced by therapy with a biologic agent may be maintained without the need for the agent, that would obviate any potential risk associated with continued treatment. Second, pharmacoeconomic considerations are crucial to the discussion of possibly withdrawing biologic agents (4). Because biologic agents have an acquisition cost far in excess of older therapies such as traditional DMARDs, some RA patients worldwide have limited or no access to them. If the benefits could be achieved with shorter treatment courses, access could be optimised. Finally, patient choice is a critical component of treatment paradigms. In the clinic, as with patients who have other chronic diseases

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commonly treated with multiple medications, RA patients not infrequently express a desire “not to take so many medicines” to their treating physicians, and they frequently ask the question: “Do I have to take this medicine all my life now?” Indeed, patients may choose to explore the paradigm of tapering or discontinuing RA therapies on their own, as evidenced by compliance data. Withdrawal of biologic therapies in a systematic manner may promote better adherence and long-term outcomes.

Some considerations would argue against withdrawing biologic agents in RA patients. RA is an immunologically driven systemic inflammatory condition that presumably arises following the exposure of a genetically susceptible host to a relevant inciting agent, under the influence of environmental and host factors. However, there are data suggesting that the immunoinflammatory profile in early RA is different from that in established RA (5). Therefore, one might be able to see differences between intensive interventions early versus late in the disease course; thus, early strong interference might abort initiation of a dysregulatory “vicious circle” and lead to a “rebooting” of a more “normal,” regular immunoinflammatory situation.

While outcomes are improved with newer agents and treatment strategies, there is no evidence we are fundamentally altering the autoimmune process or inducing immunologic tolerance. Therefore, the disease may continue to smolder, albeit at a low level. Highly sensitive imaging studies, such as magnetic resonance imaging (MRI) and ultrasound (US), as well as immunopathologic analyses have suggested that this indeed can occur. Patients with low disease activity and even patients who have met stringent remission criteria can have evidence of subclinical disease activity.

The long-term implications of this disease activity remain unknown at present, but it is possible that smoldering subclinical RA may have an impact on functional status over the years. Smoldering disease may attenuate some of the other benefits of profound disease control. RA is associated with comorbidi-

ties, including accelerated cardiovascular disease, that relate to the systemic inflammatory burden, and disease control appears to benefit cardiovascular outcomes and risk. It is theoretically possible that withdrawal of biologic agents might diminish some of this benefit.

Studies of biologic withdrawal

A number of recent studies have addressed the topic of withdrawal of biologic agents. A systematic review of the methods used indicates substantial heterogeneity among these studies (6). Nevertheless, data from these studies inform not only the ultimate question of whether withdrawal of biologic agents is feasible, but also provide some guidance on considerations of optimal trial design for future studies. A number of studies have been reviewed recently (7). Herein we focus on two large double-blind placebo controlled randomised clinical trials (DB-PC-RCT) of biologic withdrawal in more detail.

In the PRESERVE trial (8), patients who had moderately active disease while taking MTX received etanercept at 50 mg weekly for 9 months in an initial open phase. More than 80% of these patients achieved low disease activity (LDA) according to DAS28 (<2.6) or SDAI ≤11). The patients who attained a stable LDA state, indicated by a mean DAS28 <3.2 over a period of 6 months, were then randomised to continuation of etanercept at 50 mg weekly (plus MTX), continuation at a reduced dose (25 mg weekly plus MTX), or withdrawal of etanercept and continuation of MTX, in a double-blind fashion.

One year later, 57% of patients who withdrew etanercept had lost their LDA state, compared to only 18% who continued full-dose etanercept and 21% who received half the dose of the biologic agent. Similar results were seen for all other clinical and functional endpoints. Progression of joint damage was halted with both etanercept doses, but withdrawal of etanercept was accompanied by recurrence of some joint damage in a subset of patients. Thus, in patients with established RA, withdrawal of an anti-TNF agent, after attainment of a good response, is accompanied by

a disease flare; on the other hand, dose reduction appears an acceptable option, since more than 90% of patients in whom etanercept was reduced maintained their good response. These findings were essentially confirmed in the CERTAIN study of certolizumab pegol (9). In that study, also among patients with established RA, withdrawal of biologic therapy was unsuccessful for most patients.

A different situation appears to occur in patients with early RA. Preliminary data from the OPTIMA trial indicate that withdrawal of adalimumab (with continuation of MTX) in patients with early RA who attained stable low disease activity after 6 months of therapy with adalimumab plus MTX did not lead to reactivation of disease in the vast majority of patients (10). These preliminary data from the double-blind withdrawal study OPTIMA are supported by another recent study called HIT-HARD (11). In that open label study, adalimumab was withdrawn among patients with early RA in low disease activity, and many patients retained benefit over a year of follow-up. The data suggest that there may be a fundamental difference between patients who are MTX-naïve and receive an induction regimen of MTX with a TNF inhibitor, versus those who do not respond to MTX sufficiently, improve upon addition of a TNF-blocker and then are withdrawn from the biologic. Indeed, this concept echoes reports from observational studies (12, 13). On the other hand, a recent abstract presenting withdrawal of etanercept in a similar population and setting as in OPTIMA did not find a similar rate of maintenance of low disease activity: while 89% maintained LDA upon continuation of etanercept (even though the dose was halved), only 69% continued to exhibit LDA when etanercept was withdrawn in the PRIZE study (14). This suggests that there is either a difference in influencing the immunoinflammatory response between adalimumab and etanercept in the course of an induction therapy in early RA or that induction therapy may not be overly robust. Thus, more data are needed to answer these questions.

Future directions

To date, some lessons have been learned from studies on biologic withdrawal. It appears that biologic therapies can be withdrawn at least for a subset of treated patients, particularly those with early disease. At present, it is not possible to predict which patients are the best candidates for such an approach. Nevertheless, these early studies have helped clarify some of the key variables that may affect results from studies of discontinuation of biologic agents in RA. Knowing the answers to these will allow consistent and systematic analyses of the data. In addition, this will facilitate the design of future studies, such that it may be possible to better identify the most appropriate patients that could be considered for such a treatment paradigm. These key questions include:

1. What designs were considered (*i.e.* complete withdrawal *vs.* reduction of the dose or extension of the interval between applications of biologic agent)?
2. What was the goal of treatment before withdrawal was attempted (*e.g.* LDA *vs.* remission *vs.* other; what definitions were used for the goals)?
3. What was the length of time required for patients to be at the goal before biologic therapy was withdrawn?
4. What was the duration of RA among enrolled patients?
5. What prior treatments were allowed for enrolled patients?
6. What was the level of disease activity before biologic therapy was initiated, and what was the depth of response achieved with biologic therapy before discontinuation?
7. How were concomitant medications handled during the discontinuation/taper period, including DMARDs, corticosteroids, and NSAIDs?
8. How were treatment success and treatment failure defined (disease activity by signs and symptoms as

assessed by DAS, SDAI, CDAI or other, damage as assessed by x-ray, functional status as assessed by HAQ)?

9. How long were the patients followed?
10. What was the impact of re-treatment, *i.e.* could benefit be recaptured, and if so, how long did it take?
11. Were there sequelae, particularly in terms of joint damage and functional impairment, among patients stopping or tapering therapy who subsequently flared?
12. Could any predictors of response, including immunological changes, be identified?

Conclusions

Tapering or discontinuing biologic therapy in patients with RA who have achieved their therapeutic target is a concept that has substantial appeal from multiple perspectives, including pharmacoeconomics, safety, and patient preferences. A number of clinical trials have begun to address this issue recently. Analysing data from these trials in order to inform clinical decisions about this approach is complicated by heterogeneity among the studies. Nevertheless, some information can be derived that can serve as the basis for future studies. With further information, including additional large controlled trials, it is hoped that clinicians may be in a position to withdraw or taper biologic therapy in appropriate RA patients while maintaining optimal outcomes.

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