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Review

Are there dangers in biologic dose reduction strategies?

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ABSTRACT

Biologic dose reduction strategies, for patients with inflammatory rheumatic diseases, have been assessed in multiple studies to assess outcomes compared to ongoing maintenance dosing. Whilst cessation in established disease usually leads to disease flare, dose tapering approaches for those achieving low disease activity often appear to be successful in the short term. However, tapering can be associated with a higher risk of losing disease control and rates of recapture of disease control using the original biologic dose vary between studies.
Over relatively short periods of follow-up, a number of studies have shown no statistical difference in radiographic progression in patients tapering or discontinuing biologics. However, a Cochrane review found that radiographic and functional outcomes may be worse after TNF inhibitor discontinuation, and over long-term disease follow-up flares have been associated with radiographic progression and worse patient reported outcomes. To date, no studies of biological therapy dose reduction have specifically investigated the risk of increased immunogenicity or the effects on cardiovascular risk and other co-morbidities, although these remain important potential risks. In addition, whether there are greater dangers in certain dose reduction approaches such as a reduction in dose at the same frequency or a spacing of doses is not established.

Contents

1. Introduction

Biological therapies such as the TNF inhibitors are highly effective in controlling disease in multiple inflammatory diseases including rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS). Dose reduction strategies may be considered due to patient preference, reduction of potentially dose-dependent risk of infections [1,2] and malignancies [3], and to save costs.

There are a number of studies that suggest that there is an opportunity to optimise dosing of biologics through dose reduction. These stem partly from work investigating the consequences of standard doses of biological therapies on the serum trough levels in an individual and its effect on disease activity. For instance, in a study involving 103 patients with PsA, adalimumab concentrations at 28 weeks were measured as serum trough samples, and for absolute change in DAS 28 the concentration-effect curve showed an optimal dose of 5–8 mg/L, where doses above 8 mg/L appeared to have no additional benefit. In this study 47% of the patients were above this 8 mg/L threshold [4].

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This study identified a group of patients who could potentially have their biologic dose reduced without adverse effects on disease activity. After all it is hard to believe that the "one size fits all" approach of standardised dosing reflects the needs of all patients.

This article will not go into detail regarding selection strategies for dose reduction, which have been considered by interested organisations such as ACR, EULAR, and NICE, but will instead focus on the possible risks of dose reduction and how this may be mitigated. Dose reduction strategies might also consider the optimisation of the doses and route of delivery of traditional disease modifying antirheumatic drugs (DMARDs) such as methotrexate (MTX). In patients with RA on TNF inhibitors, DMARDs such as MTX may prolong drug survival by reducing immunogenicity [5]. It is also clear that there is a paucity of information regarding the patient view with regards to dose reduction. Studies in this area need to be performed as a matter of urgency.

2. Dangers in biologic dose reduction strategies

Understanding the risk of disease flare and its consequences, after discontinuation of treatment in patients who are well controlled on therapy, has always been a dilemma for rheumatologists. This was a problem initially assessed with the use of conventional non-biologic DMARDs in the late 1990s. In an observational study of 285 patients with inactive RA, 38% flared (n = 53) when randomised to replacement of DMARD with placebo whereas 22% flared on continuing the same DMARD [6]. Of the people who flared on placebo, 51 were recommenced on the same DMARD as prior, but there was lack of efficacy for 4 patients (2 taking parenteral gold and 2 taking sulphasalazine). This highlights some of the issues facing clinicians when considering reduction of the dose of biological therapies. These include loss of disease control, problems with regaining control, other risks during regain of control (such as radiographic progression, cardiovascular risk, and worsening patient reported outcomes), and immunogenicity. We will now explore these risks when dose reducing biologic drugs.

2.1. Loss of disease control

Varying relapse rates (whether by flare, loss of low disease activity (LDA) (DAS 28 <3.2), or loss of remission (DAS 28 <2.6)) have been seen across a variety of studies, mainly for RA. In the discontinuation studies, the worst outcomes have shown 84% flare within 52 weeks of stopping tociluzimab [7] and 86% not in remission at 52 weeks of stopping tociluzimab [8]. The best outcomes in the discontinuation studies have shown 52% no longer in remission at 1 year of stopping adalumimab [9], and 58.8% no longer in remission at 1 year of discontinuing abatacept [10]. Studies have taken a number of forms including randomised control trials (RCTs) with common rules of dose continuation and dose reduction for whole patient groups, disease activity driven trials that customise dose alteration to an individual's disease activity, and observational or real life data which often lacks a control group.

The results from relevant RCTs have been examined in detail in a series of reviews. A Cochrane review in 2014 found, based on moderate quality evidence, that those in a LDA state who then discontinued TNF inhibitors (adalimumab and etanercept data) had higher mean DAS28-ESR: mean difference (MD) 1.10, 95% CI 0.86 to 1.34 and DAS28-CRP: MD 0.57, 95% CI −0.09 to 1.23, and were less likely to maintain a LDA state compared to those who continued their respective TNF inhibitor (RR 0.43, 95% CI 0.27 to 0.68, absolute risk difference 40%) [11].

PRESERVE, one of the larger RCTs, investigated the efficacy of etanercept in those with moderate disease RA (DAS 28 >3.2 and ≤5.1) despite treatment with MTX, followed by a strategy of reduction or withdrawal of etanercept [12]. Having received etanercept 50 mg weekly plus MTX for 36 weeks, and having reached LDA, patients were randomised to continuation, half dose, or withdrawal of etanercept in the double blind period. At week 88, 166 (82.6%) of 201 patients who had received at least one dose of 50 mg etanercept and one or more DAS 28 evaluations had LDA, compared with 84 (42.6%) of 197 who had received placebo (mean difference 40.8%, 95% CI 32.5–49.1%; p < 0.0001). Furthermore, 159 (79.1%) of 201 patients given 25 mg etanercept had LDA at week 88 (mean difference from placebo 35.9%, 27.0–44.8%; p < 0.0001). Therefore, approximately 57% had lost LDA when moved on to placebo, compared with 21% of those with a tapered dose, but also 17% in those who continued unchanged without a dose reduction strategy.

The Spacing of TNF-blocker injections in Rheumatoid ArthritiS Study (STRASS) was a multicentre 18-month study that customised dose alteration to an individual's disease activity. The study aimed to demonstrate the equivalence of down-titrating etanercept or adalimumab by progressively spacing injections (S-arm) and maintaining a full-regimen therapy (M-arm) in terms of disease activity. Approximately one quarter (24%) of tapering S-arm patients did not relapse. The risk of relapse was significantly higher in the spacing arm than in the maintenance arm (HR 2.37 (95% CI 1.47 to 3.83); p = 0.0004) [13].

In real life settings the practical realities of adapting the knowledge gained from RCTs have been explored. In Southampton a dose reduction strategy of 30% dose reduction was tried for RA patients on TNF inhibitors with "deep remission" having been on anti-TNF for >1 year with no concomitant corticosteroid use [14]. "Deep remission" was defined as having no evidence of hand or wrist synovitis on power Doppler ultrasound, not being on corticosteroids and DAS 28 <2.6 (for at least 6 months at entry). At 6 months following dose reduction 63% of patients were still in "deep remission" but by 18 months only 34% remained in "deep remission". However, it should be noted that this group of patients had very active disease (>DAS28 5.1 at TNF inhibitor initiation) that had been present for at least 10 years and a flare was defined as any increase in DAS28 score above 2.6, any synovitis seen on power Doppler US or the patient's view that a flare was occurring. The DOSERA study also looked at a dose reduction strategy in those in remission under standard care, with more severe refractory RA compared to PRESERVE. The results were less impressive in DOSERA than in PRESERVE, with a week 48 failure (based on clinician and patient defined flare) rates of 48%, 56%, and 87% for full dose, half dose (25 mg) or placebo etanercept, all taken with MTX, respectively [15].

In summary, dose tapering or reduction has a higher risk of loss of disease control compared to continuation of existing dose biologic, but full discontinuation in those in LDA or remission with established RA has much higher risks of failure. Indeed, the most recent study shows that the hazard ratio for flare after stopping a TNF inhibitor was 3.50 (95% CI: 2.60–4.72). Mean DAS28 scores in the stop group were significantly higher during the follow-up period compared with the continuation group (p < 0.001) [16]. However, it is apparent that some individuals respond well to dose reduction strategies and perhaps the real challenge is defining this population. In most studies the identification of patients who could potentially reduce their dose of biologics has been based on selecting those with persistent remission or low disease activity. It seems likely now that a more sophisticated approach is needed that takes into account more factors than a clinical measure of disease activity; perhaps through advances from the current stratified medicine studies in RA and other inflammatory rheumatic diseases.

2.2. Failure to recapture control, and other risks in those requiring recapture

The likelihood of recapturing low disease activity or remission after dose reduction is an important consideration. A number of studies have considered this and rates in the range 80% [13] – 100% [9] to recapture LDA have been described. From the Cochrane review, radiographic and functional outcomes appear worse after TNF inhibitor discontinuation (MD 0.66, 95% CI 0.63 to 0.69, and MD 0.30, 95% CI 0.19 to 0.41, respectively) [11].