Discontinuation of biologics in patients with rheumatoid arthritis

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ABSTRACT

The use of early aggressive treatment combined with the availability of biological agents targeting pro-inflammatory cytokines such TNF and IL-6 has greatly advanced the treatment of rheumatoid arthritis (RA). Clinical remission is a realistic primary goal and its maintenance leads to stabilisation of structural deterioration and functional remission. With the achievement of sustained remission, discontinuation of biological agents has emerged as an important consideration, with subsequent reductions in medication-induced side effects and health costs.

Evidence from studies suggests that MTX-naïve, early RA patients can achieve sustained biologic-free remission with no functional or radiographic progression, after treatment with combination TNF inhibitors and MTX.

For patients with long-standing RA and who have previous inadequate responses to MTX, the evidence for sustained biologic-free remission is less convincing. The discontinuation of TNF-inhibitors after sustained remission has been shown to be possible in some long-standing RA patients with inadequate response to MTX, particularly in Japanese patients. However, high flare rates and adverse long-term outcomes have been documented in other studies. For these patients a biologic dose-reduction regimen may be preferable.

The combination of early treatment with TNF inhibitors and MTX plus tight control of inflammation provide the best chance of a biologic-free remission or at least the possibility of "biologic treatment holidays".

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease that causes significant morbidity and premature mortality. However, the early use of disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate (MTX) and the introduction of biological agents targeting TNF and other cytokines have revolutionised RA treatment (1-5). Clinical remission is perceived as an appropriate and realistic primary goal in many patients, and its maintenance – especially with biological agents – leads to structural and functional remission. Caution is required concerning decisions to discontinue synthetic DMARDs, as discontinuation results in twice as many flare-ups, difficulty in reintroducing remission, and a halt in damage prevention (6). However, similar studies are just becoming available for biological agents. The possibility of discontinuation of biological agents after achieving remission must be considered, because of both the potential long-term safety issues and the economic burden associated with their expense. Multiple studies have recently investigated whether remission can be sustained after a biological agent is discontinued, namely, "biologic-free remission." This article provides an overview of the literature regarding the discontinuation of TNF inhibitors and other biological agents in RA patients, after obtaining low disease activity or clinical remission.

Discontinuation of TNF inhibitors in patients with an inadequate response to MTX (MTX-IR)

The initial management of patients with newly diagnosed RA is aimed at controlling inflammation, maintaining function and preventing structural joint damage. For the majority of patients worldwide, MTX is now used as the first-line DMARD, with slight differences in regional and national algorithms for further DMARD and biological agents (7). The success of TNF-inhibitors in patients with inadequate responses to MTX is well documented (8, 9).

A Japanese group conducted a multi-centre prospective study, RRR (Remission induction by Remicade in RA patients), aimed at the possibility of

biologic-free remission in RA patients whose mean disease duration was 5.9 years (4, 5, 10, 11). This study included a total of 114 patients with RA who reached and maintained low disease activity (LDA; DAS28 <3.2) for more than 24 weeks with infliximab treatment, who then agreed to discontinue the treatment. Among the 102 evaluable patients who completed the study, 56 maintained LDA after one year and showed no progression in radiologic damage and functional disturbance, and 44 remained in clinical remission (DAS28 <2.6). The mean disease duration of the RRR-achieved group was 4.8±5.9 years, which made this study the first to prove that some patients with long disease duration may also aim for discontinuation. Yearly progression of total Sharp score was less than 0.5 points in 67% and HAQ-DI score was only 0.174 in patients who maintained LDA for one year after the discontinuation, indicating that infliximab could be discontinued for a year without radiographic or functional progression.

Another study from Japan, the HONOR (Humira discontinuation without functional and radiographic damage progressioN follOwing sustained Remission) study, aimed to assess sustained remission after discontinuation of adalimumab in patients with RA with MTX-IR (5, 12). Among 197 RA patients who initiated treatment with combination adalimumab and MTX (mean dose 9 mg/week), 75 achieved sustained remission for at least 24 weeks. Of the patients, 52 agreed to discontinue adalimumab. The mean disease duration and DAS28 score in 75 patients were 7.5 year and 5.1 at baseline, respectively.

Approximately 60% of patients sustained adalimumab-free remission at 6 months. A logistic regression analysis showed that the DAS28-ESR at baseline significantly predicted sustained adalimumab-free remission; a ROC analysis showed that the cut-off value of DAS28-ESR at discontinuation was 2.16. The HAQ-DI and yearly progression in total Sharp score also were unchanged after discontinuing adalimumab. Re-administration of adalimumab to the patients with flare was effective in achieving return to DAS28-4ESR <3.2 within 6 months by 90% of patients.

However, the above successful rates have not been observed in all patients. Saleem *et al*. assessed the effect of cessation of TNF inhibitor therapy (etanercept, adalimumab and infliximab) in patients with established previously severe RA (13). Twenty patients received combination therapy with TNF blocker and MTX after fulfilling the N.I.C.E prescribing guidelines for biologics therapy with median disease duration of 120 months (range 46–480 month). Patients in the delayed treatment group had failed at least two DMARDs (including MTX mean dose 15 mg/week) and 50% had also failed a previous TNF blocking drug (due to secondary non-response) (14). Only three patients were able to sustain remission after cessation of TNF blocking therapy.

Prior to stopping TNF blocking therapy, no significant differences were seen in DAS28 scores between patients who would subsequently sustain remission and those who would flare (median DAS28 1.96 *vs*. 1.67; p=0.84). However, patients who sustained remission after cessation of TNF blocking therapy tended to have lower HAQ (0 *vs*. 1; p=0.04) and RAQoL scores (1 *vs*. 4; p=0.17). No difference was seen in duration of remission before stopping therapy (12 *vs*. 12 months; p=0.68), but sustained remission also was associated with shorter total disease duration compared to flare (median 72 *vs*. 144 months; p=0.09). Of particular importance, despite reinstitution of TNF inhibitor therapy after flaring, DAS28 remission rates were lower than in patients who continued TNF inhibitor therapy (15).

Brocq *et al*. reported that patients with an average duration of RA of 11 years were withdrawn from TNF inhibitor therapy after being in DAS28-defined remission for at least six months. Seventy-five percent (15/20) of patients flared 12 months after the withdrawal of TNF inhibitor therapy (16).

Similar results were observed in the CERTAIN study, which aimed to evaluate the maintenance of remission following withdrawal of certolizumab pegol in patients with low-to-moderately active, long-standing RA despite DMARDs (17). Following 24 weeks double-blinded treatment with certolizumab pegol (n=96) or control (MTX and steroid) (n=98), patients in remission at both weeks 20 and 24 stopped the randomised therapy but remained on conventional DMARD. Among patients randomised to certolizumab pegol, 18.8% had CDAI remission at both weeks 20 and 24 and stopped the therapy, compared to 6.1% of patients randomised to control treatment. After discontinuation, CDAI remission or LDA was retained up to week 52 in 3/17 or 7/17, respectively, in patients with prior certolizumab pegol *vs*. 2/6 in patients with prior control treatment. SDAI remission was observed in 4/17 prior certolizumab pegol and DAS28 (ESR) remission in 4/17 prior certolizumab pegol. Median time to loss of CDAI remission was 42.5 days. These results indicate that most patients with long-standing RA were unable to maintain remission after discontinuing certolizumab pegol.

There are differences between types of patients studied in the above trials that may account for the different clinical outcomes. The patients from the Japanese trials (4, 5, 10-12) were begun on TNF-inhibitor therapy after failing MTX, defined as DAS28 >3.2, whereas the patients in the Leeds cohorts (13) fulfilled much stricter criteria before they were considered MTX inadequate responders and TNF inhibitor therapy was commenced. The latter group would therefore represent a more severe, treatment-resistant group of patients with longer disease duration. The mean doses of MTX in the Japanese studies were 7.7±2.3 mg/week in RRR and 8.9±2.7 mg/week in HONOR, which, as is generally the case in Japan, were considerably lower than in other studies from elsewhere. These differences in study protocol, along with the potential impact of genetic differences of the patients, must be considered.

Dose reduction of TNF inhibitors in patients with an inadequate response to MTX (MTX-IR)

The PRESERVE trial was undertaken to determine whether LDA could be sus-

tained with reduced doses or withdrawal of etanercept in patients with moderately active RA despite MTX (18). After treatment with 50 mg etanercept plus MTX for 36 weeks, 604 patients were randomised to 3 groups in equal numbers: 50 mg etanercept plus MTX; 25 mg etanercept plus MTX; or placebo plus MTX. At week 88, 52 weeks after randomisation, LDA had been maintained in 84 (42.6%) of 197 patients randomised to placebo plus MTX, *versus* 166 (82.6%) of 201 patients who had received at least one dose of 50 mg etanercept and 159 (79.1%) of 201 given 25 mg etanercept. From these results, conventional or reduced doses of etanercept with MTX in patients with moderately active RA more effectively maintain LDA than does MTX alone after withdrawal of etanercept, but LDA was sustained with MTX alone in 42.6% of patients after discontinuing etanercept.

Discontinuation of Abatacept in patients with an inadequate response to MTX (MTX-IR)

The ORION (Orencia Remission Induction and Outcome Navigation) study group assessed abatacept-free remission in 51 RA patients with a DAS28 <2.3 while taking abatacept, in whom the agent was then discontinued or continued. At week 52, 41.2% of the discontinuation group and 64.6% of the continuation group maintained low disease activity. The patients in the discontinuation group (who were given the option of stopping therapy) had a lower mean disease duration compared to those who chose to continue therapy. Furthermore, 14.3% of patients who discontinued abatacept sustained rapid radiographic deterioration; it is unclear from the abstract whether these patients continued a traditional DMARD such as MTX (19).

Discontinuation of Tocilizumab in patients with an inadequate response to MTX (MTX-IR)

Mexican patients in DAS28 remission discontinued tocilizumab and continued MTX therapy (20). Forty patients were recruited, mean disease duration 14 years, and 44% maintained remission at 12 month follow-up. These patients all had received tocilizumab as part of different trial protocols, *i.e*. some patients received tocilizumab after failing TNF inhibitors, some after DMARD failures, and others were MTX-naïve.

The DREAM [Drug-free REmission/low disease activity after cessation of tocilizumab (Actemra) Monotherapy] study investigated remission and LDA after cessation of tocilizumab monotherapy in patients with previous inadequate response to MTX (21). At the time of stopping tocilizumab, patients had received a mean 4 years of treatment. The rate of LDA without concomitant use of synthetic DMARDs was 35.1% at 24 weeks and 13.4% at 52 weeks according to the Kaplan-Meier estimate. DAS28 remission and 2011 ACR/EULAR remission criteria (Boolean approach) were maintained in 17 patients (9.1%) and 14 patients (7.5%), respectively, at 52 weeks. In patients who flared after cessation of tocilizumab, 88.5% regained remission after restarting tocilizumab and therapy was well tolerated.

The rate of drug-free remission after tocilizumab monotherapy seems comparable to rates of sustained remission after stopping TNF inhibitor therapy and continuing MTX, but may be improved if DMARDs are continued. However, the heterogeneous nature of the prior therapies in clinical trials prevents direct comparison.

Discontinuation of TNF inhibitors in MTX-naïve RA patients

The central dogma of "treat-to-target" is that abrogation of inflammation from the onset of the disease should prevent joint damage and preserve physical function, which leads to overall improved quality of life and survival. Thus, the management of RA should shift towards earlier and more intensive treatment strategies. Studies using biologic agents targeting TNF, IL-6 and T cells have proven that intensive initial biologic therapy in early RA patients who have never been treated with MTX results in the improvement of clinical, structural and physiological outcomes over both the short and long terms. Several studies, including TNF20, BeSt, OPTIMA, HIT HARD, IDEA and PRIZE have recently been undertaken to investigate whether remission can be sustained even if a TNF-inhibitor is discontinued after controlling disease activity in early RA patients

A pivotal study concerned with biologic-free remission was performed by Quinn *et al*. (22, 23). Patients with early, active RA were recruited into a 12-month randomised placebo-controlled double-blind trial of infliximab with MTX, with the aim of inducing remission. The primary outcome was synovitis as measured by MRI. At 12 months, all MRI scores were significantly better, with no new erosions in the infliximab+MTX group. The patients in the active treatment arm also achieved higher ACR 50 and 70 responses. Importantly, one year after stopping induction therapy, response was sustained in 70% of patients who had received infliximab+MTX, with a median DAS28 of 2.05.

Saleem *et al*. published a sustained remission rate of 60% after discontinuation of TNF inhibitor therapy in MTX-naïve patients in DAS28 remission after one year of combination therapy. Evidence was found that sustained TNF-inhibitor-free remission was associated with shorter symptom duration prior to receiving therapy (median 5.5 *vs*. 9.0 months, p=0.008) (13).

In the Netherlands, the Behandel-Strategieën (BeSt) study was conducted to compare four treatment strategies and to observe clinical and radiological outcomes in patients with early RA (24-28). Patients with disease duration less than 2 years after onset were enrolled and the mean disease duration was 0.8 years. This pragmatic non-blinded study design recruited 508 patients with high disease activity into four treatment arms. Patients were evaluated by DAS44 every three months. If DAS44 >2.4 (moderate to high disease activity), change or addition of medications is required; if DAS44 ≤2.4 (remission or LDA), current medication is continued; and if DAS44 ≤2.4 continued over 6 months, decrease and/or discontinue concomitant medications including infliximab (see Allaart *et al*. p. S14-S18).

Ninety (75%) patients of 120 in the fourth group who started treatment with infliximab achieved DAS44 ≤2.4; infliximab was withdrawn in 77 patients because DAS44 ≤2.4 was maintained for 6 months. LDA was maintained and progress of joint damage was inhibited in 67 of 77 (87%) patients who were treated with MTX monotherapy for 2 years after infliximab withdrawal. Furthermore, 5 years after receiving infliximab and MTX as initial treatment for RA, 58% of 120 patients discontinued infliximab and 19% of patients have discontinued all DMARD and remained in clinical remission, with minimal joint damage progression. In addition, the total cost of work loss and medical expenses could be suppressed to less than half in the fourth group which was treated with MTX and infliximab initially, compared to other groups whose initial therapy involved only DMARD.

The withdrawal of adalimumab in early RA patients (with a mean RA duration of 3.9 months) was also assessed in a randomised, placebo-controlled, double-blind trial OPTIMA (Optimal Protocol for Treatment Initiation with Methotrexate and Adalimumab) (29, 30). The OPTIMA study showed a significant advantage of initial treatment with adalimumab+MTX *vs.* placebo+MTX to achieve improved disease activity, structural changes, patient-reported outcomes and work productivity outcomes in patients with MTX-naïve RA. The requirement for randomisation to discontinuation was achievement of LDA at both 22 and 26 weeks.

Of the 466 RA patients treated with adalimumab+MTX for 24 weeks, 207 (44%) achieved the stable LDA and were re-randomised to placebo+MTX or adalimumab+MTX. At week 78, 86% treated with adalimumab+MTX and 66% treated placebo+MTX maintained DAS28 remission. SDAI-remission and ΔmTSS remission were comparable for both groups. More patients with continuous adalimumab maintained LDA (91%) than did patients in the adalimumab-free group (81%). In the combined group (consisting of placebo+MTX or adalimumab+MTX), patients with sustained LDA between weeks 26 and 78 maintained or improved work productivity, whilst those who did not sustain LDA worsened with respect to these outcomes. However, continued use of adalimumab+MTX yields better benefits with respect to work productivity than discontinuation of adalimumab for patients who achieve LDA following 26 weeks of adalimumab+MTX.

The withdrawal of adalimumab in early RA patients with mean RA duration of 1.7 months was also assessed in a German study, HIT HARD (High Induction THerapy with Anti-Rheumatic Drugs) (31). During the first 24 weeks, 172 patients were treated with adalimumab+MTX or placebo+MTX. After week 24, both groups were treated with MTX alone for 24 weeks. During the induction phase, 47.0% of patients treated with adalimumab+MTX achieved DAS28 remission, and at week 48, 43.8% were still in remission after 24 weeks of adalimumab-free treatment.

Other studies have been designed to determine rates of TNF-inhibitor-free remission in MTX-naïve patients with early RA. The IDEA (Infliximab as induction therapy in Early rheumatoid Arthritis) study was a randomised controlled trial in DMARD-naïve early RA to compare the efficacy of MTX plus a TNF inhibitor *versus* MTX combined with IV steroid therapy as remission-induction, followed by a treat-to-target approach. A treat-to-target approach was used with treatment escalation if DAS44 >2.4. In the IFX group, IFX was discontinued for sustained remission (DAS44 <1.6 for 6 months). Of the IFX group, 24.5% (14/55) had stopped IFX due to sustained (>6 months) remission and 78.6% (11/14) of them maintained remission (32).

The PRIZE study aimed to determine the effectiveness of etanercept (ETAN) and MTX therapy in MTX-naïve early RA patients who had moderately active disease (33). DAS28 remission was achieved by 70% of patients, and these patients were subsequently randomised to a double-blind 39-week period of reduced-dose etanercept (25 mg) plus MTX, or MTX plus placebo sc, or placebo PO and placebo sc. Sustained remission was observed in 63.5% of patients with ETAN25/MTX, 38.5% with MTX (those who discontinued etanercept) and 23% with placebo (those who discontinued etanercept and MTX). There was no significant radiographic progression in any treatment group (34).

Discontinuation of TNF inhibitors in MTX naïve very early RA patients

With accumulating evidence in support of early treatment with combination TNF inhibitor/biological agent and MTX therapy, identification of patients with very early disease is paramount, and the question arises to whether treatment in the at the onset of IA can prevent or delay the development of RA. The results so far are inconclusive, with evidence that abatacept may reduce the progression to RA (35), but a 6-month course of infliximab monotherapy was unsuccessful (36). The EMPIRE (Etanercept and Methotrexate in Patients to Induce Remission in Early Arthritis) trial aimed to investigate clinical, radiographic and functional outcomes, comparing the efficacy of combination therapy with MTX+ETAN *versus* MTX monotherapy, in subjects with DMARD-naïve very early inflammatory arthritis with the minimum of one synovitic joint. One hundred and ten DMARD-naïve patients were recruited into this 78-week multicentre randomised controlled trial and were randomised 1:1 to receive MTX+ETAN or MTX+placebo (PBO) for 52 weeks. Injections were stopped in all patients at week 52; in those with no tender or swollen joints (NTSJ) for >26 weeks, injections were stopped early. If patients had NTSJ >12 weeks after stopping the injections, MTX was weaned. Initial results suggest that of the patients in the MTX+ETN group, 41.9% remained in DAS28 remission from week 52 to week 78 and 57.7% remained in LDA according to DAS28 (37).

Tight control and treatment holiday

Although there are limited studies, "a biologic treatment holiday" not only in patients with early RA but also some select group of patients with long-established RA is possible. Infliximab

and adalimumab seem to have a better potential for their discontinuation than certolizumab pegol or etanercept as shown in the studies of TNF20, BeSt, HIT HARD, OPTIMA and PRIZE in early RA, and RRR and HONOR in established RA (10-37). However, there is evidence that etanercept dose reduction can maintain sustained remission (18, 34). A direct comparison of the studies presented here is not possible due to differences in study design, inclusion criteria and outcomes, *i.e.* remission *versus* LDA, and diverse remission criteria. Further work is also required to determine the effect of cessation of other biological drugs such as tocilizumab and abatacept, and the roles their different mechanisms of action may play.

There are pharmacologic differences between the available TNF inhibitor drugs. A monoclonal antibody to the TNF, such as infliximab or adalimumab, blocks the biological functions of TNF via binding to not only soluble TNF but also transmembrane TNF, whose binding induces complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and outside-to-in signaling, which would produce apoptosis to pathogenetic cells bearing membrane-bound TNF (38-40). Therefore, biologic-free remission might be highly expected in infliximab and adalimumab with the mechanisms of action to be able to eradicate the root cause of joint inflammation.

After achieving LDA or remission the goal of therapy is to maintain a clinical, functional and structural remission state. For some patients this is possible even after the cessation of the biological drug. However, there are no guidelines or reliable predictive markers that allow the identification of such patients. Questions arise as to the optimal method of defining remission and whether there is a need for more objective assessments of remission that would include imaging (MRI, US) and immunological markers of inflammation (T cells, T regulatory cells).

Guidelines exist for the initiation of biological drugs exist, but not for their discontinuation. EULAR 2012 guidelines suggest that after remission has been sustained for at least 12 months, gradual dose reduction should be attempted. van den Broek *et al*. recently published three recommendations for discontinuation of biological drugs (41):

1. If patients have low disease activity or been in remission for at least 6 months, consider trying it.
2. Once biologics are discontinued, keep monitoring disease activity, functional ability and radiological damage progression.
3. Restart treatment as soon as it appears that the disease is relapsing.

Conclusion

For patients with established disease (MTX-IR), the evidence suggests that for some patients, especially in Japan, successful biological drug cessation is possible but dose reduction is more consistently successful. For MTX-naïve patients, treatment with combination TNF inhibitor therapy and MTX results in high remission rates and also a 60–70% chance of sustaining remission after cessation of TNF inhibitor therapy. Such an early intensive approach to patients with new-onset RA, with limited biologic use, would have the potential of reducing drug-induced adverse effects and reducing long-term health costs – although the risks of worsening clinical, functional and radiographic outcomes must be considered, with measures in place for careful monitoring of status, prompt re-assessment and re-introduction of therapy. Further data are eagerly awaited that will provide evidence for the ideal remission induction regime and predictors for successful cessation of therapy. Such data could provide objective markers of disease to enable an individualised approach to the management of patients in remission.

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