
Impact of dosing on treatment with TNF inhibitors: managing dose adjustment

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ABSTRACT

The introduction of tumour necrosis factor (TNF) inhibitors for the treatment of rheumatoid arthritis (RA) represented a significant advance in the treatment of this debilitating disease, and led to dramatic changes in overall treatment goals and guidelines. Despite these advances, best practice use of TNF inhibitors in the clinical setting still needs to be determined. In particular, although all TNF inhibitors have standard, recommended doses that were determined in clinical trials, dose adjustments are often necessary in clinical practice to optimise therapeutic outcomes for individual patients. Dose escalation may be necessary in patients who experience disease flares, or because of insufficient initial efficacy or loss of efficacy over time, while dose tapering can be a response to adverse events, or if a patient achieves remission of disease. The amount of available evidence for managing dose adjustments for the currently available TNF inhibitors varies, and thus the strategies used with each are different. At present, although dose adjustments are common, data are insufficient for consensus guidelines to be recommended.

Introduction

The first widely used and effective agents for the treatment of rheumatoid arthritis (RA), methotrexate (MTX) and sulfasalazine, provided relief of the signs and symptoms of the disease, which remained the expected outcome of treatment for the first decade of RA therapy. With the introduction of the tumour necrosis factor (TNF) inhibitors in the late 1990s, however, treatment expectations increased. This was because, in addition to alleviating the signs and symptoms of RA, these agents were found to decrease the progression of joint damage and also to improve physical function, especially when used in combination with MTX

(1-3). New TNF inhibitors continue to provide effective relief of disease as well as improving patients' overall quality of life. For example, the most recently introduced agent for the treatment of RA, certolizumab pegol used in combination with MTX, provides a rapid and sustained reduction in the signs and symptoms of RA and inhibits joint damage progression; in addition, it improves patients' physical function, quality of life, and productivity both at work and in the home (4-7).

As a result of these advances, the overall goals of RA therapy have evolved, and new treatment guidelines have been developed. Explicitly, the European League Against Rheumatism (EULAR) guidelines for early arthritis state that remission is the main goal of treatment (8), while recommendations from the American College of Rheumatology (ACR) focus on improving disease activity, function, and quality of life and/or slowing radiographic progression as therapeutic goals (9). Although these developments changed the overall RA treatment paradigm and have improved standards of care, best-practice use of TNF inhibitors in the clinical setting still needs to be determined.

Standard doses of TNF inhibitors

In particular, one aspect of TNF inhibitor therapy that has not yet been optimised in clinical practice is dosing. All currently available TNF inhibitors have recommended doses that were established and confirmed in randomised clinical trials in patients with active RA (Table I). These recommended doses were then confirmed in larger groups of patients and over longer periods, and later studies included outcomes of radiologic progression and quality of life. For infliximab, a randomised phase 3 trial, conducted in 428 patients with active RA despite MTX, investigated four dose regimens over 30 weeks (10). At weeks 0, 2, and 6, patients were given

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Table I. Standard doses of TNF inhibitors.

Therapy	Administration	Maintenance dose	Frequency
Infliximab	IV	3 mg/kg	Every 8 weeks
Etanercept	SC	25 mg	Twice weekly
Adalimumab	SC	40 mg	Every other week
Golimumab	SC	50 mg	Monthly
Certolizumab pegol	SC	200 mg	Every other week

IV: intravenous; SC: subcutaneous.

infliximab 3 mg/kg or 10 mg/kg intravenously (IV), with similar doses then given every 4 or every 8 weeks, or placebo, and patients were maintained on MTX throughout the study. All infliximab-treated patients, at any of the doses or regimens, achieved significantly better outcomes than those given placebo, although ACR responses were lower in the 3 mg/kg group than the 10 mg/kg group at week 54. The rate of discontinuation due to adverse events, however, was lowest in the group of patients receiving infliximab 3 mg/kg every 8 weeks, and infections were more common in patients in the infliximab 10 mg/kg groups. In a larger study of 1049 MTX-naïve patients, infliximab doses of 3 mg/kg and 6 mg/kg IV every 8 weeks with MTX were compared with placebo plus MTX over 54 weeks (1). Patients in both of the infliximab treatment groups achieved significantly improved efficacy outcomes compared with those in the placebo group, again with no significant differences between infliximab doses. Based on these data, the recommended dose of infliximab for adult patients with RA is 3 mg/kg given as an IV infusion in combination with MTX, followed by additional similar doses at 2 and 6 weeks after the first infusion, then every 8 weeks IV thereafter (11).

The recommended dose of etanercept was derived from data collected in four randomised, double-blind, controlled studies (2, 12-14). A dose of 25 mg twice weekly (i.e., 50 mg/wk) administered subcutaneously (SC) was established as effective, in combination with MTX, over 24 weeks in a study of 89 patients with active RA despite MTX (12). The efficacy of this dose regimen was confirmed in a larger study of 682 patients with RA despite disease-modi-

fying anti-rheumatic drugs (DMARDs) other than MTX over 1 year (2). The efficacy of etanercept as monotherapy at doses of 10 mg and 25 mg twice weekly versus placebo was also investigated in a 26-week study in 234 patients with an inadequate response to DMARDs (13). The 25 mg twice-weekly dose was significantly more effective than the etanercept 10 mg twice-weekly dose. Safety outcomes were equivalent between the two etanercept groups. Furthermore, similar clinical outcomes were reported when patients were treated with etanercept administered either 50 mg once weekly or 25 mg twice weekly (15). The efficacy of the 25 mg twice-weekly dose of etanercept monotherapy was then further established in a 12-month study of 632 MTX-naïve patients with early RA (14). As a result of these studies, the recommended dose of etanercept for adult patients with RA is 50 mg per week (25 mg twice weekly or 50 mg weekly) given as an SC injection as monotherapy or in combination with MTX (16).

The recommended dose of adalimumab was also identified through four randomised, double-blind, clinical studies in adult patients with RA (3, 17-19). Three doses of adalimumab (20 mg, 40 mg, and 80 mg SC every other week) in combination with MTX were evaluated against placebo plus MTX in a total of 271 patients with inadequate response to MTX for 24 weeks (17). The two higher doses were significantly more effective than placebo, and the 40 mg dose was found to be superior to the 20 mg and 80 mg doses in terms of reducing the signs and symptoms of disease. The incidences of adverse events in all three adalimumab groups were similar. The superior efficacy of the adalimumab 40 mg every-other-week

regimen (in combination with MTX, other DMARDs, and other more traditional therapies) was also reported in a 24-week study of 636 patients with RA despite standard therapy (18). Interestingly, a study of adalimumab, in combination with MTX, at doses of 40 mg every other week and 20 mg weekly in 619 patients with inadequate response to MTX over one year found that both adalimumab regimens were significantly more effective than placebo, with no reported differences in efficacy between the two dose regimens (3). A study of adalimumab monotherapy, comparing adalimumab 20 mg weekly, 20 mg every other week, 40 mg weekly, and 40 mg every other week with placebo in 544 patients who had failed at least one DMARD over 26 weeks found that all of the adalimumab doses were statistically superior compared with placebo (19). Based on these studies, the recommended dose of adalimumab for adult patients with RA is 40 mg every other week as monotherapy or in combination with MTX (20).

Golimumab, a TNF inhibitor that is fully human, like adalimumab, has also recently been approved for use in patients with RA. In one 24-week study, 444 patients with active RA despite MTX were assigned to treatment with golimumab (100 mg, 50 mg, or 50 mg plus MTX) or placebo plus MTX at monthly intervals (21). Both doses of golimumab achieved significantly greater efficacy than placebo plus MTX, although adverse events were more common with the higher dose. Furthermore, the efficacy of higher dose golimumab monotherapy was not significantly better than that achieved with continuation of MTX. As a result, golimumab is recommended at 50 mg monthly, in combination with MTX only, and not as monotherapy, and is indicated for the treatment of adult patients with moderately to severely active RA (22).

Certolizumab pegol is the most recently available anti-TNF for the treatment of RA, and consists of a humanised Fab' fragment fused to a 40-kDa polyethylene glycol moiety. In two large randomised clinical trials enrolling 1601 patients with active RA despite MTX,

certolizumab pegol at an initial dose of 400 mg given at weeks 0, 2, and 4, with subsequent doses of either 200 mg or 400 mg given every 2 weeks, plus MTX, was compared with placebo plus MTX (4, 5). Certolizumab pegol plus MTX resulted in a rapid and sustained reduction in RA signs and symptoms, inhibition of the progression of structural joint damage, and improvement in physical function compared with placebo plus MTX. No differences in efficacy or adverse event rates were observed between the two certolizumab pegol doses. As with adalimumab and etanercept, certolizumab pegol has also been shown to be effective as monotherapy, dosed every 4 weeks, for the treatment of RA (23). The recommended dosage of certolizumab pegol for RA is 400 mg initially and at weeks 2 and 4, followed by 200 mg every other week, as monotherapy or in combination with MTX or other DMARDs.

Dose adjustment strategies

Although the recommended doses for infliximab, etanercept, and adalimumab discussed above were shown to be effective in clinical trials, dose adjustments are often necessary in clinical practice due to a patient's response (or lack thereof) to therapy. In particular, dose escalation may be a necessary strategy in patients who experience disease flares, because of insufficient efficacy (*i.e.* failure to respond to the initial dose), or loss of efficacy over time. The latter has been associated with the development of anti-drug antibodies (24, 25), supporting dose escalation as a strategy in these cases. Dose tapering may be necessary if the patient experiences adverse events; dosing may also be decreased if a patient achieves remission of disease (26). Several studies are ongoing to investigate this latter strategy, although results are yet to be published. Tight control of treatment using dose adjustment in response to therapeutic outcomes achieved is also increasingly used to optimise therapy to the individual patient's needs. Recommended dose escalation strategies include increasing the amount of drug administered and/or the frequency of administration (27). For patients tak-

ing infliximab at 3 mg/kg every 8 weeks who have an incomplete response, both strategies may be considered by adjusting the dose up to 10 mg/kg (or 7.5 mg/kg in the European Union) or treating as often as every 4 weeks (11, 28). The dose of adalimumab may be increased from 40 mg every other week to 40 mg weekly in patients not taking concomitant MTX (20). In a clinical trial, more patients achieved efficacy end points with the weekly dose than the every-other-week dose when administered as monotherapy (19). In contrast, increasing the dose of etanercept to higher than 50 mg per week is not recommended (16), since a study to specifically compare etanercept doses of 50 mg and 100 mg as monotherapy over 24 weeks ($n=77$) did not find an increased benefit for the higher dose in terms of efficacy, but reported significantly higher incidences of adverse events for the higher dose (29). A further randomised, double-blind study of etanercept plus MTX also demonstrated that increasing the dosage from 50 mg once weekly to 50 mg twice weekly in suboptimal responders did not significantly improve efficacy (30). Dose escalation is not recommended for certolizumab pegol, but there is scope for dosing flexibility and 400 mg every 4 weeks rather than 200 mg every other week can be considered in the United States (31).

Evidence of dose adjustments in clinical practice

A number of studies in recent years have assessed dose escalation patterns for the TNF inhibitors in clinical practice (32-37). An early retrospective cohort study examined patterns of infliximab and etanercept dosing in 1,548 patients (32). A dose increase for infliximab was defined as at least two occurrences of an increase in the number of vials reported or two infusions within 7 weeks on at least two occasions. For etanercept, a dose increase was defined as at least two prescriptions with a higher average daily dose than the patient's maintenance dose. Significantly more patients taking infliximab had dose increases compared with those taking etanercept (58% vs. 18%). Patients who were older than 35 years and those who

had not responded to MTX alone were more likely to have dose escalation with infliximab than younger or MTX-naïve patients. A similar analysis of longitudinal claims data from 4,426 patients treated with infliximab or etanercept also found greater incidences of dose increase for infliximab (29%) than etanercept (doses remained stable) (33). A dose increase for infliximab in this study was defined as an increase in the number of vials compared with the previous claim, while for etanercept it was defined as a dose that was at least 5 mg/wk greater than the previous claim. Reasons for dose escalations in both of these studies of infliximab and etanercept were not available to the investigators. A recent study that examined dose escalation in patients treated with infliximab who had an inadequate response, or whose disease flared after an initial response, to the standard dose found that 30% of 329 evaluable patients required at least one dose escalation (in 1.5 mg/kg increments) (35).

In an analysis of data from published references on infliximab, etanercept, and infliximab and/or etanercept, dose increase was found to be common in patients treated with infliximab, and less so in those treated with etanercept (34). Approximately half (53%) of patients treated with infliximab required a dose escalation, while only 17% of those treated with etanercept did. Of the patients treated with infliximab who needed a dose escalation (reasons not available), 44% had their dose increased (doses higher than 3 mg/kg), while only 8% had an increase in frequency of administration (more than every 8 weeks).

A retrospective claims analysis of dosage adjustment patterns of infliximab, etanercept, and adalimumab also found greater dose increases with infliximab (35%) compared with etanercept (0%) and adalimumab (4%) (37). In this analysis, dosage increases (reasons not available) were defined from the healthcare provider point of view as being at least twice the initial dose or at least two infusions at intervals less than 49 days following the third infusion for infliximab, and at least twice the recommended dosages for etanercept or

adalimumab. Similarly, in a retrospective observational study of 739 patients, dose escalation was seen in significantly more patients treated with infliximab (29%) compared with either etanercept (<1%) or adalimumab (8%) (36).

Dose escalation is just one strategy for optimising the dosing (and efficacy) of TNF inhibitors, and is successful in some patients, leading to a clinical response. However, some patients still do not respond, and there are no clear guidelines for how to treat these patients with the currently available TNF inhibitors. While data in support of switching between TNF inhibitors in patients with inadequate response are increasing (38-40), such an approach remains an area that lacks clear guidelines (41, 42). The introduction of golimumab and certolizumab pegol may increase switching as a strategy, despite the current controversy (43).

Dose escalation is also associated with increased treatment costs. Thus, the higher rates of dose escalation with infliximab relative to etanercept contribute to substantially higher 1-year medical costs (32, 33), and these increased costs are related to dispensing dose increases for infliximab (highest), adalimumab, and etanercept (least) (44). Costs are also a key reason why dose escalation is not recommended with adalimumab (45).

As golimumab and certolizumab pegol have recently been approved for the treatment of RA, real-world experience in the clinical setting is needed to assess whether dose optimisation strategies will be needed. With time, we will know whether any issues of, for example, loss of response over time will emerge, which may require dose adjustment with these therapies.

Summary

Dose escalation is a practical response to insufficient efficacy of available TNF inhibitor therapies in particular patients. It also plays an important role in strategies of tight control of therapy and individualising treatment to the patient, particularly with infliximab, where efficacy-limiting antibody formation is most common. However, insufficient robust data are available for a consensus or guidelines for dose adjustment to

be confirmed for the currently available TNF inhibitors, and thus best practice remains to be determined. Any means of simplifying patient management, for example by reducing the need for dose adjustment, would be advantageous.

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