Defining the value of structural inhibition

Is low-dose etanercept inferior to the standard dose?

This editorial refers to ‘Comparison of joint destruction between standard- and low-dose etanercept in rheumatoid arthritis from the Prevention of Cartilage Destruction by Etanercept (PRECEPT) study’, by Masahiro Tada et al., doi:10.1093/rheumatology/kes188.

TNF inhibitors are important as the standard of care for the management of RA. These agents have dramatically improved rheumatologists’ ability to control the disease, so that clinical remission can now be achieved in ~50% of patients, when treated early and aggressively. With this success have come questions about differential efficacy, however, as clinicians and clinical investigators strive to understand why all patients do not respond similarly to this therapy. Equally important questions have been raised about the management of patients who do respond. With the high cost of these drugs and high toxicity, it is appropriate to consider dose reduction, or even discontinuation, in patients who reach goal response.

Several recent, controlled trials, while not specifically looking at the effect of initiating lower dose TNF inhibitor therapy, have addressed the feasibility of withdrawing TNF inhibitors in patients who achieve disease control on standard therapy. In a Japanese withdrawal study, 9 of 56 patients in remission after at least 24 weeks of infliximab therapy maintained remission for 1 year after discontinuing infliximab, 2 with no radiographic progression [1].

In the PRESErve study (a prospective, randomized etanercept study to evaluate reduced dose etanercept + MTX vs full dose etanercept + MTX vs MTX alone for efficacy and radiographic endpoints in a moderate RA population), 604 patients with moderate disease activity despite MTX added weekly etanercept to the MTX [2]. At 9 months, those with low disease activity were randomly selected to discontinue etanercept, continue etanercept at 50 mg/week or continue etanercept at a reduced dose of 25 mg/week. Over the next year, low disease activity was maintained in those who continued etanercept (82.6% of 50 mg group, 79.1% of 25 mg group), but in only 42.6% of those who discontinued etanercept. The mean change in modified total Sharp score (mTSS) was 0.06 U/year with the 50 mg dose, 0.5 U/year with the 25 mg dose and 0.6 U/year without etanercept (significant compared with the 50 mg dose).

Finally, in the Optimal Protocol for Treatment Initiation With Methotrexate and Adalimumab Combination Therapy in Patients With Early Rheumatoid Arthritis (OPTIMA) study, 926 early RA patients were randomly assigned to start initial therapy with MTX or MTX plus adalimumab [3]. At 24 weeks, patients who achieved low disease activity on combination therapy were randomly reassigned, in a double-blinded manner, to continue the same treatment or withdraw from the use of adalimumab. In those who discontinued adalimumab, 57% met the composite endpoint of low disease activity with no radiographic progression (increase in mTSS ≤ 0.5) after an additional year of therapy. Radiographic non-progression was seen in 89.3% of those who continued adalimumab and 80.6% of those who did not.

These studies suggest that TNF inhibitors can be successfully tapered, or even withdrawn in some situations, a finding with enormous economic implications. Despite clinical success with discontinuation or dose reduction of the TNF inhibitor in these trials, however, there were at least modest differences in radiographic progression compared with continuing therapy.

In this issue of Rheumatology, the authors of the PRECEPT study address the question of structural damage with lower dose etanercept in patients starting treatment with etanercept [4]. They evaluated the lower dose of etanercept as initial therapy, rather than assessing dose modification after initial response. Patients were randomly selected to receive 25 or 50 mg of etanercept weekly. Background DMARD therapy was permitted, but not specified; 81% received MTX, at a mean dose of 8 mg/week.

Clinical outcomes were equivalent in both arms when measured either as DAS28 response or as a percentage of patients who achieved low disease activity or remission, although the time to response was somewhat slower in the lower dose group. HAQ scores also improved more rapidly in the higher dose group, but improvement was comparable in both arms by 52 weeks.

The key point that the authors make, however, is that radiographic progression was greater in the etanercept group who received the lower dose. Mean change in mTSS over 52 weeks was 1.03 U for etanercept 25 mg and −0.13 U for 50 mg, a difference that was not statistically significant. However, non-progression (change in mTSS ≤ 0.5 U) was seen in 67.7% of the high-dose group but in only 36.7% of the low dose group; this difference was significant.

Based on these findings, the authors of this study conclude that etanercept 25 mg/week, as an initial therapy, is inferior to 50 mg/week, at least in terms of structural damage. They suggest that the lower dose may be inadequate to prevent joint destruction, particularly given the
delayed clinical response observed in this group. They raise particular concern about using the lower dose in seropositive patients, who are at higher risk of structural damage.

Recognizing the enormous financial implications of lower dose therapy with TNF inhibitors, I do not believe that the conclusions by authors from the PRECEPT study are completely appropriate. The differences in radiographic progression between the two doses in this trial were quite small, and were not associated with differences in clinical or functional outcome. One cannot necessarily assume that such short-term, small differences will translate into important functional differences over time. There are, however, few studies that specifically link progression of structural damage to changes in function. While radiographic progression appears to be linear in RA patients in the absence of effective therapy, it may take many years for these changes to have a meaningful impact on measurements of function [5].

One analysis showed that a single unit increase in mTSS may correlate to a 0.01 U change in HAQ score [6]. At that rate, it would take nearly 25 years for the additional radiographic progression seen with the lower dose of etanercept in the PRECEPT trial to translate to the minimum clinically important difference in HAQ score of 0.22 U. While prevention of joint damage is ideal, structural damage is ultimately a surrogate for function, and one wonders whether such modest differences in functional outcome are worth doubling the cost of therapy. There are, of course, other benefits that may accrue with TNF inhibitor therapy, such as reduced cardiovascular risk, and these, too, may be decreased with lower doses. We may also find that dose reduction is more successful at specific points in the disease course. At a time when the cost of therapy is an unavoidable component of health care treatment decisions, additional data on such outcomes are needed before dismissing potential savings associated with lower doses of TNF inhibitors that achieve comparable primary clinical endpoints.

Disclosure statement: E.R. has received research funding and/or payments for consulting from Abbott, Amgen, Bristol Meyers Squibb, Genentech, Pfizer and Union Chimique Belge.

Eric M. Ruderman¹
¹Northwestern University - Medicine/Rheumatology, Chicago, IL, USA.
Accepted 16 August 2012
Northwestern University - Medicine/Rheumatology, 675 North St Clair Suite 14-100 Chicago, IL 60611, USA.
E-mail: e-ruderman@northwestern.edu

References