When Less Is More

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*The Journal of Rheumatology* is a monthly international serial edited by Earl D. Silverman featuring research articles on clinical subjects from scientists working in rheumatology and related fields.
When Less Is More

Axial involvement is the hallmark of ankylosing spondylitis (AS), and it is unique in many ways among inflammatory arthritides. By its very anatomical location, it is difficult to assess clinically. Laboratory investigations including inflammatory markers are often unrevealing, and simple imaging such as radiographs remain normal for several years after the onset of the disease and change very slowly — if at all — later in the disease course1. Unlike their efficacy in other inflammatory arthritides, traditional disease-modifying antirheumatic drugs (DMARD) have been ineffective in improving function or reducing signs and symptoms of spinal involvement in AS. The significant efficacy of anti-tumor necrosis factor (TNF) agents in axial disease of AS is therefore even more striking2-5.

With the limited therapeutic armamentarium for the management of spinal disease in AS (e.g., physical therapy, non-steroidal antiinflammatory drugs), the use of anti-TNF agents is likely to grow, although the biggest hurdle remains their cost. A systematic review along with an economic evaluation of the use of the original 3 anti-TNF agents approved for the treatment of AS (etanercept, adalimumab, and infliximab) by the National Institute of Clinical Excellence (NICE) of Britain showed that the incremental cost-effectiveness ratios (ICER) of etanercept and adalimumab were roughly similar, falling below the conventional £30,000 (US $50,000) threshold per quality-adjusted life-year (QALY). However, the ICER for infliximab (IFX) used in the “approved” dose of 5 mg/kg every 6 weeks was in the range of £40,000 to £50,000 (US $60,600 to $75,800) making it the “least attractive” option6.

With national healthcare budgets coming under increasing pressure all over the world, the challenge of providing optimum care to more people with fewer resources is becoming acute. On a local level in a rheumatology clinic, we face daily the dilemma of how to optimize the use of these expensive medications. There are several strategies described in the literature that one can pursue. One would be to target those patients who are likely to benefit most by use of anti-TNF agents. These could be identified by baseline characteristics that predict response7. Another strategy would be to investigate novel dosing regimens. Could we use lower doses of biologics and still get an optimal outcome? Could we use them less frequently? A study by Maksymowych and Inman8 for the CANDLE study group in this issue of The Journal investigates these questions for the use of IFX in AS.

The CANDLE study group assessed the safety and efficacy of low-dose (3 mg/kg every 8 weeks) IFX therapy for active AS — a dose that is 55% lower than the approved dose of 5 mg/kg every 6 weeks4. Over the first 12 weeks of the placebo-controlled part of the study, 54% of IFX-treated patients achieved an ASsessment in Ankylosing Spondylitis 20 (ASAS20) response compared to 31% of the placebo-treated patients, a result that was statistically and clinically significant. However, during the 46-week extension phase of the study, nearly 70% of patients required to increase the dose to 5 mg/kg — albeit at 8-weekly intervals — because of not meeting the prespecified “target response.” By the study’s end at Week 50, two-thirds of all patients had achieved a respectable Bath Ankylosing Spondylitis Disease Activity Index 50% (BASDAI 50%) improvement.

Since the efficacy and safety of IFX in AS is already well established, the above described results are not surprising. An important and interesting question, however, would be: How does the efficacy of “low-dose” IFX compare with the “approved dose.” The study by Maksymowych and Inman cannot answer that question since they did not include a “third group” of patients receiving the “approved dose” of IFX for comparison. We could still get some idea by comparing the differences (or deltas) in efficacy between the active and the placebo groups in published studies. The pivotal ASSERT study4 on IFX using the dose of 5 mg/kg q 6 weeks showed a 61% ASAS20 response in the IFX group compared to 19% response in the placebo group, a delta of 42%. The deltas between the “active” and the placebo groups in the 3 other pivotal trials on etanercept, adalimumab, and golimumab in AS were 35%, 37%, and 38%,

See Double-blind, placebo-controlled trial of low dose infliximab in AS, page 1203
respectively. The CANDLE group study, however, shows a much smaller delta of 23.2% and therein may lie the true difference between the efficacy of the “approved” dose versus that of the “low-dose” IFX.

The CANDLE study, however, does improve our understanding of the dose-response curve of IFX in AS. The “target response criteria” of BASDAI score improvement of 50% or the total score being less than 3 used in the CANDLE study to decide who would increase their IFX dose are similar to those used in the extension phase of the ASSERT study. In the CANDLE study, IFX dose increases did substantially improve outcomes (as measured by BASDAI 50% improvement), whereas in the ASSERT study, patients not responding to IFX 5 mg/kg by Week 24 had a lower likelihood of responding to a higher dose of IFX than patients who initially responded but then lost response. Combining the findings of these 2 studies would indicate that if there is no response to IFX 3 mg/kg q 8 weeks, one could go up to the “approved” dose of 5 mg/kg q 6 weeks. If there is no response to the “approved” dose, the likelihood of response to an even higher dose is low.

Should the results of the CANDLE study change our practice? It appears that nearly 38% of patients met the “target response criteria” at the low-dose IFX regimen and did not require further increase in their dose. This is a significant enough number, which should make us give the low-dose regimen a try in all patients initially. If an adequate response is not achieved by 22 weeks (at the time of second infusion after the initial loading dose), the dose could then be increased. Quite apart from the obvious pharmacoeconomic benefits, the low dose is likely to be safer, and the 22-week delay in getting optimum response is not likely to be detrimental to the patient’s health.

The field of spondyloarthritis therapeutics is playing catchup with the field of rheumatoid arthritis (RA) management. There are several studies in RA investigating combination therapy of biologics with DMARD, the “inverted pyramid” strategy of treating with multiple drugs and then withdrawing therapy, investigations on maintaining “drug-free remissions” after intense therapy in early RA, etc. Such studies remain to be done in AS. In order to better understand longterm consequences and cost-effectiveness of anti-TNF agents, trials that aim to address the following question need to be conducted: Could we titrate down or withdraw treatment with biologic agents if we treat patients very early (in the “Axial spondyloarthritis” stage)? How long will “drug-free remission” last in AS? Will combining anti-TNF agents with DMARD or NSAID be a better strategy to halt or slow the progression of AS? The study by Maksymowych and Inman is a step in the right direction informing us that more than one-third of patients with AS may be successfully treated with a much smaller dose of infliximab.

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