

## Is There a Rationale for Switching from One Anti-Tumor Necrosis Factor Agent to Another?



Anti-tumor necrosis factor (TNF) therapy constitutes a major breakthrough in the management of rheumatoid arthritis (RA), psoriatic arthritis, ankylosing spondylitis, and a host of other inflammatory conditions such as Crohn's disease, psoriasis, and certain vasculitides. The rationale for this therapeutic approach is based on the *in vitro* and *ex vivo* demonstration of a pivotal role for TNF- $\alpha$  in the pathogenesis of these various diseases.

Cytokine blockade can be achieved through different means. For TNF- $\alpha$ , 2 different approaches were developed: Etanercept is made up of two P75 soluble receptors capable of binding both TNF- $\alpha$  and TNF- $\beta$ , while infliximab and adalimumab are monoclonal antibodies specific for TNF- $\alpha$ .

Based on separate clinical trials (with no head-to-head comparisons) and on their postmarketing use, one can safely state that these different molecules have comparable efficacy in RA, with 50% to 70% of patients achieving a clinically significant improvement.

Confronted with rheumatoid patients who develop side effects or fail to adequately respond to one anti-TNF, physicians have treated them with a second available anti-TNF agent. Because adalimumab has just recently been introduced, the broadest experience exists with etanercept and infliximab. In this issue of *The Journal*, Hansen and colleagues retrospectively compared response to a combination of infliximab and leflunomide in 2 groups of patients with active RA<sup>1</sup>. The first group was naive to anti-TNF agents and the second group comprised patients who had stopped etanercept therapy primarily because of inadequate response. Both groups had comparable clinical improvement.

This observation is similar to those of other investigators who have switched patients from infliximab to etanercept or vice-versa<sup>2-4</sup>. Indeed, the efficacy and the tolerability of the second agent were not compromised by the previous experience with the first agent, regardless of the reason for the discontinuation of the first anti-TNF agent.

Therefore, the obvious question is: Why do patients with RA who fail to improve with or tolerate one anti-TNF agent have a beneficial response when switched to a second agent. The response must lie in their different characteristics, as summarized in Table 1. This may also explain the differ-

ences in response observed in other disease states; for example, etanercept, but not infliximab, is efficacious in juvenile rheumatoid arthritis (JRA); infliximab is indicated for the treatment of refractory Crohn's disease, while etanercept provides only marginal benefit.

Effective suppression of TNF- $\alpha$  is believed to be an important factor in determining clinical response. This goal is influenced by the pharmacokinetics of the different molecules. The intermittent administration of large doses of infliximab leads to high peak levels, which decrease to undetectable levels after 6 to 8 weeks. This might explain the loss of the clinical benefit in a number of patients when the end of the cycle is reached, warranting shortening of the interval between infusions. Nevertheless, refinement in dosing also sometimes fails to bring significant improvement, raising the possibility of yet other unknown important factors. On the other hand, the shorter half-life of etanercept and its administration twice a week leading to more sustained levels may prove inadequate in some patients who require more rapid and drastic suppression of TNF. This subset might be the one to most benefit from a switch to infliximab.

Antibodies directed against etanercept or infliximab are detected in the sera of 5% and 13%, respectively, of patients with RA. The presence of antibodies to infliximab (ATI) was shown to be related to infusion reactions in RA and to a reduction in clinical response in patients with Crohn's disease<sup>5</sup>. Measurement of levels of ATI and determination of their neutralizing potential is not readily available and is hampered by the presence of circulating infliximab. ATI are thought to contribute to the loss of response over time in some patients with RA, who may in turn improve when switched to etanercept. The concomitant use of methotrexate or other immunosuppressive agents was shown to reduce the immunogenicity of infliximab<sup>6</sup>. The role of antibodies directed against etanercept is poorly studied; however, they do not seem to have a significant impact on its efficacy or toxicity.

Patients with active JRA respond well to etanercept, while infliximab seems to have a marginal effect based on open-label small series and case reports<sup>7</sup>. This difference in efficacy between the 2 molecules could be due to the

Table 1. Characteristics of the anti-TNF agents etanercept, infliximab, and adalimumab.

|   | Etanercept                 | Infliximab               | Adalimumab        |
|---|----------------------------|--------------------------|-------------------|
| Class                                     | Soluble TNF receptor       | TNF- $\alpha$ mAb        | TNF- $\alpha$ mAb |
| Construct                                 | Recombinant fusion protein | Chimeric mAb             | Human mAb         |
| Neutralizes soluble TNF- $\alpha$         | Yes                        | Yes                      | Yes               |
| Neutralizes cell-bound TNF- $\alpha$      | Yes                        | Yes                      | Yes               |
| Neutralizes TNF- $\beta$ (LT $\alpha$ )   | Yes                        | No                       | No                |
| Lyses TNF-producing cells <i>in vitro</i> | No                         | Yes                      | Yes               |
| Human origin                              | Entirely                   | Partially                | Entirely          |
| Half-life, days                           | 4.8                        | 9.5                      | 12–14             |
| Antibodies directed against, %            | < 5                        | 13                       | < 1–12            |
| Concomitant use of MTX                    | Optional                   | Required                 | Optional          |
| Dosage                                    | Fixed 25 mg SC, twice/week | 3–10 mg/kg IV, q 4–8 wks | 40 mg SC, eow     |

mAb: monoclonal antibody; LT $\alpha$ : lymphotoxin $\alpha$ .

capacity of etanercept to suppress lymphotoxin- $\alpha$ , which is thought to play a more important role in juvenile compared to adult RA.

Granulomatous diseases, including refractory Crohn's, Wegener's, and Behçet's disease, rapidly improve and in some cases experience longterm remissions when treated with infliximab<sup>6</sup>. On the other hand, etanercept does not have a significant therapeutic effect in Crohn's disease. Several hypotheses have been put forward to explain this difference in efficacy: one is the higher doses and the strategy of intermittent administration of infliximab, possibly leading to greater concentrations in the target organs. Another hypothesis has to do with infliximab inducing apoptosis of inflammatory cells as demonstrated *ex vivo*<sup>8</sup>. Infliximab does not have the same effect in RA<sup>9</sup>. This supports the hypothesis that different inflammatory mechanisms are operating in Crohn's disease and RA and that both infliximab and etanercept are therefore efficacious therapies in RA.

However, it is widely accepted that RA is a heterogeneous disease with different architectural inflammatory infiltrates in the synovial membrane<sup>10</sup>. It is possible that in certain subsets of patients the main pathogenic mechanisms resemble those operating in granulomatous diseases or in JRA. Therefore, in these subgroups of patients one anti-TNF agent may be more effective than another.

Much remains to be learned about the exact mechanisms of action of this class of drugs; such knowledge will help us use anti-TNF agents in a more efficient manner. Until predictors of response have been identified, use of these agents will be governed by clinical judgment and accumulated experience. If one agent fails to deliver a satisfactory clinical response, a trial with a second anti-TNF may be safely started.

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