

# Anti-Tumor Necrosis Factor- $\alpha$ Agents for Rheumatoid Arthritis: Assessing Longterm Safety



The introduction of anti-tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) therapies has dramatically improved treatment for severe rheumatoid arthritis (RA). The main mechanism of action of these agents centers on blockade of TNF- $\alpha$ , a key cytokine driving synovial inflammation in the RA joint<sup>1</sup>. Currently, 3 such agents are available: etanercept, infliximab, and adalimumab.

Anti-TNF- $\alpha$  agents were shown to be effective in randomized clinical trials of patients with active RA despite treatment with conventional disease modifying antirheumatic drugs including methotrexate<sup>2-5</sup>. These agents control disease activity to a greater degree than placebo as well as reduce radiologic progression. Reassuringly, these “pivotal” clinical trials did not find a significant increase in toxicity compared to placebo. However, there remains apprehension about longer term safety of TNF- $\alpha$  blockade, particularly as their use becomes more widespread. Such data can be derived from 3 key sources: (1) open label extensions of clinical trials, (2) spontaneous adverse event reports, and (3) prospective observational studies.

In this issue of *The Journal*, Moreland, *et al* present results of open-label extensions of clinical trials of etanercept for established RA<sup>6</sup>. The main objective of their study was to assess longterm safety of this agent. Of 714 patients enrolled in 7 initial clinical trials, 514 (81%) were enrolled in these extensions. These patients were regularly followed on a 3–6 monthly basis for up to 8 years, and details of disease activity and serious adverse events were recorded. About half the patients (366) had completed at least 6 years of therapy, of whom 73% were classified as achieving American College of Rheumatology 20% response at the end of year 6. Overall, the rate of adverse events did not increase with increased use. The authors conclude that adult patients treated with etanercept experienced durable clinical responses maintained for up to 7 years or more, with no increase in rates of adverse events compared to patients with RA in general.

Unfortunately, there are drawbacks to such data, which limit the generalizability of these results. There is concern that enrolment in clinical trials is heavily selected; for example, exclusion criteria restrict recruitment of those with pre-existing comorbidities. Thus such data may not address the longterm safety in patients who are prescribed these agents in routine clinical practice. There are also problems with maintaining the original cohort, as patient numbers decrease over time due to patient dropouts, losses to followup, and migration to newer therapies. The final cohort may not be comparable to the patients originally recruited to the clinical trials.

Finally, open-label extensions rarely include the initial placebo or other comparator group, thus making comparability of the results difficult. Patients with severe chronic RA have been shown to have increased risk of infections<sup>7</sup>, malignancies<sup>8</sup>, and cardiovascular disease<sup>9</sup>, even before the widespread use of anti-TNF- $\alpha$  agents. These same patients may be more likely to receive new biologic therapies, thus making it difficult to disentangle the risk of the new drug from that of the underlying disease in patients who develop serious adverse events. Indeed, Moreland, *et al* note 7 cases of lymphoma among this cohort, which is higher than would be expected for an age and sex matched general US population. However, without a direct comparison group, it is difficult to interpret the significance of this lymphoma rate among this cohort of patients with longstanding RA. A comparison of the results to published studies may allow us to draw some conclusions, but without the ability to adjust for differences in disease activity and duration between the cohorts, it is impossible to determine an exact relative risk. Given these concerns, other ways of gathering longer-term patient data must be considered.

A spontaneous adverse event reporting system, such as the US Food and Drug Administration’s Medwatch program, allows physicians to report new or unexpected

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See Etanercept treatment in adults with established RA, page 854

adverse events after a drug has been marketed. A success of this system was demonstrated by the report of 70 cases of tuberculosis in patients receiving infliximab<sup>10</sup>, a potential risk not originally identified during clinical trials. However, such systems are limited in their ability to draw any firm conclusions regarding drug risk. They are relatively inefficient, with significant under-reporting. Important missing data related to individual case reports, a lack of details about the true exposure of the investigational drug among the general population, and a lack of a comparison group make estimations of adverse event risk from these systems difficult and inaccurate. However, surveillance systems are useful for signal generation. At the time of the FDA publication of tuberculosis (TB) following infliximab therapy, the baseline risk of TB among patients receiving standard therapies for RA was not clear, making the interpretation of these results difficult. Data from observational studies in Spain have now found that not only is RA itself associated with increased risk of TB<sup>11</sup>, but that this risk is further increased with the use of infliximab<sup>12</sup>. A national screening program set in place following reports of these findings has resulted in a marked decline in new reports of TB in this population<sup>12</sup>.

Perhaps the most robust way to collect longterm drug safety data in clinical practice is to develop large patient registries. Such large, longitudinal observational studies (LOS) of anti-TNF- $\alpha$  agents have now been established in numerous countries<sup>13</sup>. The goal of these registers is to collect all pertinent information, including safety data, on patients starting anti-TNF- $\alpha$  therapies for RA in routine clinical practice, thus being more reflective of "real-world" clinical use. Although ideal in theory, LOS also have their limitations. They are very expensive, time-consuming, and must deal with missing data. In addition, as patients are not randomized to therapies, a substantial bias may be introduced as patients are assigned to therapies by their treating physician. There is also the challenge of finding an appropriate comparison group with which to compare results. However, when carried out properly, LOS can provide invaluable data on a drug's performance that cannot be collected from other sources.

The most important question LOS will answer relates to longterm drug safety. Due to their inclusive nature, a more accurate picture of the risk of adverse events will emerge. LOS may be able to identify which patients may be at increased risk of certain adverse events, which will guide individual patient therapeutic decisions. Many of the population registries are also of a sufficient size that the rates of less common adverse events, particularly lymphoma, can be calculated with more precision.

Wolfe and Michaud have reported on the lymphoma experience of 8614 patients receiving anti-TNF- $\alpha$  therapies enrolled in the US National Databank for Rheumatic Diseases, followed for a mean of 1–2 years<sup>14</sup>. Compared to rates in the general US population, the risk of lymphoma

among patients receiving anti-TNF- $\alpha$  therapies was 2.9 (95% CI 1.7, 4.9). Although the rate for lymphoma among anti-TNF- $\alpha$  treated patients was increased compared to RA controls, this analysis did not adjust for baseline differences in disease duration and severity between the 2 cohorts. More recently, the lymphoma experience of 4160 Swedish patients receiving anti-TNF- $\alpha$  therapies between 1999 and 2003 has been published<sup>15</sup>. After adjustments for age, sex, and disease duration, the investigators could not identify an increased risk of lymphoma in this cohort compared to over 50,000 RA controls.

Although the results from these registers are reassuring, it is still early, and further data are required before we can be confident in our knowledge of the true risks of these agents. We still have more to learn about the risks of infections, including the various subtypes of infection. Thus far, the data have suggested that the risk of lymphoproliferative diseases is not substantially increased. However, the majority of these patients have been followed for less than 4 years and the effects of longer-term therapy have yet to be determined.

Other issues need to be addressed. There are patients who have switched therapies, but the longterm safety of multiple anti-TNF- $\alpha$  agents is not established. Increasingly, as new biologic agents become available, the risks of multiple consecutive or, in the future, combinations of biologic therapies will need to be established. Moreover, it will be important to balance their longterm safety with the overall beneficial effects of these agents on longterm outcomes, including reductions in disability, returns to work, prevention of joint replacement surgeries, and perhaps most importantly, reduction in the increased mortality associated with RA<sup>16</sup>.

The possibility is real that longterm control of disease activity will result in improved prognoses for patients with RA. Only through longterm observation of patients receiving these agents will issues be addressed. Answers to these questions should ideally emerge when such therapies are licensed for routine use; however, robust answers may require several more years of carefully studied experience.

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