

# The Evolving Use of Tumor Necrosis Factor Inhibitors in Rheumatoid Arthritis



Young blood must have its course, lad, and every dog its day  
— Charles Kingsley (1819-1875)

In 1998 we wrote an editorial concerning tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) inhibitors as 2 of them, etanercept and infliximab, were about to be introduced into the clinic<sup>1</sup>. At that time, rheumatologists had experienced nearly a decade of disappointment with various other biologic agents (anti-CD4 monoclonal antibody, mAb, anti-CD5 mAb, etc.) whose appealing scientific rationale and early promise were subsequently disproven in rigorous clinical trials in rheumatoid arthritis (RA)<sup>2</sup>. Hence for our title we borrowed a Texas colloquialism: “Inhibitors of Tumor Necrosis Factor in Rheumatoid Arthritis: Will that Dog Hunt?”. Any hunter knows the moment of truth when a newly trained dog goes hunting for the first time; some make the grade and others head back to the truck. At the time, we were unsure to what extent these promising new therapies would succeed in the clinic, and how they should optimally be utilized.

It is clear now that TNF inhibition as a treatment for RA and other systemic inflammatory disorders has dramatically improved patient outcomes. A third TNF inhibitor, adalimumab, was approved in 2002 and others are under development. To date, more than 700,000 patients worldwide have been treated with these agents. The success achieved with TNF inhibitors has tangibly altered the approach to treating RA. Indeed, the efficacy of TNF inhibitors has been such that the types of studies upon which they gained approval are no longer considered ethical; for example, allowing patients with active RA to receive placebo for 6 months. In the clinic, the introduction of powerful new therapies has “raised the bar” of treatment goals closer to the ideal outcome — remission. In the past, the concept of remission was as sublime as it was rare; now it is considered both appropriate and achievable. In research, the success of the TNF inhibitors fueled additional development in targeted therapies. Several novel approaches

to modulate the function of T cells, B cells, various cytokines, and other components of the immune response are being evaluated in current trials.

Since approval, much has been learned about the benefits and risks of TNF inhibition. Longterm followup of patients from clinical trials and the development of patient registries worldwide are beginning to answer questions relating to durability of response, longterm safety issues, and the issue of response to alternative TNF drugs. While common safety issues of TNF inhibitors were delineated in the pivotal randomized clinical trials, shortly after approval, issues arose regarding serious infections, opportunistic infections, lymphoma, and other rare events such as demyelinating disease, autoimmune phenomena, hematologic toxicities, and congestive heart failure. At approval, none of the datasets for the 3 TNF inhibitors had more than 2700 patient-years’ exposure, so it should not have been surprising that rare events, e.g., those occurring with a frequency of 1/1000–10,000, could have been missed in the trials. This highlights the need for observational studies concerning these agents, such as that by Wasserman and colleagues in this issue of *The Journal*<sup>3</sup>. Their report highlights key practical information concerning infusion reactions related to infliximab administration, which were generally mild and manageable.

The treatment of RA continues to evolve. Even with the volume of data available on TNF inhibitors, questions persist. In 1998 we posed 5 general questions that remain relevant today: (1) Which RA patients should be treated with TNF inhibitors? (2) How should patients be treated? (3) Will TNF inhibitors be safe? (4) Which TNF inhibitors should be used? (5) What about cost? In this editorial we readdress these questions with the benefit of some “tincture of time” and evidence-based medicine.

**Which RA patients should be treated with TNF inhibitors?**  
Initial clinical use of TNF inhibitors in RA followed data

See Infusion-related reactions to infliximab in patients with RA in a clinical practice setting, page 1912

from the pivotal clinical trials. In their original labeling all received indications for patients with “moderate to severely active RA despite treatment with methotrexate (MTX) or another DMARD.” The actual use of these agents has varied worldwide, due to local availability, standards, and requirements. Driven largely by costs, access to TNF inhibitors has been restricted in some cases to patients with the most severe and active disease who have failed numerous other drugs. In an effort to optimize their use, international groups of rheumatologists have tried to create guidelines for the use of TNF inhibitors, based on the best available scientific evidence<sup>4</sup>.

With traditional disease modifying antirheumatic drugs (DMARD), data suggest that treatment earlier in the disease course can achieve greater efficacy<sup>5</sup>. The potency of TNF inhibitors in patients with refractory RA has therefore raised the hypothesis that even greater clinical benefit might be achieved in patients with early RA. In the Early Rheumatoid Arthritis trial, etanercept and aggressively dosed methotrexate both achieved notable and comparable clinical efficacy; however, etanercept was superior in inhibiting radiographic damage<sup>6</sup>. In the ASPIRE study, the combination of infliximab and MTX was superior to aggressively dosed MTX, particularly in radiographic outcomes<sup>7</sup>. A study of adalimumab, MTX, and the combination has been completed and the data are being analyzed.

While there is tremendous excitement concerning the potential for true disease modification, it remains to be defined whether TNF inhibitor therapy is capable of inducing a drug-free remission if used very early in the disease course, and also to what extent TNF inhibitor therapy is superior to DMARD or combination DMARD treatment. Studies addressing these questions are under way.

### How should patients be treated?

As noted, TNF inhibitors were initially used primarily for patients with refractory RA, most of whom were already taking MTX. For the mAb TNF inhibitors, combination therapy with MTX had 2 important and probably related benefits: (1) a pharmacokinetic benefit, with about 25% increase in area under the curve, and (2) decreased immunogenicity. In practice, for patients who had been doing well on combination therapy, clinicians began to taper or even discontinue MTX. Recently, however, results from the TEMPO study demonstrated a synergistic effect of MTX and TNF inhibitor (etanercept), with superior efficacy in reducing the signs and symptoms of RA, improving functional status, and preventing radiographic joint damage<sup>8</sup>. Similar results were seen in the above noted ASPIRE trial. Thus, combination TNF inhibitor-MTX therapy has become somewhat of a standard for patients with evidence of aggressive disease. Whether similar benefits might be achieved with other DMARD remains to be established.

In clinical studies and practice, about a quarter of treated patients have excellent responses, and about a quarter do not

respond to TNF inhibitor therapy. An emergent question has been what to do with the half of treated patients who have a meaningful response but still have some residual disease, the so-called “partial responders.” In animal models of arthritis, the combination of TNF inhibitor along with an interleukin 1 (IL-1) inhibitor was shown to achieve additive or even synergistic benefit in controlling inflammation and joint damage<sup>9</sup>. When this approach was tried in patients with RA, combination TNF inhibitor plus IL-1 inhibitor did not achieve any additional clinical benefit, suggesting the role of IL-1 in RA may not be as pivotal as in animal models<sup>10</sup>. There was nonetheless a “biologic” effect, in that there were more serious infections seen with the combination. While this particular approach is no longer tenable, combinations of TNF inhibitors with biologic therapies targeting other components of the immune system (e.g., TNF inhibitor combined with a T cell inhibitor or costimulatory molecule inhibitor or B cell inhibitor) might still prove valuable.

Because of cost and other considerations, the idea of using TNF inhibitors in an “induction-consolidation” type of regimen was raised in our original editorial. This has been tested in the BEST trial; preliminary results suggest a benefit to beginning the treatment of early RA with TNF inhibitor plus MTX, with superiority to other approaches<sup>11</sup>. Whether the initial benefit can be sustained after alterations in the therapeutic arms will be an important observation from the longterm followup of these patients.

### Will TNF inhibitors be safe?

Since their introduction, there has been concern about the potential for adverse events that might occur as a result of inhibiting TNF<sup>12</sup>. As noted, there has been a large and growing experience with these agents, and hence longer term safety data, that has either allayed concerns or put them into perspective. A key area of concern is proclivity to infections<sup>13</sup>. By appropriately screening, stratifying, and monitoring patients, infectious complications can be minimized. One issue is whether there are important differences between the agents in susceptibility to particular adverse events. In the case of tuberculosis (TB), for example, there were more early reports (before the approval of adalimumab) noted with infliximab than with etanercept. However, for all 3 TNF inhibitors, approximately half of the cases presented with disseminated or miliary TB, far exceeding the frequency seen in the normal population<sup>14</sup>. That, combined with information from animal studies, suggests there is a relationship common to all TNF inhibitors, even if the relative risks may be different between agents. Of note, routine screening for TB (e.g., with purified protein derivative testing and chest radiography) has substantially, although not completely, reduced the incidence of new cases.

Another safety concern has been lymphoma. From clinical studies, the frequency of lymphoma among patients with RA treated with TNF inhibitors exceeds that of the general popu-

lation, but it may well approximate the risk observed in patients with severe refractory RA<sup>12</sup>. This may be expected, as patients with severe refractory RA were the most likely to receive such therapy. Longer term safety data should provide additional information in that regard.

Defining the appropriate patients to receive TNF inhibitors is an ongoing and difficult task. However, it may be easier to define those who should not receive TNF blockers. Existing guidelines consistently invoke the following relative contraindications for the use of TNF inhibitor therapy: pregnancy; immunosuppressed states or active infections; multiple sclerosis or other demyelinating disorders; and congestive heart failure. Despite these areas of concern, areas of needed research include the use of these agents in systemic lupus erythematosus, pregnancy, patients infected with human immunodeficiency virus or hepatitis C, and the use of these agents perioperatively in those undergoing major surgery, among others.

### Which TNF inhibitor should be used?

As with all medications, the determination of which TNF inhibitor to use will depend on factors such as efficacy, safety, ease of administration, and cost. Although there are differences in the molecular structure and some characteristics of the agents, it is not clear to what extent such differences influence safety or efficacy. In RA, data from randomized clinical trials of all 3 agents show comparable efficacy in terms of American College of Rheumatology (ACR) responses; in fact, some have referred to this as the “60/40/20 response,” i.e., about 60% achieve ACR 20, 40% ACR 50, and 20% ACR 70. Additionally, while head to head studies have not been performed, the inhibition of joint damage assessed radiographically and improvement in physical function and quality of life may also be comparable among the TNF inhibitors. It appears that clinical response rates may be higher in clinical practice, where patients may not be as severely affected as those tested in clinical trials.

Interestingly, it has recently been suggested that patients who cannot continue treatment with one TNF inhibitor for either lack of efficacy or toxicity have been successfully treated with another, although responses as measured by the Disease Activity Score or ACR response may not be as robust as that seen in TNF inhibitor-naïve patients<sup>15</sup>. Despite these favorable responses, withdrawal of TNF inhibitor therapy occurs at a rate of roughly 10% per year, such that after 2–3 years, about 30%–40% of patients in the clinic are no longer taking TNF inhibitors. Reasons for drug cessation are varied and include toxicity, loss of efficacy, cost and reimbursement issues, and others.

Differences in these molecules do exist. Etanercept binds lymphotoxin- $\alpha$  whereas the mAb do not. mAb are more effective at engaging Fc-mediated interactions, effectively bind cell-bound forms of TNF, and may have a higher avidity for binding target. Studies assessing the ability of these agents to

induce apoptosis in various target organs have generated conflicting results. All agents have a volume of distribution suggesting predominantly intravascular distribution, and infliximab, which is given intravenously, has a higher peak concentration than the other agents. Clinically, and similar to what was seen in RA, recent trials have reported similar improvement with infliximab and etanercept in ankylosing spondylitis and psoriatic arthritis; trials are continuing for adalimumab in these conditions. Of note, infliximab is effective in Crohn's disease whereas etanercept, at the standard RA dose of 25 mg biw, was not more effective than placebo; studies are also continuing with adalimumab. Similarly, in psoriasis, the extent of efficacy observed with infliximab exceeds that seen with etanercept, although a double dose of etanercept was superior to the standard dose for RA. Whether these differences in outcomes in various diseases reflect different mechanisms of action, different dosing requirements, or some other factors remains to be defined. If there are indeed mechanistic differences affecting efficacy in certain conditions, the converse, differences in safety, may also be possible.

### What about cost?

At the time of our original editorial, although prices for TNF inhibitors were not yet announced, it was assumed that such treatment would be “more expensive than traditional drugs” for treating RA. That certainly was the case, and currently, average wholesale prices for a year of therapy with all of the TNF inhibitors are approximately (US)\$16,000. Given the high price of these agents, most rheumatologists (some due to local constraints) have been responsible stewards of limited health care resources, and use them judiciously. Any discussion of cost, however, must recognize that untreated or incompletely treated RA exacts a significant economic toll on affected patients, in terms of impaired work productivity, increased consumption of healthcare resources, and also impaired quality of life. Therefore, seemingly expensive treatments that not only control signs and symptoms, but that improve quality of life and prevent progression of damage, may indeed be cost-effective.

Studies assessing all 3 available agents, using standard economic assessment methods and including only direct medical costs, have shown an incremental cost-effectiveness for TNF inhibitor therapy of approximately (US)\$30,000 per quality-adjusted life-year (QALY) gained<sup>16</sup>. If indirect costs, such as work productivity, are accounted for, this falls to about \$10,000/QALY. These costs are well within the widely cited range of \$50–100,000 below which therapies are considered “cost-effective,” and is lower than many interventions accepted as appropriate. Thus, the issue of costs becomes more of a political consideration.

### Conclusion: the bottom line

Six years into their availability in the clinic, it is clear the TNF inhibitors have fulfilled their promise and have dramatically

altered the approach to the management of patients with inflammatory arthritis. Several of the questions we originally posed have been answered, but questions remain and are being addressed through continuing clinical trials and patient registries (Table 1). In response to our original question, "Will that dog hunt," the answer seems to be, "Yup; that dog hunts just fine."

Table 1. Lessons learned for TNF inhibitors 6 years after approval.

What has been learned

- Results in the clinic meet or exceed those from clinical trials
- Some patients have remission or near remission; many improve
- Treatment improves signs and symptoms of disease, quality of life, and attenuates the progression of joint damage
- There is synergistic efficacy with MTX plus TNF inhibitor
- Switching from one agent to another may be effective
- There is guarded optimism concerning safety
- Despite differences between agents, all work comparably in RA, AS, and PsA; it is unknown whether differences in other conditions are mechanistic or dose related
- TNF inhibitor therapy is cost-effective for patients with RA

Areas for further research

- How can we identify patients likely to have significant efficacy (and also those who are likely to have toxicity)?
- What is the best strategy for treating partial responders?
- Will DMARD other than MTX also be synergistic with TNF inhibitors?
- Will other strategies targeting TNF (e.g., p38 MAP kinase inhibitors, nuclear factor- $\kappa$ B inhibitors) be effective and safe?
- Will treatment of early RA with TNF inhibitors allow induction of remission?
- Should TNF inhibitors be the initial therapy in early RA?

**ARTHUR KAVANAUGH, MD.**

Professor of Medicine,  
Director, the Center for Innovative Therapy,  
Division of Rheumatology, Allergy and Immunology,  
The University of California, San Diego,  
9500 Gilman Drive,  
La Jolla, California 92093-0943  
E-mail: akavanaugh@ucsd.edu;

**STANLEY COHEN, MD.**

Clinical Professor of Internal Medicine,  
The University of Texas,  
Southwestern Medical Center,  
Medical Director,  
Radiant Research Dallas,  
Dallas, Texas;

**JOHN J. CUSH, MD.**

Medical Director,  
Arthritis Center, Presbyterian Hospital of Dallas,  
Clinical Professor of Internal Medicine,  
The University of Texas,  
Southwestern Medical Center,  
Dallas, Texas, USA.

Address reprint requests to Dr. Kavanaugh. E-mail: akavanaugh@ucsd.edu

**REFERENCES**

1. Kavanaugh A, Cohen S, Cush J. Inhibitors of tumor necrosis factor in rheumatoid arthritis: will that dog hunt? *J Rheumatol* 1998;25:2049-53.
2. Kavanaugh A. Overview of immunomodulatory intervention in rheumatoid arthritis. *Drugs of Today* 1998;35:275-86.
3. Wasserman MJ, Weber DA, Guthrie JA, Bykerk V, Lee P, Keystone EC. Infusion-related reactions to infliximab in patients with rheumatoid arthritis in a clinical practice setting: relationship to dose, anti-histamine pre-treatment, and infusion number. *J Rheumatol* 2004;31:1912-7.
4. Furst DE, Breedveld FC, Kalden JR, et al. Updated consensus statement on biological agents for the treatment of rheumatoid arthritis and other immune mediated inflammatory diseases. *Ann Rheum Dis* 2003;62:2-9.
5. Jarrett S, Quinn M, Emery P. The evidence for early intervention in rheumatoid arthritis. *Int J Adv Rheumatol* 2003;1:42-52.
6. Genovese MC, Bathon JM, Martin RW, et al. Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. *Arthritis Rheum* 2002;46:1443-50.
7. Smolen J, van der Heijde D, Emery P, et al. Infliximab inhibits radiographic joint damage in patients with early rheumatoid arthritis regardless of clinical response after 54 week treatment. *Ann Rheum Dis* 2004;63 Suppl 1:260.
8. Klareskog L, van der Heijde D, de Jager JP, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: Double-blind randomised controlled trial. *Lancet* 2004;363:675-81.
9. Feige U, Hu YL, Gasser J, Campagnuolo G, Munyakazi L, Bolon B. Anti-interleukin-1 and anti-tumor necrosis factor-alpha synergistically inhibit adjuvant arthritis in Lewis rats. *Cell Mol Life Sci* 2000;57:1457-70.
10. Genovese M, Cohen S, Moreland L, et al. Combination therapy with etanercept and anakinra in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate. *Arthritis Rheum* 2004;50:1412-9.
11. De Vries-Bouwstra JK, Goekoop-Ruiterman YPM, van Zeben D, et al. A comparison of clinical and radiological outcomes of four treatment strategies for early rheumatoid arthritis: Results of the BEST trial. *Ann Rheum Dis* 2004;63 Suppl 1:58.
12. Cush J, Kavanaugh A. ACR Hotline. FDA meeting March 2003: Update on the safety of new drugs for rheumatoid arthritis. Part I: The risk of lymphoma with RA and TNF inhibitors. II. CHF, infections and other safety issues. Internet. [Cited August 16, 2004]. Available from: <http://www.rheumatology.org/research/hotline/0303TNFL.htm>[www.rheumatology.org/publications/hotline/0303TNFL.asp?aud=mem](http://www.rheumatology.org/publications/hotline/0303TNFL.asp?aud=mem)
13. Kroesen S, Widmer AF, Tyndall A, Hasler P. Serious bacterial infections in patients with rheumatoid arthritis under anti-TNF-alpha therapy. *Rheumatology Oxford* 2003;42:617-21.
14. Bieber J, Kavanaugh A. Consideration of the risk and treatment of tuberculosis in patients with rheumatoid arthritis receiving biologic treatments. In: Kremer J, editor. *New treatments for rheumatoid arthritis*. *Rheum Dis Clin N America* 2004;30:257-70.
15. van Vollenhoven RF. Switching between biological agents. *Clin Exp Rheumatol* 2004 Suppl; in press.
16. Wong JB. Cost-effectiveness of anti-tumor necrosis factor agents. *Clin Exp Rheumatol* 2004 Suppl; in press.