The introduction of tumor necrosis factor-α alpha (TNF-α) antagonists has dramatically changed the treatment of rheumatoid arthritis (RA). Approved in November 1999 by the United States Food and Drug Administration (FDA) for the treatment of RA, infliximab has been shown in large, randomized, placebo controlled trials to be efficacious and well tolerated in the treatment of RA. However, the safety of TNF antagonists has recently been the focus of growing concern among health care providers. Serious infections, including disseminated tuberculosis (TB) and opportunistic infections, have been reported in patients with RA treated with infliximab1. Additionally, there have been recent reports of worsening congestive heart failure (CHF) and CHF related mortality in patients with RA given infliximab2. Uncertainties remain about the development of serious infections and malignancies with longterm use. In the current issue of The Journal, Shergy, et al report results from an open label, multicenter trial evaluating infliximab use in 553 patients with RA3. The goals of this trial were: (1) to determine the time of onset of clinical benefit following the infusion of infliximab, (2) to determine the safety of reducing the infusion time from 2 hours to one hour, and (3) to obtain additional safety experience with infliximab when administered in an office setting to patients with RA.

A prior study of infliximab in RA showed clinical benefit as early as 2 weeks after initial infusion in about half of the patients treated4. Shergy, et al report that patients with RA have decreased morning stiffness, pain, and global physician and patient disease assessments as early as 48 hours after the initial infliximab infusion. However, in contrast to the ATTRACT trial, the present study is open label and uncontrolled. Thus, a prospective, double blind, placebo controlled trial would better determine the time of onset of clinical benefit after initial infusion of infliximab.

All patients received 3 mg/kg infusions of infliximab over a 2 hour period at baseline, and at weeks 2, 6, and 14. Over one-third of these patients then participated in a study extension, receiving 2 additional infliximab infusions over a one hour period. Infusion reactions were assessed during the infusion and up to one hour after completion, and were rated as mild, moderate, or severe, according to functional limitation. As a group, the patients who were selected to receive the one hour infusion had previously experienced fewer infusion reactions during the preceding 2 hour infusions, and had no cardiac or renal dysfunction. Thus, selection bias and lack of a control group limit any meaningful comparison between the dosing regimens.

The authors conclude that infliximab is well tolerated when given in an office setting, yet note that up to 10% patients experienced an infusion related adverse event, most of these events classified as mild to moderate. However, up to 8.5% of patients experienced serious adverse events, including 2 deaths during study participation, one death occurring 21 weeks after the last study infusion, several hypersensitivity reactions, and one anaphylactic reaction. In this study, reactions were monitored during the actual infusion, one hour after infusion, and by self-report at the next study visit.

In the ATTRACT trial, infusion reactions were more common with infliximab treatment (16–20%) than with placebo (10%). Of concern, there have been recent reports of delayed infusion reactions, occurring up to 14 days after infliximab infusion. These included fever, maculopapular rash, arthralgias, dyspnea, nausea, and vomiting, all thought to be secondary to complement activation and immune complex formation5. Thus, monitoring for infusion reactions and other adverse events related to therapy is warranted at the time of infusion, over the course of treatment, and for months after treatment.

The ATTRACT trial also showed that the frequency of
serious adverse events was comparable between the infliximab and placebo arms, as was the frequency of serious infection and malignancy. However, 2 patients treated with infliximab died as the result of infection, one from TB and one from coccidiomycosis. Other reports have found that serious adverse events occurred in 4.4% and 1.8% of infliximab and placebo treated patients, respectively. Most recently, 84 infliximab-treated patients have been reported to have TB. In other reports of infliximab-treated patients diagnosed with TB, the majority was found to have extra-pulmonary disease, and over one-fourth had disseminated disease upon diagnosis. Of concern, the development of TB occurred at a median interval of only 12 weeks after the initial infusion of infliximab. Most patients were taking concomitant disease modifying antirheumatic agents, with methotrexate and prednisone being the most frequently prescribed concurrent therapies. Prior infection with TB was unknown in most patients, with only 8 patients reporting prior infection, and 2 patients recounting recent exposure to TB. Moreover, the patients were predominantly from non-endemic areas with a low incidence of TB. Four patients were thought to have died as a consequence of TB.

In the study by Shergy, et al, one patient died of TB about 3 months after the last dose of infliximab. TNF is thought to be involved in the containment and isolation of tubercle bacilli, and TNF inhibition may lead to reactivation of latent TB in some patients. Other serious opportunistic infections, including listeriosis, *Pneumocystis carinii* pneumonia, histoplasmosis, atypical mycobacteria, candidiasis, coccidiomycosis, and aspergillosis have also been reported in RA patients treated with infliximab. As of August 17, 2001, 9 cases of histoplasmosis, 11 cases of *Listeria monocytogenes*, 12 cases of *Pneumocystis carinii*, and 6 cases of aspergillosis were reported to the FDA in patients treated with infliximab.

Although their clinical relevance remains undefined, other concerns regarding longterm safety of infliximab therapy include the development of antibodies, including antinuclear, anti-dsDNA, and anticardiolipin antibodies. In an evaluation of longterm safety, 16% of infliximab treated patients were found to develop anti-dsDNA antibodies. A small percentage of these (0.2%) developed a self-limited lupus-like syndrome. Similarly, 16% of infliximab-treated patients in the ATTRACT trial also developed anti-dsDNA antibodies, with one patient developing a lupus-like syndrome that resolved after discontinuation of therapy. Anticardiolipin antibodies have also been detected in a small number of patients receiving infliximab. To date, these antibodies have not been associated with an increase in thrombotic events in the small numbers of patients evaluated. Larger trials with longer observation periods will be necessary to determine whether autoantibodies developing in the context of infliximab treatment confer a worse outcome.

In the present study by Shergy, et al one patient died from a CHF exacerbation 21 weeks after the last infliximab infusion. Two additional patients withdrew from the study secondary to worsening CHF. Although the investigators considered these outcomes unrelated to infliximab therapy, an ongoing phase II trial (ATTACH: Anti-TNF-α Therapy Against Congestive Heart Failure) has shown increased mortality and hospitalization rates in patients with Class III/IV CHF who were given 5 mg/kg or 10 mg/kg infusions of infliximab. Current recommendations by the manufacturer include a moratorium on initiating infliximab in patients with CHF, reevaluating CHF patients already receiving infliximab, and discontinuing infliximab in patients with worsening heart failure. Additional recommendations include considering the discontinuation of infliximab in patients with stable CHF.

There have been reports of demyelinating diseases occurring in patients receiving TNF antagonists. In a phase I open label study, infliximab was given to 2 patients with multiple sclerosis, both of whom developed new enhancing lesions on cranial magnetic resonance imaging (MRI). At this time, the causal relationship between TNF antagonists and the demyelinating process is unclear, and it seems prudent to avoid use of these agents in patients who have an underlying demyelinating disease. Further trials are needed to better define the association between TNF antagonists and the development of demyelinating diseases.

Longterm followup (mean followup of 25 mo) of patients with RA receiving etanercept has shown no increase in development of malignancies as compared to the general population. Similar results were found in the ATTRACT study of infliximab (445 patient-years of followup), with the incidence of malignancies similar to that of the general population. However, as RA patients are known to have higher rates of lymphoproliferative malignancies, a much longer followup (20 to 30 yrs) may be needed to truly assess the impact of TNF antagonists on development of malignant disease.

Prospective longterm studies involving large numbers of RA patients treated with TNF antagonists are clearly warranted to determine the risks of serious infection over time and malignancy. In the meantime, patient screening to determine the presence of underlying infection, symptoms of CHF, and demyelinating disorders may be warranted prior to initiating therapy with infliximab. Additionally, concerns regarding infusion related adverse events persist, underscoring the need for careful monitoring during and after infliximab therapy. Attention to shortened infusion times of the drug, and rapid onset of efficacy within hours, will need to be addressed in controlled studies.

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REFERENCES