The Comparative Safety and Effectiveness of TNF-α Antagonists

DANIEL H. SOLOMON, MD, MPH

ABSTRACT

OBJECTIVE: To describe the current knowledge on safety and effectiveness of the tumor necrosis factor (TNF-α) antagonists and identify current knowledge/evidence gaps for study by the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program.

BACKGROUND: Evidence-based Practice Centers (EPCs) and the Developing Evidence to Inform Decisions about Effectiveness (DeCIDE) network of AHRQ’s Effective Health Care Program will study the safety and effectiveness of biologic and nonbiologic disease-modifying antirheumatic drugs (e.g., TNF-α antagonists). The current knowledge of safety and effectiveness of TNF-α antagonists is reviewed.

SUMMARY: Treatment of adult rheumatoid arthritis (RA) involves determining which agents are safe, effective, and cost effective for an individual. Each individual patient’s health system may also play a role in which agents are chosen. Many agents are available for the management of RA, some with high cost and unknown safety. Section 1013 of the Medicare Modernization Act of 2003 authorizes AHRQ to study comparative effectiveness and safety of RA treatments through both EPCs and DeCIDE centers to develop scientific knowledge for RA management as well as through epidemiologic studies. Results will be compiled through a Clinical Decisions and Communications Science Center, then disseminated to all appropriate stakeholders, including patients, payers, and health care professionals. The current knowledge of safety and effectiveness of TNF-α antagonists in the treatment of RA is reviewed. Increased rates of serious infections, including Mycobacterium tuberculosis (MTB), or tuberculosis reactivation, may occur with the use of TNF-α antagonists. It is still unclear if RA increases the risk of developing cancer, or if use of TNF-α antagonists increases cancer risk.

CONCLUSIONS: TNF-α antagonists are costly, yet effective treatments for early and late RA. Use of these agents provides rapid relief of RA symptoms and provides positive outcomes, defined as improvements in American College of Rheumatology 20, 50, 70 scores; Health Assessment Questionnaire ratings; activities of daily living; joint space narrowing; erosions; and acute-phase reactants. Reactivation of latent MTB or onset of other infections or cancers may occur in RA patients with TNF-α antagonists.

KEYWORDS: Cost-effectiveness, Infliximab, Adalimumab, Etanercept, Effective health care, Safety, Medicare, Effectiveness, TNF-α antagonists, Anti-TNF-α therapies

J Manag Care Pharm. 2007;13(1)(suppl):S7-S18

Author

DANIEL H. SOLOMON, MD, MPH, is a practicing rheumatologist and epidemiologist and associate chief in the Division of Pharmacoeconomics and Pharmacoeconomics at Brigham and Women’s Hospital, Boston, Massachusetts, and an associate professor of medicine at Harvard Medical School.

AUTHOR CORRESPONDENCE: Daniel H. Solomon, MD, MPH, Associate Chief, Division of Pharmacoeconomics and Pharmacoeconomics, Brigham and Women’s Hospital, 1620 Tremont St., Suite 3030, Boston, MA 02120. Tel: (617) 278-0930; Fax: (617) 232-8602; E-mail: DSolomon@partners.org.

Copyright © 2007, Academy of Managed Care Pharmacy. All rights reserved.

A Case of Rheumatoid Arthritis

Marie is a 54-year-old woman with seropositive rheumatoid arthritis (RA). She presented to her rheumatologist with painful, swollen hands 18 months ago. She has taken several leaves of absence from work due to pain and stiffness in her hands. She had trials of a number of nonbiologic disease-modifying antirheumatic drugs (DMARDs, including methotrexate (MTX), sulfasalazine, and leflunomide, which have all had minimal effect. She is maintained on 20 mg/day prednisone and asks the rheumatologist about the tumor necrosis factor (TNF-α) antagonists because she has seen some of the direct-to-consumer advertising. In this patient, is therapy with a TNF-α antagonist appropriate? If a TNF-α antagonist is appropriate, which agent should be chosen on the basis of relative effectiveness and safety?

Medicare Modernization Act Section 1013

Section 1013 of the Medicare Modernization Act (MMA) of 2003 authorizes research demonstration and evaluations to improve the quality, effectiveness, and efficiency of treatments covered under Medicare.1 There are 13 National Agency for Healthcare Research and Quality (AHRQ) Developing Evidence to Inform Decisions about Effectiveness (DeCIDE) centers.2 The Vanderbilt University DeCIDE center, under principal investigator Marie Griffin, MD, is studying the comparative effectiveness and safety of treatments for RA. The AHRQ Effective Health Care Program can be viewed as “the best of times” as well as “the most confusing of times” in the world of arthritis. In the last 12 years, there has been a rapid pace of drug discovery in rheumatology, with 11 treatments being approved for RA by the U.S. Food and Drug Administration (FDA). Cyclosporine was approved in 1995, followed by leflunomide in 1998,3 then the early cyclooxygenase-2 inhibitors (celecoxib 4 in 1998 and rofecoxib 5 in 1999). The first anti-TNF-α agent, etanercept, 6 was approved in late 1998, followed by infliximab7 in late 1999 (infliximab was already on the U.S. market, having received FDA approval for treatment of Crohn’s disease in mid-1998). Adalimumab8 was approved in late 2002, followed by anakinra, valdecoxib, abatacept, and, most recently, rituximab9 which crossed over from the oncology world to the rheumatology world in February 2006. In addition, a number of different types of biologic agents for the treatment of RA are currently undergoing clinical trials (in all phases of clinical review).10 Since the armamentarium for treatment has significantly expanded in the last 12 years, a number of different agents are available in monotherapy or in combination therapy regimens. However, with so many different agents available to treat RA, a tremendous dilemma often exists for practitioners, patients, and health systems administrators about how to choose the “right” drug(s).
The Comparative Safety and Effectiveness of TNF-α Antagonists

### TABLE 1 Comparison of TNF Antagonists

<table>
<thead>
<tr>
<th>Structure</th>
<th>Adalimumab</th>
<th>Etanercept</th>
<th>Infliximab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Human MAb</td>
<td>Fusion protein (P75/Fc of IgG)</td>
<td>Chimeric MAb</td>
</tr>
<tr>
<td>Half-life</td>
<td>12-14 days</td>
<td>4-5 days</td>
<td>8-10 days</td>
</tr>
<tr>
<td>Administration</td>
<td>SC</td>
<td>SC</td>
<td>IV</td>
</tr>
<tr>
<td>Dosage</td>
<td>40 mg QOW</td>
<td>50 mg QW</td>
<td>3-10 mg/kg q 6 week</td>
</tr>
</tbody>
</table>

IgG = immunoglobulin G; IV = intravenous; MAb = monoclonal antibody; Q = every; QOW = every other week; QW = weekly; SC = subcutaneous; TNF = tumor necrosis factor.

---

**Review of Drugs**

TNF-α is a proinflammatory cytokine involved in the pathogenesis of RA. The TNF-α antagonists—etanercept, infliximab, and adalimumab—block the effects of TNF-α, leading to a number of anti-inflammatory effects such as reduced production of other proinflammatory cytokines (e.g., interleukin [IL]-6, IL-1), chemokines, vascular endothelial growth factor, and metalloproteinases. These effects cause decreased movement of inflammatory cells into the synovium, decrease neogenesis, and decrease joint and cartilage damage. Both adalimumab and infliximab are monoclonal antibodies, and etanercept is a fusion protein (Table 1). These agents all have a 1- to 2-week half-life. Adalimumab and etanercept are both administered by subcutaneous (SC) injection; infliximab is administered by intravenous (IV) infusion.

---

**Comparative Effectiveness in Late Disease—the Current Evidence**

**Anti-TNF-α Drugs Versus Nonbiologic DMARDs (e.g., MTX)**

There are 3 pivotal clinical trials for the anti-TNF-α therapies. They are the ATTRACTION (Anti-Tumor Necrosis Factor Factor Trial in Rheumatoid Arthritis with Concomitant Therapy) trial for infliximab, the Pivotal Study II trial for etanercept, and the ARMADA (Anti-TNF Research Study Program of the Monoclonal Antibody D2E7 in Rheumatoid Arthritis) trial for adalimumab; all are similar in their methodology. The patients were compared on the basis of their American College of Rheumatology (ACR) 20, 50, and 70 scores. In some studies, general health status was assessed by the Medical Outcomes Study Short-Form Health Survey (SF-36). The active treatment groups were compared with placebo.

Before discussing the actual studies of comparative effectiveness of anti-TNF-α agents in RA, we need to discuss outcome assessment methods of disease activity and disease severity. A commonly used outcome measure in rheumatology is the ACR 20, 50, and 70. The ACR 70 score is the second most difficult to achieve, followed by the ACR 90. Most RA studies use the ACR 70 as the primary endpoint. The ACR 20 is a 20% improvement in 3 of the 5 following objective or subjective measures in RA:

1. swelled joint count and tender joint count and physician global assessment,
2. patient global assessment,
3. visual analog scale (VAS, 0-10 [10 = worst score]) for pain,
4. health assessment questionnaire (HAQ, a measure of disability),
5. C-reactive protein (CRP). The ACR 50, 70, and 90 reflect a 50%, 70%, or 90% improvement, respectively, in 3 of the 5 measures.

The HAQ is a patient questionnaire covering 8 domains of activities of daily living (ADLs) and 20 items related to the need for assistive devices. It is scored on a scale of 0 to 3, with 0 indicating no disability and 3 indicating very severe disability. The HAQ is strongly associated with work disability and is often used in pharmacoeconomic studies of RA therapy cost-effectiveness.

The DAS28 (Disease Activity Score 28) is a validated index of RA disease activity. The DAS28 uses 4 measures (i.e., 28 tender joints, 28 swollen joints, the erythrocyte sedimentation rate, and the patients’ general health measured on a visual analog scale). A score below 2.8 indicates disease remission.

In early RA, the Sharp scoring method is a highly sensitive and reproducible measure of disease progression. This scoring method uses erosion scores and joint space narrowing (JSN) scores based on radiographic measurements. The erosion score is based on a 6-point scale, where a 0 means no new erosions and 0 worsening of existing erosions. Each point increase indicates new bone erosion or a 20% worsening of current erosion. JSN is based on a 5-point scale: 0 = no narrowing, 1 = minimal narrowing, 2 = loss of 50% of the joint space, >3 = loss of 75% of joint space, and 4 = complete joint space loss.

Lipsky et al. conducted a 54-week, multicenter, randomized, placebo-controlled trial in 428 patients. Patients were randomized to receive either 3 mg/kg infliximab or 10 mg/kg via IV infusion every 4 or 8 weeks, or a placebo infusion, for the study duration. Patients also randomly received the same weekly dose of MTX that they had been receiving before entering the study. ACR 20, 50, and 70 were measured. Forty-four patients (50%) in the groups that received MTX alone discontinued treatment compared with 71 (of 340 patients, 21%) of the infliximab + MTX-treated patients. Patients discontinued treatment due to lack of efficacy (36% MTX alone; 12% infliximab + MTX) and adverse events (8% for both MTX alone and infliximab + MTX-treated patients). The signs and symptoms of RA decreased more in the patients treated with infliximab + MTX than in the patients treated with MTX alone, as noted by the percentages with ACR 20, ACR 50, and ACR 70 responses. There was a tendency for the infliximab dosing of 3 mg/kg every 8 weeks to be less effective than the other treatments, which was significant only for the ACR 50 responses (P = 0.008 for the comparison with the group receiving 10 mg/kg infliximab every 8 weeks, and P = 0.02 for the comparison with the group receiving 10 mg/kg infliximab every 4 weeks).

When the individual components of the ACR criteria were evaluated, all dosages of infliximab + MTX were superior to MTX + placebo (P < 0.001, except for pain in the group that received 3 mg/kg infliximab every 8 weeks, P = 0.016). All infliximab +
MTX dosages also significantly reduced serum rheumatoid factor (RF) values by approximately 40% at week 54 (P < 0.001). Placebo + MTX had no significant effect on serum RF. The combination treatment also had a significantly greater effect on the HAQ and on the physical components of the SF-36. The results of the study can be seen in Table 2. There was significantly more progression of joint damage from baseline in the MTX-alone group compared with the combination treatment (P < 0.001). When erosion and JSN were independently examined, and when the hands and feet were separately examined, infliximab treatment had significant effects (P < 0.001). Thirty-one percent of patients who received MTX alone had radiographic evidence of major progression.

Minor adverse events were common in all treated groups, occurring in 94% in the MTX-alone group and in 95% of infliximab + MTX-treated patients. Serious adverse events (SAEs) were less common but occurred relatively equally in the MTX-treated patients (21%) compared with the combination therapy-treated patients (17%). The number of patients developing infections requiring antibiotic treatment was similar between the MTX-treated patients (35%) and the combination therapy patients (44%). The serious infection rate was also similar in the MTX-treated patients (8%) compared with the combination therapy patients (6%). Although not significant, several adverse effects occurred more frequently in the combination therapy-treated patients and included upper respiratory tract infections (URIs), sinusitis, pharyngitis, and headache. Cancer developed in 5 infliximab-treated patients during the trial (2 were recurrences, 3 were new cases; 2 were basal cell carcinomas, and 1 was rectal carcinoma). There were 8 deaths in the trial, 3 (3%) in the MTX-alone group and 5 (1%) in the infliximab + MTX-treated group.

The study’s authors concluded that therapy with infliximab + MTX resulted in sustained reduction in signs and symptoms of RA and increased function (measured by the HAQ and SF-36). The combination was also well tolerated, with serious infections occurring with similar frequency between infliximab + MTX compared with MTX alone. This study showed that the combination of infliximab + MTX improves the signs and symptoms of inflammation, physical function, and components of quality of life. In addition, it provides radiographic evidence that it prevents progressive joint damage in a majority of treated RA patients who have not responded to treatment with MTX alone.

Weinblatt et al. conducted a 24-week, double-blind, randomized, placebo-controlled trial in 89 patients with persistently active RA despite at least 6 months’ treatment with MTX (usual dose 15-25 mg/week). Patients were randomized to receive either SC 25 mg etanercept twice weekly (BIW) or SC placebo injection BIW for the study duration, while continuing to receive the same weekly dose of MTX they had been receiving before entering the study. The mean duration of RA in the study patients was 13 years. Clinical and laboratory assessments were conducted along with ACR 20, 50, and 70. Of the 59 patients randomly assigned to receive etanercept + MTX, 57 (97%) completed the 24-week

### Table 2: Clinical and Laboratory Responses at 54 Weeks

<table>
<thead>
<tr>
<th>Response</th>
<th>Methotrexate + Placebo (N=88)</th>
<th>3 mg of Infliximab/kg Every 8 Weeks</th>
<th>3 mg of Infliximab/kg Every 4 Weeks</th>
<th>10 mg of Infliximab/kg Every 8 Weeks</th>
<th>10 mg of Infliximab/kg Every 4 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACRI criteria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20% improvement (%) P value</td>
<td>17 ± 61</td>
<td>42 ± 62</td>
<td>48 ± 54</td>
<td>59 ± 38</td>
<td>59 ± 34</td>
</tr>
<tr>
<td>50% improvement (%) P value</td>
<td>8 ± 61</td>
<td>21 ± 65</td>
<td>34 ± 52</td>
<td>39 ± 37</td>
<td>38 ± 34</td>
</tr>
<tr>
<td>70% improvement (%) P value</td>
<td>2 ± 52</td>
<td>10 ± 63</td>
<td>17 ± 53</td>
<td>25 ± 38</td>
<td>19 ± 34</td>
</tr>
<tr>
<td>Decrease in number of swollen joints (%) P value</td>
<td>13 ± 61</td>
<td>37 ± 62</td>
<td>50 ± 54</td>
<td>60 ± 38</td>
<td>63 ± 34</td>
</tr>
<tr>
<td>Decrease in number of tender joints (%) P value</td>
<td>23 ± 63</td>
<td>49 ± 52</td>
<td>55 ± 48</td>
<td>56 ± 52</td>
<td>65 ± 33</td>
</tr>
<tr>
<td>Serum C-reactive protein (mg/dL) P value</td>
<td>2.8 ± 3.1</td>
<td>1.6 ± 1.9</td>
<td>1.5 ± 2.5</td>
<td>1.2 ± 1.7</td>
<td>1.1 ± 1.4</td>
</tr>
</tbody>
</table>

*Plus-minus values are means ± SD. P values are for the comparison with the group given methotrexate and placebo. ACR = American College of Rheumatology.
The Comparative Safety and Effectiveness of TNF-α Antagonists

### Table 3

<table>
<thead>
<tr>
<th>Amount of Improvement and Duration of Treatment</th>
<th>Placebo + Methotrexate (N=30)</th>
<th>Etanercept + Methotrexate (N=59)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>20% (ACR 20)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 weeks</td>
<td>33</td>
<td>66</td>
<td>0.003†</td>
</tr>
<tr>
<td>24 weeks</td>
<td>27</td>
<td>71</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>50% (ACR 50)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 weeks</td>
<td>0</td>
<td>42</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>24 weeks</td>
<td>3</td>
<td>39</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>70% (ACR 70)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 weeks</td>
<td>0</td>
<td>15</td>
<td>0.03‡</td>
</tr>
<tr>
<td>24 weeks</td>
<td>0</td>
<td>15</td>
<td>0.03‡</td>
</tr>
</tbody>
</table>

* Patients who withdrew from the study were considered not to have a response at all points after withdrawal regardless of the actual clinical response.
† The P value was calculated by the chi-square test.
‡ The P value was calculated by Fisher’s exact test.

Two patients withdrew due to side effects (1 from abdominal pain from previous hernia surgery and 1 from a shoulder fracture). Of the 30 patients who received MTX + placebo, 24 (80%) completed the trial. Four patients withdrew due to lack of efficacy, 1 withdrew due to a myocardial infarction, and 1 was lost to follow-up.

According to the ACR response criteria, the etanercept + MTX group had significantly superior outcomes for all endpoints. The primary efficacy endpoint was the proportion of patients reaching ACR 20 at week 24. This was achieved in 71% of the etanercept + MTX group compared with 27% of the placebo + MTX group (P < 0.001). At all evaluations, the response to etanercept + MTX was rapid and sustained. Beginning at week 1, a significantly greater proportion of etanercept + MTX-treated patients achieved ACR 20. Significantly greater proportions of patients achieved ACR 50 at month 1 and ACR 70 at month 3 and each subsequent evaluation (Table 3). Patients who received etanercept + MTX also had significantly greater improvement in all measures of disease activity at weeks 12 and 24. The HAQ improved 47%, from 1.5 to 0.8, in the etanercept + MTX-treated group. The HAQ score for the placebo + MTX group did not significantly change (27%, from 1.5 to 1.1). The erythrocyte sedimentation rates and CRP improved significantly in the etanercept + MTX groups compared with the placebo + MTX group. Some patients used corticosteroids (inha-articular and oral); however, it was felt that this did not alter the primary efficacy endpoint.

Etanercept was well tolerated. Injection site reactions were the only events that more frequently occurred in the etanercept + MTX group compared with the placebo + MTX group (42% versus 7%). All injection site reactions were mild (erythema with or without itching, pain, or swelling), most resolved without treatment, and none required discontinuation of the study drug. Infection was the most common overall adverse event. No significant inter-group differences were in the types or incidence of infections. Approximately one third of infections in both treatment groups were URIs or sinusitis. There were no deaths during the study or within 30 days after receiving the last dose of the study drug. Most laboratory abnormalities in both treatment groups were mild. More serious laboratory abnormalities included lymphocytopenia (<500 cells/mm³, 2 patients in each group), hyponatremia (116-124 mmol/L sodium, 1 placebo-treated patient), and anemia (Hb < 6.5 gm/dL, secondary to a gastrointestinal bleed in a placebo-treated patient). No other serious laboratory abnormalities were noted in the etanercept + MTX group.

This study demonstrated that in patients with persistently active RA despite MTX therapy, the addition of etanercept provided benefit without potentiating toxic effects of MTX or inducing any dosage-limiting side effects. At 24 weeks, ACR 20 criteria were achieved in 71% of etanercept + MTX-treated patients compared with 27% of placebo + MTX-treated patients. The ACR 50 criteria were met in 39% of etanercept + MTX-treated patients compared with 3% of MTX-treated patients, and the ACR 70 criteria were achieved in 15% of etanercept + MTX-treated patients and 0% of the MTX-treated patients.

Weinblatt et al. conducted a 24-week, multicenter, randomized, double-blind, placebo-controlled study in 271 patients with persistently active RA despite at least 6 months’ treatment with MTX (usual dose: 12.5-25.0 mg/week). Patients were randomized to receive either SC 20 mg, 40 mg, or 80 mg adalimumab, every other week (QOW) or SC placebo injection QOW for the study duration. Patients continued to receive the same weekly dose of MTX that they had been receiving before entering the study. The mean duration of RA in the study patients was 12.3 years. For entry into the study, patients had to have failed 1 additional DMARD aside from MTX, but no more than 4. Clinical and laboratory assessments were conducted along with ACR 20, 50, and 70. Of the 271 randomized patients, 62 (22.9%) received placebo, 69 (25.5%) received 20 mg adalimumab, 67 (24.7%) received 40 mg adalimumab, and 73 (26.9%) received 80 mg adalimumab. Of the 271 randomized patients, 161 patients completed the study. Patients who did not meet ACR 20 at week 16 were offered open-label continuation between weeks 16 and 24 (n = 92). Of these patients, 23 had received 20 mg adalimumab, 27 had received 40 mg adalimumab, 27 had received 80 mg adalimumab, and 35 had received placebo. Additionally, another 18 patients withdrew from the study—7 due to side effects, 5 due to consent withdrawal, 3 due to lack of efficacy, 2 lost to follow-up, and 1 due to a protocol violation. All these study patients withdrew before week 16 and therefore had not been offered open-label continuation.
An ACR 20 response at week 24 was achieved by a significantly greater proportion of adalimumab + MTX-treated patients (P <0.001) compared with MTX alone. ACR 20 responses were 47.8% (20 mg adalimumab), 67.2% (40 mg adalimumab), and 65.8% (80 mg adalimumab) versus MTX + placebo (14.5%). The ACR 50 response rates were significantly greater than placebo: 31.9% (20 mg adalimumab; P ≤ 0.003), 55.2% (40 mg adalimumab; P < 0.001), 42.5% (80 mg adalimumab; P <0.001), and 8.1% (placebo + MTX). ACR 70 responses that were statistically significantly greater than placebo occurred with 40 mg adalimumab (26.9%, P <0.001) and 80 mg adalimumab (19.2%, P ≤ 0.020). The placebo response was 4.8%. The ACR responses can be seen in Table 4.

Patient responses were rapid, with the greatest number of adalimumab-treated patients attaining an ACR 20 response at week 1. The proportion of patients attaining an ACR 20 response at week 1 was 26.1% (20 mg adalimumab), 25.4% (40 mg adalimumab), 31.5% (80 mg adalimumab) and 6.5% (placebo + MTX). In each adalimumab dosage group, the percentage of patients who achieved an ACR 20 response increased from week 1 through week 12 and continued at that level throughout week 24. All adalimumab + MTX groups had a statistically significant improvement over baseline with respect to the ACR core components (e.g., mean tender joints, swollen joints). The disability index of the HAQ also decreased by at least 0.54 over time compared with a decrease of 0.27 for placebo. Serum concentrations of the cartilage destruction markers promatrix metalloproteinase 1 (proMMP-1) and proMMP-3 were measured. Levels of proMMP-1 decreased with adalimumab treatment and increased with MTX treatment, as did CRP levels. Levels of proMMP-3 decreased slightly with placebo + MTX treatment (this change was not significant).

Hemoglobin, hematocrit, and the percentage of lymphocytes increased in the MTX + adalimumab-treated patients, and the platelet count decreased. These changes were all considered to be statistically significant (P ≤ 0.05 compared with baseline). Adalimumab was well tolerated. Injection site reactions occurred in 15.3% of adalimumab-treated patients and in 3.2% of placebo-treated patients. The most common adverse effects were rhinitis, URI, nausea, flu syndrome, and headache. These effects were similar to treatment with infliximab and etanercept. Two adalimumab-treated patients developed pneumonia and were treated with antibiotics; both patients remained in the study. One study patient developed a new malignancy (colon adenocarcinoma). Seven patients withdrew from the study due to adverse events: 4 receiving 20 mg adalimumab (skin hypertrophy, pruritus, injection-site reaction, and cough with asthenia), 1 receiving 80 mg adalimumab (colon adenocarcinoma), and 2 receiving placebo (femur avascular necrosis and allergic reaction). The infection rate was comparable between the adalimumab and the placebo-treated patients. No opportunistic infections (OIs) or cases of Mycobacterium tuberculosis (MTB) were observed. Most of the adverse effects were mild to moderate in severity and occurred in comparable numbers with those patients receiving MTX alone.

These study findings indicate that the addition of 20 mg, 40 mg, or 80 mg adalimumab given QOW to MTX therapy substantially and rapidly improves signs and symptoms of RA. This assessment includes standard measures of disease activity, such as acute-phase reactants, RA disease markers, and quality of life scores over 24 weeks in RA patients with inadequate response to MTX alone. These results occurred without added toxicity.

### Comparative Effectiveness in Early Disease—Summary of the Current Evidence

#### Anti-TNF-α Drugs Versus Nonbiologic DMARDs (e.g., MTX)

In the early-disease randomized trials, patients had a mean RA duration of <3 years. These studies are very similar with respect to their baseline disease activity, and they are all for a duration of about 1 year. Some of the same assessments/endpoints that were used for the late-disease studies were also used to assess early disease (e.g., ACR 20, ACR 50, and ACR 70).16-18

St. Clair et al. conducted a randomized, blinded, controlled trial in 1,049 patients to compare benefits of starting MTX and infliximab versus MTX alone in early RA.19 Patients received MTX + placebo (n = 298), MTX + 3 mg/kg infliximab (n = 373), or MTX + 6 mg/kg infliximab (n = 378). Infliximab or placebo infusions were given at weeks 0, 2, and 6, and every 8 weeks thereafter through week 46. Oral corticosteroids and nonsteroidal anti-inflammatory drugs versus nonbiologic DMARDs (e.g., MTX) were compared at 12 weeks as follows: ACR 20, ACR 50, and ACR 70. The proportion of patients attaining an ACR 20 response at week 24 was achieved by a significantly greater proportion of adalimumab + MTX-treated patients (P <0.001) compared with MTX alone. ACR 20 responses were 47.8% (20 mg adalimumab), 67.2% (40 mg adalimumab), and 65.8% (80 mg adalimumab) versus MTX + placebo (14.5%). The ACR 50 response rates were significantly greater than placebo: 31.9% (20 mg adalimumab; P ≤ 0.003), 55.2% (40 mg adalimumab; P < 0.001), 42.5% (80 mg adalimumab; P <0.001), and 8.1% (placebo + MTX). ACR 70 responses that were statistically significantly greater than placebo occurred with 40 mg adalimumab (26.9%, P <0.001) and 80 mg adalimumab (19.2%, P ≤ 0.020). The placebo response was 4.8%. The ACR responses can be seen in Table 4.

Patient responses were rapid, with the greatest number of adalimumab-treated patients attaining an ACR 20 response at week 1. The proportion of patients attaining an ACR 20 response at week 1 was 26.1% (20 mg adalimumab), 25.4% (40 mg adalimumab), 31.5% (80 mg adalimumab) and 6.5% (placebo + MTX). In each adalimumab dosage group, the percentage of patients who achieved an ACR 20 response increased from week 1 through week 12 and continued at that level throughout week 24. All adalimumab + MTX groups had a statistically significant improvement over baseline with respect to the ACR core components (e.g., mean tender joints, swollen joints). The disability index of the HAQ also decreased by at least 0.54 over time compared with a decrease of 0.27 for placebo. Serum concentrations of the cartilage destruction markers promatrix metalloproteinase 1 (proMMP-1) and proMMP-3 were measured. Levels of proMMP-1 decreased with adalimumab treatment and increased with MTX treatment, as did CRP levels. Levels of proMMP-3 decreased slightly with placebo + MTX treatment (this change was not significant).

Hemoglobin, hematocrit, and the percentage of lymphocytes increased in the MTX + adalimumab-treated patients, and the platelet count decreased. These changes were all considered to be statistically significant (P ≤ 0.05 compared with baseline). Adalimumab was well tolerated. Injection site reactions occurred in 15.3% of adalimumab-treated patients and in 3.2% of placebo-treated patients. The most common adverse effects were rhinitis, URI, nausea, flu syndrome, and headache. These effects were similar to treatment with infliximab and etanercept. Two adalimumab-treated patients developed pneumonia and were treated with antibiotics; both patients remained in the study. One study patient developed a new malignancy (colon adenocarcinoma). Seven patients withdrew from the study due to adverse events: 4 receiving 20 mg adalimumab (skin hypertrophy, pruritus, injection-site reaction, and cough with asthenia), 1 receiving 80 mg adalimumab (colon adenocarcinoma), and 2 receiving placebo (femur avascular necrosis and allergic reaction). The infection rate was comparable between the adalimumab and the placebo-treated patients. No opportunistic infections (OIs) or cases of Mycobacterium tuberculosis (MTB) were observed. Most of the adverse effects were mild to moderate in severity and occurred in comparable numbers with those patients receiving MTX alone.

These study findings indicate that the addition of 20 mg, 40 mg, or 80 mg adalimumab given QOW to MTX therapy substantially and rapidly improves signs and symptoms of RA. This assessment includes standard measures of disease activity, such as acute-phase reactants, RA disease markers, and quality of life scores over 24 weeks in RA patients with inadequate response to MTX alone. These results occurred without added toxicity.

### Comparative Effectiveness in Early Disease—Summary of the Current Evidence

#### Anti-TNF-α Drugs Versus Nonbiologic DMARDs (e.g., MTX)

In the early-disease randomized trials, patients had a mean RA duration of <3 years. These studies are very similar with respect to their baseline disease activity, and they are all for a duration of about 1 year. Some of the same assessments/endpoints that were used for the late-disease studies were also used to assess early disease (e.g., ACR 20, ACR 50, and ACR 70).16-18

St. Clair et al. conducted a randomized, blinded, controlled trial in 1,049 patients to compare benefits of starting MTX and infliximab versus MTX alone in early RA.19 Patients received MTX + placebo (n = 298), MTX + 3 mg/kg infliximab (n = 373), or MTX + 6 mg/kg infliximab (n = 378). Infliximab or placebo infusions were given at weeks 0, 2, and 6, and every 8 weeks thereafter through week 46. Oral corticosteroids and nonsteroidal anti-inflammatory drugs versus nonbiologic DMARDs (e.g., MTX) were compared at 12 weeks as follows: ACR 20, ACR 50, and ACR 70.
The Comparative Safety and Effectiveness of TNF-α Antagonists

drugs were maintained at baseline dosages. No other DMARDs were allowed during the study. Joint examinations, laboratory and global assessments, and the disability index, HAQ, and SF-36 were evaluated. Screening for MTB began 7 months into the enrollment period (February 2001).

The primary endpoint for the reduction in signs and symptoms was the percentage of ACR improvement from baseline to week 54 (ACR-N). The ACR 20, ACR 50, ACR 70, and ACR 90 were also evaluated. Major clinical response was defined as an ACR 70 response for 6 consecutive months. Radiographic and physical functioning changes were also evaluated.

The 1,004 patients who were evaluated had similar demographics, including disease duration with moderate disease activity. Most patients were able to tolerate 20 mg/week MTX (n = 731) and maintained this dose throughout the trial. Premature study discontinuation occurred in 201 patients, mostly due to lack of efficacy in the MTX + placebo group (9.6%). Withdrawal due to adverse events was more common in the infliximab-treated groups (9.5%, 3 mg/kg; and 9.6%, 6 mg/kg, respectively), than in the placebo + MTX-treated group (3.2%).

The MTX + infliximab-treated groups achieved a statistically significant higher median ACR-N than the MTX + placebo-treated group (P < 0.001). There were no significant clinical efficacy differences between the 2 infliximab groups. In addition, the ACR 20, ACR 50, and ACR 70 results were significantly higher in the infliximab-treated groups compared with the MTX-treated group. The ACR 90 response rates were significantly higher in the MTX + 6 mg/kg-infliximab-treated group than in the MTX + placebo-treated group (16.9% versus 6.6%, P < 0.001). The proportion of patients achieving a sustained ACR 70 response was also higher for the infliximab-treated patients compared with the MTX monotherapy (7.7%). Greater reductions in the DAS28 scores in the joint damage and JSN and higher remission rates (P < 0.001 for these last 2 measures) were noted in the infliximab-treated patients. The HAQ scores improved more with infliximab than MTX, as did the SF-36.

The most commonly reported adverse events were URI, nausea, headache, sinusitis, and pharyngitis. Infusion reactions also occurred (15% to 20%). The proportion of patients with one or more serious reactions was higher in the infliximab + MTX groups (14%) than in the MTX-alone group (11%). Serious infections were more common in the infliximab-treated groups (5.6%, n = 21 for 3 mg/kg infliximab; 5.0%, n = 19 for 6 mg/kg infliximab; 2.1%, n = 6 for MTX). Active MTB was diagnosed in 4 infliximab-treated patients (none were extrapolmonary). They were all withdrawn from the study. Malignancy was diagnosed in 4 MTX + 6 mg/kg infliximab-treated patients. Four patients died during the trial, 2 who were treated with infliximab and 2 who were treated with MTX. In 1 of the MTX-treated patients, the cause of death was respiratory failure attributed to MTX-related lung toxicity.

This study demonstrates that treatment of active RA in its early stages with infliximab + MTX improves the signs and symptoms of disease activity, inhibits radiographic progression of joint damage, and improves physical function compared with MTX monotherapy over 1 year. Infliximab therapy was also associated with a significantly higher rate of serious infections.

Bathon et al. conducted a randomized, blinded, placebo-controlled trial in 632 patients with early RA. They received either SC etanercept (10 mg or 25 mg) BIW + MTX, or MTX (mean, 19 mg/week) + placebo weekly for 12 months so these researchers could study the efficacy of etanercept in reducing disease activity and preventing joint damage. Clinical response was defined as the percentage improvement in ACR 20, ACR 50, and ACR 70. Bone erosions and JSN were measured radiographically and scored on the Sharp method.

Etanercept-treated patients had more rapid improvement than MTX-treated patients, which was evident at week 2 of treatment. Additionally, significantly more etanercept-treated patients than MTX-treated patients had ACR 20, ACR 50, and ACR 70 response at month 6 (P < 0.005) but were approximately the same thereafter. Patients treated with 25 mg etanercept had significantly greater areas under the curve for ACR-N for months 3, 6, 9, and 12 than did MTX-treated patients and these patients had less radiographic evidence of joint progression than did the MTX-treated patients. Most patients had no new or worsening erosions. Of the 25-mg etanercept-treated patients, 72% had no increase in erosion score compared with 60% of MTX-treated patients (P = 0.007). There were no significant differences among treatment groups in the changes in scores for JSN at either month 6 or month 12. The responses in the 10-mg etanercept-treated patients were similar to those of MTX alone.

Adverse effects were mild to moderate in severity. Significantly more MTX-treated patients than etanercept-treated patients experienced adverse events. MTX-associated pneumonitis was diagnosed in 1% of patients (n = 3). Injection-site reactions occurred in 37% of 25-mg etanercept-treated patients and 7% of MTX-treated patients (placebo injection, P < 0.001). The number of patients with one or more infections was similar between treatment groups; however, in an analysis of the rate of all infection types per patient-year, significantly more MTX-treated patients than etanercept-treated patients had infections (1.9 versus 1.5 events per PY, P = 0.006). Infections requiring hospitalization occurred in <3% of patients in each group. Laboratory test abnormalities were similar between the 3 treatment groups, except for elevated liver enzymes, which were twice as high in the MTX-treated patients compared with the etanercept-treated patients (P < 0.001 for both).

There was no evidence of an increased cancer rate in any treatment group, as compared with the age- and sex-matched general population (SEER [Surveillance Epidemiology and End Results] database). One patient in each of the MTX- and 25-mg etanercept-treated patients died during the study.

The conclusion of this study is that use of DMARDs early after RA disease onset stopped erosions in 72% of etanercept-treated
patients and 60% of MTX-treated patients, emphasizing the importance of early intervention to slow or arrest joint damage. The clinical responses in the first 6 months of therapy were more rapid with 25-mg etanercept-treated patients than with MTX-treated patients. Etanercept and MTX were relatively well tolerated and had similar safety and tolerability profiles to those patients with long-standing disease.

Breedveld et al. conducted a 2-year, multicenter, randomized, double-blind, placebo-controlled efficacy and safety study (n = 799) comparing SC 40 mg adalimumab QOW + oral MTX every week (QOW), SC 40 mg adalimumab alone every other week (QOW), or oral 20 mg MTX alone weekly, in patients with early, aggressive RA who had not used prior MTX therapy (the PREMIER trial).14 Study endpoints were ACR 50 improvement at year 1 and mean change from baseline in the modified Sharp score at year 1 (for combination therapy compared with MTX alone). Other efficacy endpoints were the percentage of patients who achieved clinical remission (DAS28); the HAQ DI (Disease Index, improvement in physical function from baseline); and ACR 20, ACR 50, ACR 70, and ACR 90 response at year 2, change from baseline in Sharp score, and maintained clinical response (ACR 70 response ≥26 continuous months). Patients were screened for MTX before receiving the study drug.

There were 539 patients who completed 2 years of treatment. More combination therapy patients completed the 2-year treatment (75.7%, n = 203) than monotherapy-treated patients (adalimumab, 60.9% [n = 167]; MTX, 65.8% [n = 169]), P <0.001 across treatment arms. Withdrawal due to adverse events occurred in 77 patients (combination therapy n = 32, adalimumab therapy n = 26, MTX therapy n = 19). Only 13 patients (4.9%) in the combination therapy group withdrew due to lack of efficacy compared with 52 (19%) of adalimumab-treated patients and 46 (17.9%) of MTX-treated patients.

At year 1, combination therapy was significantly better than either adalimumab or MTX monotherapy. More patients receiving combination therapy at year 1 had an ACR 50 response (62%) than did the MTX-treated patients (46%) or adalimumab-treated patients (41%, P <0.001; for both comparisons). At year 2, ACR 50 responses were maintained in the combination therapy group and remained clinically and statistically superior to both of the monotherapy treatments (P <0.001). Similar statistical significance of combination over monotherapy was also achieved for ACR 20, ACR 70, and ACR 90 response rates at years 1 and 2.

Significantly less radiographic progression occurred in the combination-treated patients at month 6 and years 1 and 2 than in the MTX or adalimumab-treated patients. There was significantly less disease progression in the adalimumab-treated patients compared with the MTX-treated patients at month 6, year 1, and year 2 (all P <0.001). After year 2 of treatment, 49% of the combination therapy patients exhibited disease remission, and 49% achieved a major clinical response. These rates were twice those in either of the mono-therapy treatment groups.

Adverse events were comparable between the 3 treatment groups. The DAS28 clinical remission and HAQ DI were statistically significantly greater with combination therapy than with monotherapy following years 1 and 2 of treatment (P <0.001). Adverse events were comparable across treatment groups, with similar percentages experiencing serious adverse events. The rate of serious infections in the adalimumab monotherapy arm (n = 3) was significantly lower than in the combination treatment arm (n = 9, including 1 case of pleural MTB), but not in the MTX arm (n = 7). A lupus-like reaction with a positive antinuclear antibody occurred in an adalimumab-treated patient (this patient was withdrawn from the study). There was 1 death in the MTX-treated arm, 1 in a combination-treated patient, and 4 in adalimumab-treated patients. Ten malignancies were found in study patients: 2 were in the combination-treated patients, 4 were in adalimumab-treated patients, and 4 were in MTX-treated patients.

The authors concluded that combination treatment with adalimumab and MTX in early, aggressive RA was statistically significantly superior to monotherapy with either adalimumab or MTX. However, adalimumab monotherapy also led to a significant decrease in radiographic progression.

The anti-TNF-α agents adalimumab, etanercept, and infliximab are effective in managing early RA. Yet despite these reviewed studies, their direct comparative effectiveness is not known at this time.

**Anti-TNF-α Drugs Versus Other Anti-TNF-α Drugs: Observational Data**

As has been already discussed, there are many randomized, controlled trials using anti-TNF-α agents in treating both early and late RA,12-14,16-18 but no “head-to-head” randomized controlled trials. By reviewing the observational epidemiologic data, Finckh et al. conducted a longitudinal observational comparative effectiveness study to evaluate patients on etanercept without DMARDs, etanercept with DMARDs, or infliximab with DMARDs.19 Sequential radiographs were compared to evaluate the rates of erosion progression and JSN with these treatment regimens. They determined that combined use of infliximab with DMARDs was more effective than etanercept alone (P = 0.04) and that the combined use of infliximab with DMARDs was more effective than the combination of etanercept and DMARDs (P = 0.02) in decreasing progression of JSN. Additionally, the combined treatment with infliximab and DMARDs was significantly more effective than etanercept alone for controlling erosion progression (P <0.001), but was similar to etanercept with DMARDs for controlling erosion progression (P = 0.07). Use of etanercept and DMARDs was more effective in preventing progression of erosions compared with etanercept alone (Figure 1). Overall, this study concluded that combined use of the anti-TNF-α agents infliximab or etanercept with DMARDs was more effective in controlling JSN and erosion progression than anti-TNF-α therapy alone (etanercept).
A potential limitation to the use of observational study data is lack of control over treatment assignments, which can lead to selection bias or confounding by indication. Confounding by indication would be more likely to occur with anti-TNF-α agents used with or without DMARDs because patients with more severe disease may be selected for the combination therapy regimens. Additional limitations can also include missing data or including only patients with complete follow-up. Including patients with complete follow-up tends to oversample patients with good response to therapy and good tolerability, inducing a bias toward completers. Although observational studies may be useful when controlled comparative trials are unavailable, there are obvious limitations. Therefore, the need for more controlled comparative studies still exists.

**Sequential Therapy With Anti-TNF-α Drugs**

In clinical practice, a patient who is not responding well to one anti-TNF-α agent may be changed to another agent. One study evaluated this concept of sequential effectiveness in switching anti-TNF-α agents. Nikas et al evaluated the safety and efficacy of switching from infliximab to adalimumab (40 mg QOW) in a 12-month, open-label study. There were 24 “switchers” who were compared with 25 patients treated with adalimumab who had never received previous anti-TNF-α treatment (controls). Clinical response (tender and swollen joint counts) was evaluated using ACR 20 and DAS28. Concomitant DMARDs and/or prednisone (≤7.5 mg/day) were allowed and remained stable during the study. “Switcher” patients had received infliximab for a mean of 18.5 (SD 3.8) months.

After 12 months of treatment with adalimumab, a significant reduction in the tender and swollen joint count, improvement in pain scores, and patient and physician global assessments were observed in both groups. There were no statistical differences between the 2 groups regarding these evaluations. The ACR 20 response criteria were reached by 75% (18/24) of the “switchers” and by 76% (19/25) of the control group. Additionally, significant improvements in DAS28 were in both groups. Of 18 patients in the “switcher” group who achieved an ACR 20 response, 8 had previously discontinued infliximab treatment due to lack of efficacy, and 10 had stopped infliximab due to side effects.

Eleven “switchers” (46%) and 11 (44%) controls had adverse drug reactions, most resolved without sequelae. Four “switchers” discontinued the study, 2 due to lack of efficacy and 2 due to adverse events (herpes zoster infection and immediate hypersensitivity reaction [this patient had a similar reaction to infliximab]). Three control patients discontinued the study, 1 due to lack of efficacy and 2 due to side effects (herpes zoster infection and lower respiratory tract infection).

This study showed that adalimumab was well tolerated and effective in treating RA, even when patients had discontinued treatment with infliximab. Although this study reported data on “switching” between anti-TNF-α agents, the data are limited. There is a need for more studies on this topic, particularly regarding “switching” between all the different anti-TNF-α agents.

**Summary: Comparative Safety of Anti-TNF-α Drugs**

**Infections and Cancer**

Serious infections were defined as those requiring hospitalization or IV antibiotic treatment or leading to death. Dixon et al. reported comparative safety data from the British Society for Rheumatology Biologics Register (BSRBR) of anti-TNF-α-treated patients. The purpose of evaluating the data was to determine whether the rate of serious infections was greater in anti-TNF-α-treated RA patients than in traditional DMARD-treated RA patients.

Of 7,664 anti-TNF-α-treated patients, 3,596 were etanercept-treated patients, 2,878 were infliximab-treated patients, and 1,190 were adalimumab-treated patients. There were 525 serious infections in the anti-TNF-α-treated cohort and 56 serious infections in the comparator cohort. The crude rate of infections was higher in the anti-TNF-α cohort (53 events/1,000 person-years) than the comparator group (41 events/1,000 person-years), with an incidence rate ratio of 1.28 (95% CI [confidence interval], 0.94-1.76). After adjustment for disease severity, comorbidity, extra-articular manifestations, baseline steroid use, and smoking, there was no apparent risk of infection increase (incidence rate ratio 1.03, 95% CI, 0.68-1.57). The severity of all infections was not significantly different between the 2 groups, and both had a median hospital admission time of 6 days.

The most common infections involved the lower respiratory tract, skin and soft tissue, bone and joint, and urinary tract. There were 19 bacterial intracellular infections, which were all in the anti-TNF-α-treated cohort (10 of which were MTB). Compared with etanercept, the adjusted incidence rate ratios for MTB were 4.9 (95% CI, 0.5-49.8) and 3.5 (95% CI, 0.3-47.3) for infliximab and adalimumab, respectively.
Overall, the rate of serious bacterial infections was not increased in anti-TNF-α-treated patients compared with the DMARD-treated patients. Extrapulmonary cases of MTB with anti-TNF-α agents are becoming more commonplace.\(^\text{21-23}\)

**Mycobacterium Tuberculosis**

Infliximab was approved by the FDA in August 1998 for the treatment of Crohn's disease and fistulizing Crohn's disease.\(^\text{26}\) It was approved in November 1999 for the treatment of RA.\(^\text{27}\) At the time of these early approvals, the risk of serious infection, particularly with MTB, had not yet been identified. Through continued study, more cases of MTB have been elucidated.

The effect of TNF on granuloma biology may be related to cases of MTB in anti-TNF-treated patients.\(^\text{28}\) According to Wallis and Ehlers, in the field of the biological sciences, it is known that TNF-α is involved in the formation and maintenance of protective granulomas. Following MTB infection, the human immune system is not always able to completely eradicate the infection and the granulomas containing the infectious bacilli (e.g., MTB) that sometimes form. These granulomas are a host defense mechanism to contain intracellular pathogens whose growth cannot be inhibited by other cellular immune mechanisms. Recently, with the increased use of anti-TNF-α agents, there have been increased reports of granulomatous infections. These infections include MTB, histoplasmosis, and other less common presentations. In experimental animal studies, there is additional support of this hypothesis that TNF blockade increases infection risk, particularly those infections that are normally contained by granulomas. In experimental animal studies, granuloma formation was delayed in mice that were deficient in TNF or where neutralizing antibodies blocked TNF function or one of its receptors (TNFαp55).

The formed granulomas subsequently collapsed. Since anti-TNF-α agents are all different, there may also be differences in their granulomatous infection risk.

Beginning in mid-2001, Keane et al. conducted a collaborative study in patients diagnosed with MTB after infliximab treatment for Crohn's disease.\(^\text{22}\) Seventy cases of MTB were reported, with a median time from the start of treatment to the development of MTB of 12 weeks (range, 1-52 weeks). More than half of the patients (n = 40) had extrapulmonary MTB, and 17 of these cases had disseminated disease. Most of the 70 reports (91%) were from countries with a low incidence of MTB. After the MTB diagnosis was made, anti-MTB medication commenced and infliximab was discontinued.

Asking et al. studied risks of hospitalization for MTB in RA patients in Sweden, a low-incidence MTB area.\(^\text{23}\) This cohort study reviewed the relative risk of hospitalization for MTB in patients with early RA not treated with biologics and the relative risk of hospitalization for TB in RA patients treated with TNF-α antagonists (from 1999 to 2001), compared with controls. The cohort of patients treated with TNF-α antagonists consisted of 983 etanercept-treated patients (1,722 person-years) and 1,565 infliximab-treated patients (2,050 person-years).

RA patients who were not treated with TNF-α antagonists were at increased risk of MTB compared with the general population. RA patients who were treated with TNF-α antagonists had a 4-fold increased risk of MTB compared with RA patients not treated with TNF-α antagonists. The MTB cases reported were predominantly pulmonary and occurred up to 3 years following TNF-α antagonist treatment.

Mohan et al. reviewed reports of MTB following etanercept therapy that were reported to the Adverse Event Reporting System (AERS), the voluntary spontaneous program of the FDA through March 2002, and found 25 cases, 13 of which were extrapulmonary.\(^\text{24}\) The median interval between starting etanercept and being diagnosed with MTB was 11.5 months (range, 1-20 months).

The authors noted that these cases of etanercept-induced MTB were clinically similar to (and fewer in number than) infliximab-induced MTB.\(^\text{22}\) Product labeling for both infliximab and etanercept were modified after these reports to include warnings to screen for MTB before initiating therapy. Subsequently, adalimumab also received a label warning to screen for MTB.

Schiff et al. evaluated the safety of adalimumab in RA patients from postmarketing spontaneous reports, phase 3b clinical trial data, and additional premarketing clinical trials.\(^\text{25}\) Additionally, cancer incidence rates and types were also evaluated in all patients in the clinical trial database. As of August 31, 2002, 2,468 patients received adalimumab in clinical trials, representing 4,870 patient-years of exposure. The SAE rate in the clinical trial safety database as of April 2005 was 5.1/100 patient-years, which was the same as that observed in August 2002 and similar to rates reported in the general RA population. There were 34 cases of MTB (0.27/100 PYs). Following the initiation of MTB screening in trials, the infection rates declined.

Dixon et al. noted that the crude rates of serious infection for patients treated with all 3 TNF-α antagonists were similar.\(^\text{26}\) Compared with DMARD-treated patients (n = 1,354), TNF-α antagonist-treated patients (n = 7,334) had no increased risk of all-site serious infections.

**Cancer**

In an adalimumab safety evaluation conducted by Schiff et al., there were 25 cases of lymphoma.\(^\text{27}\) Analysis of the lymphoma incidence in this review resulted in a standardized incidence ratio (SIR) of 3.19 (95% CI, 0.013-5.26), which was consistent with SIRs reported for TNF-α antagonist therapy-naive RA patients. Other SAEs were reported and included systemic lupus erythematosus or lupus-like reactions, demyelinating disorder, and others.

The chronic inflammation and stimulation of the immune system in RA may cause cancer via an unknown mechanism, with an increased risk of lymphoma in these patients. Additionally, drugs used to treat RA may also increase the risk of lymphoproliferative...
The Comparative Safety and Effectiveness of TNF-α Antagonists

In a prospective study of RA patients enrolled in the National Data Bank for Rheumatoid Diseases (NDB, an open cohort with patients continually added), Wolfe and Michaud biannually surveyed (via patient questionnaire) for lymphoma occurrence in 18,572 RA patients without a previous lymphoma diagnosis. Potential lymphoma cases received detailed follow-up. The SEER cancer data resource was used to derive the expected number of lymphoma cases in a comparable cohort. Comparator data from SEER was also used in the safety evaluations in the efficacy studies by Lipsky and Bathon.

Eighty-eight lymphomas were identified, 59 before NDB enrollment and 29 after NDB enrollment and during extensive follow-up. The SIR and incidence rates for lymphoma can be seen in Table 5. For “new starts” on infliximab, the SIR for lymphoma was 1.0 (95% CI, 0.46-7.4) and for “new starts” on etanercept, it was 0.95 (95% CI, 0.5-8.3). Lymphoma patients were older, had more comorbidities, were more likely to be male, and were more likely to be non-Hispanic whites. The duration of RA was not significant (P = 0.876). Those patients in the anti-TNF-α groups had slightly more severe disease as measured by the HAQ.

These study results show that lymphoma is increased in RA patients compared with the general population. These authors also note that in the 5 largest studies of lymphoma risk, the risk ratio is approximately 2.0, and that these data are consistent with this current study.

In a recent meta-analysis, Bongartz et al. attempted to elucidate the possible connection between adalimumab and infliximab, and malignancies. Serious infections (defined as requiring antimicrobial therapy or hospitalization) were also evaluated. Abstracted outcomes from only 9 of 144 initially identified randomized, placebo-controlled, 12-week minimal duration clinical trials were evaluated. Other data sources were also evaluated. Sensitivity analyses were used to exclude trials with moderate or high risk of bias, omission of trials with malignancies reported within 6 weeks of beginning the study, and omission of nonmelanoma skin malignancies. Overall, 5,014 patients received anti-TNF-α therapies or control treatment. In these patients, 29 malignancies were reported for active treatments and 3 malignancies were reported for placebo. Malignancies were significantly more common in patients treated with higher doses of anti-TNF-α therapies than in those who received lower dosages. For patients treated with anti-TNF therapies, the number needed to harm was 154 (95% CI, 91-500) for 1 additional malignancy. This meta-analysis suggests an increased risk of malignancies and infections in anti-TNF-α-treated RA patients with a dosage-dependent association. Use of etanercept was not analyzed.

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>No. of Lymphomas</th>
<th>No. of Patients at Risk</th>
<th>Time at Risk</th>
<th>Incidence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients/treatments</td>
<td>29</td>
<td>15.5</td>
<td>1.9</td>
<td>13.2</td>
</tr>
<tr>
<td>All biologics</td>
<td>14</td>
<td>4.9</td>
<td>2.9</td>
<td>1.7-4.9</td>
</tr>
<tr>
<td>Infliximab or infliximab + etanercept</td>
<td>9</td>
<td>3.4</td>
<td>2.6</td>
<td>1.4-4.5</td>
</tr>
<tr>
<td>Etanercept or etanercept + infliximab</td>
<td>8</td>
<td>2.1</td>
<td>3.8</td>
<td>1.9-7.5</td>
</tr>
<tr>
<td>Infliximab</td>
<td>6</td>
<td>2.7</td>
<td>2.2</td>
<td>1.0-4.9</td>
</tr>
<tr>
<td>Etanercept</td>
<td>3</td>
<td>1.4</td>
<td>3.5</td>
<td>1.5-8.4</td>
</tr>
<tr>
<td>Infliximab + etanercept</td>
<td>3</td>
<td>0.7</td>
<td>4.3</td>
<td>1.4-13.2</td>
</tr>
<tr>
<td>Anakinra</td>
<td>0</td>
<td>0.2</td>
<td>0.0</td>
<td>–</td>
</tr>
<tr>
<td>Leflunomide only</td>
<td>0</td>
<td>0.5</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Leflunomide only (switched)</td>
<td>0</td>
<td>0.9</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>No MTX/no biologics</td>
<td>5</td>
<td>3.9</td>
<td>1.3</td>
<td>0.5-3.1</td>
</tr>
<tr>
<td>No MTX/no biologics (switched)</td>
<td>5</td>
<td>4.8</td>
<td>1.0</td>
<td>0.4-2.5</td>
</tr>
<tr>
<td>MTX only</td>
<td>10</td>
<td>6.8</td>
<td>1.5</td>
<td>0.8-2.7</td>
</tr>
<tr>
<td>MTX only (switched)</td>
<td>10</td>
<td>5.8</td>
<td>1.7</td>
<td>0.9-3.2</td>
</tr>
</tbody>
</table>

* CI = confidence interval; RA = rheumatoid arthritis; SIR = standardized incidence ratio (adjusted for age and sex).
The serious infections reported in this meta-analysis included 128 patients treated with anti-TNF-α agents and 26 control patients (odds ratio, 2.0; 95% CI, 1.3-3.1). The number needed to harm was 59 (95% CI, 39-125) within a 3- to 12-month treatment period. Additional study limitations included the definition of “serious,” which was inconsistent with prior trials.21,25,29

Demyelinating Conditions

In the safety evaluation conducted by Schiff et al., 4 cases of demyelinating disorders were reported after 4,870 PYs of adalimumab exposure.25 An additional 10 cases were reported after 12,506 PYs of exposure: multiple sclerosis (MS, n = 6), nonspecific demyelination (n = 2), and Guillain Barré (n = 2).

Mohan et al. evaluated the AERS database (e.g., MedWatch) for “new-onset” neurologic signs and symptoms indicative of demyelinating disorders that were associated with etanercept or infliximab treatment in patients with inflammatory arthritides.21 The index case developed neurologic signs and symptoms following treatment with etanercept, and an additional 17 cases were identified in the AERS database, along with 2 cases in infliximab-treated patients. Presentations included paresthesias (n = 13), visual disturbances secondary to optic neuritis (n = 8), and confusion (n = 5). Other signs and symptoms included facial palsy, gait disturbance, and Guillain-Barré syndrome. Four patients had a prior history of MS or an MS-like syndrome with flares of their previous symptoms. One patient had a positive rechallenge on etanercept. Most patients had a partial (n = 7) or complete response (n = 4), and resolution of neurologic symptoms upon anti-TNF-α therapy discontinuation. Some patients had symptom continuation (n = 4) and 5 patients’ responses were unknown.

Despite the small number of patients in this series, there may be an association between neurologic events and anti-TNF-α therapies. Further surveillance and studies are needed to better define risk factors for and frequency of adverse events and their relationship to anti-TNF-α therapies. It is critically important to monitor these patients for the development of new neurologic signs and symptoms and discontinue therapy in those with new neurologic presentations. Additionally, anti-TNF-α therapy should be avoided in those individuals with preexisting MS.

The Case of Marie, Continued

In light of all the evidence presented, the question remains: Should Marie be treated with an anti-TNF-α agent? Based on Marie’s clinical history of having failed multiple traditional DMARDs, having been maintained on only 20 mg oral prednisone daily at the present time without any benefit, and having functional limitation (e.g., work loss), the answer is “yes.” The evidence presented here clearly substantiates effectiveness of anti-TNF-α therapies in early and late RA, with significant improvement.12-14,16,17 Another option might include triple synthetic DMARD therapy with hydroxychloroquine, MTX, and sulfasalazine, which is an effective combination. High-dose intermittent steroids may also be effective.31

After having decided that Marie should receive anti-TNF-α therapy to treat her RA, we must ask, which agent should be used? Since Section 1013 has not yet been concluded and the Effective Health Care Program does not yet have a result on this topic, based on effectiveness or safety, there is no clear answer and no clear first choice.12-14,16,17,20-25 All 3 anti-TNF-α agents require PPD before commencing therapy since they are all associated with the possibility of typical and atypical (e.g., extrapulmonary) MTB.21-27 Any history of MS must also first be ascertained from the patient.32 However, since many RA patients do not achieve sufficient benefit with nonbiologic DMARDs, any of the 3 anti-TNF-α agents may improve RA symptoms and structural outcomes. Meta-analyses suggest that adalimumab and infliximab may be associated with higher cancer rates, but etanercept was not included in this analysis. Infliximab may be associated with higher rates of typical or atypical (extrapulmonary) MTB.21-25 It is unclear whether biologic or nonbiologic DMARDs are associated with higher infection rates, so extra caution is prudent.21,25 In addition, etanercept may be associated with a higher risk for demyelination.32

Summary: Safety and Effectiveness and the Effective Health Care Program

The results of the AHRQ Effective Health Care Program have the potential to facilitate the setting of policy regarding anti-TNF-α agents, since currently, the choice is relatively random. Comparative safety and effectiveness data are critical in determining the “best” therapy. There are no current or ongoing “head-to-head” randomized, controlled trials comparing these agents. Current data suggest we should move through different anti-TNF-α agents if one is ineffective or the patient is unable to tolerate it.20

Observational studies have many limitations; therefore, the next best thing is Section 1013, which offers some interesting hope once the comparative safety and effectiveness data are synthesized, generated, and disseminated. However, while Section 1013 may drive evolution of a benchmark, there is significant variability in patient clinical response, and there needs to be appropriate access to all available therapies.

DISCLOSURES

This article is based on a presentation given by the author at a symposium titled “Cross-Firing the Impact of the AHRQ Effective Health Care Program on Access to Biologic Therapies” held on October 6, 2006, at the Academy of Managed Care Pharmacy’s 2006 Educational Conference in Chicago, Illinois. The symposium was supported through an unrestricted educational grant from Centocor, Inc. The author discloses that he receives grant/research support from Pfizer, Merck, and Savient Pharmaceuticals. He has received an honorarium from PRIME, Inc. for participation in this supplement.

REFERENCES

The Comparative Safety and Effectiveness of TNF-α Antagonists


