Modernization Versus Limitation: Cross-Firing the Impact of the AHRQ Effective Health Care Program on Access to Biologic Therapies

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1. Disclose the principal sources of funding in a manner that permits easy recognition by the reader.

2. Disclose the existence of all potential conflicts of interest among supplement contributors, including financial or personal bias.

3. Describe all drugs by generic name unless the use of the brand name is necessary to reduce the opportunity for confusion among readers.

4. Strive to report subjects of current interest to managed care pharmacists and other managed care professionals.

5. Seek and publish content that does not duplicate content in the Journal of Managed Care Pharmacy.

6. Subject all supplements to expert peer review.
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### Target Audience

Managed care pharmacists and managed care medical directors

### Learning Objectives

Upon completion of this program, participants will be able to

1. describe Section 1013 of the Medicare Modernization Act and its implications for managed care pharmacy practice;
2. compare and contrast the impact of the Effective Health Care Program on the determination of outcomes, comparative therapeutic effectiveness, and clinical appropriateness of pharmaceuticals in chronic disease states;
3. compare the effectiveness and safety of the different TNF-α antagonists used in the management of rheumatoid arthritis;
4. understand the potential impact of the AHRQ Effective Health Care Program on the access and utilization of biologic therapies in immune-mediated diseases, with a focus on the DEcIDE rheumatoid arthritis project; and
5. describe some of the managed care perspectives regarding the data development and coverage issues.

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*A total of 0.25 CEUs (2.5 contact hours) will be awarded for successful completion of this continuing education program (ACPE Program No. 255-000-06-022-H01) and 2.5 AMA PRA Category 1 credits. For faculty disclosures, please see pages S6, S17, and S20. For accreditation information, please see page S21.

The articles published in this supplement represent the opinions of the authors and do not reflect the official policy or views of the Academy of Managed Care Pharmacy, the authors’ institutions, or Centocor, Inc. unless so specified. The authors have disclosed if any unlabeled use of products is mentioned in their articles. Before prescribing any medicine, clinicians should consult primary references and full prescribing information.
Introduction:
Medicare Section 1013 and AHRQ’s Effective Health Care Program

SCHUMARRY H. CHAO, MD, MBA, and FRANK L. URBANO, MD, FACP

ABSTRACT

OBJECTIVE: To introduce Section 1013 of the Medicare Prescription Drug, Improvement, and Modernization Act (MMA) of 2003 and the Agency for Healthcare Research and Quality’s (AHRQ) Effective Health Care Program.

BACKGROUND: AHRQ, under Section 1013 of the MMA of 2003, has been charged with conducting specific health care outcomes studies through the Effective Health Care Program. This research is aimed specifically at determining the safety and effectiveness of certain pharmaceuticals since comparative data is currently lacking. Highly utilized, high-cost (or both) treatments are the focus of the studies that will be conducted through AHRQ’s Evidence-based Practice Centers (EPCs) and the Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) Network. Current and completed projects are noted, including more detailed information on the reviews pertaining to treatment of rheumatoid arthritis with nonbiologic disease-modifying antirheumatic drugs (DMARDs) and biologics (anti-tumor necrosis factor TNF-α therapies).

SUMMARY: AHRQ’s EPCs and the DEcIDE Network are studying safety and the comparative effectiveness of a number of different pharmaceutical-related topics, including the safety and effectiveness of biologic and nonbiologic DMARDs (e.g., TNF antagonists). The final reports, once complete, will be translated (explained in terms that can be more easily understood by all decision makers) and then disseminated to all stakeholders.

KEYWORDS: AHRQ, Cost-effectiveness, Medicare, TNF-α therapies (anti-TNF-α), Effective health care, Health outcomes

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n December 8, 2003, President George W. Bush signed the Medicare Prescription Drug, Improvement, and Modernization Act (MMA) of 2003. This legislation was enacted to address several shortcomings in the existing Medicare program, including the lack of a prescription drug benefit for seniors in the United States. Other important components, aside from outpatient prescription medications for seniors, are:

- grants for physicians to implement electronic prescribing
- payment/reimbursement for inhalation drugs
- recognition of nurse practitioners as attending physicians to serve hospice patients
- coverage of an initial preventive physical examination
- study/report on concierge care and coverage of chiropractic service
- Medicare Advantage quality-improvement programs and research strategies for the chronically ill
- study and report on drug importation

One of the provisions of the MMA that is relevant to health care practitioners, managed care payers, and patients, is Section 1013.

Section 1013

Section 1013 is titled “Research on Outcomes of Health Care Items and Services.” It is significant because it focuses on the effectiveness, quality, and efficiency of delivered health care and improved health outcomes. Specifically, MMA Section 1013 is designed to address the lack of comparative data with respect to prescription drugs. This Act instructs the Secretary of the Department of Health & Human Services (DHHS), acting through the Agency for Healthcare Research and Quality (AHRQ), to conduct and support research with a focus on outcomes, comparative clinical effectiveness, and appropriateness of devices, pharmaceuticals, and services to meet priorities and requests for scientific evidence in a number of topics.

AHRQ is the government agency whose mission is to improve the quality, safety, efficiency, and effectiveness of health care for all Americans. The AHRQ Effective Health Care Program has 3 basic components to gauge comparative effectiveness of different treatments and clinical practices: (1) to review and synthesize existing knowledge through Evidence-based Practice Centers (EPCs), (2) to promote and generate new knowledge through the DEcIDE (Developing Evidence to Inform Decisions about Effectiveness) Research Network, and (3) to compile the findings from the EPCs and DEcIDE Network and then translate (synthesize scientific evidence about effectiveness and explain it in terms that can be more easily understood by all decision makers) and disseminate that knowledge. The John M. Eisenberg Clinical Decisions and Communications Science Center was chosen to compile the research results into a variety of useful formats for stakeholders.
Introduction: Medicare Section 1013 and AHRQ's Effective Health Care Program

This center is a collaboration of the Oregon Health and Science University, the Portland Veterans Affairs Medical Center, and the Kaiser Permanente Center for Health Research. More detailed information on the AHRQ Effective Health Care Program includes the review, evaluation, and synthesis of existing research, including potential clinical trial information, as well as other published information. AHRQ will review the already published literature and compare different therapies used to treat the same diseases. Additionally, AHRQ will identify gaps in the existing research and will support this with new research. The AHRQ EPCs are centers throughout the United States with the responsibility to systematically review published and unpublished scientific evidence. The DEcIDE Research Network will then facilitate the development of new scientific evidence and analytical tools through work with public and private sectors and provide the results in an accelerated and practical format.

The information, once translated and disseminated, has the potential to be far reaching. The information will be disseminated and translated for individual practicing physicians, other health care providers, health plans, pharmacy benefit management (PBM) companies, and consumers, in terms understandable to each of them, to aid in health care decision making.

Section 1013 is designed to assist the Centers for Medicare & Medicaid Services (CMS) in determining the most effective therapies for a number of high-utilization disease states. Currently, the U.S. Food and Drug Administration (FDA) drug approval process only requires that a new drug be superior to placebo to gain FDA approval. Until now, no pharmaceutical company or government agency has taken the initiative to conduct this type of research— to directly compare therapies “head-to-head” to determine if one treatment is superior to another in a given disease state. Although this research and its results are not meant to be a government benchmark, the outcomes may have this result. For example, when the results of these studies are disseminated and/or published, they have the potential to shape how some of these pharmaceutical products may be covered, not covered, or reimbursed under Medicare, although it is not the intended goal of CMS under Section 1013 to withhold coverage of a prescription drug based on the results of the studies conducted therein.

According to MMA, the highest priorities for study may include pharmaceuticals (or other health care items and services) that impose a high cost, may be underutilized or overutilized, and may significantly improve the prevention, treatment, or cure of diseases and conditions (including chronic conditions) that may impose high direct or indirect costs on patients or society. As can be inferred, this legislation can significantly impact the use of pharmaceuticals as well as other products. In December 2004, following extensive public comment, DHHS identified a list of 10 “initial” priority conditions to be addressed in the Effective Health Care Program.

The DEcIDE Network is a new network of research centers that AHRQ created in 2005 to fulfill this requirement of the MMA, specifically, to generate new knowledge. The DEcIDE Network is conducting accelerated practical studies regarding the outcomes, comparative clinical effectiveness, safety, and appropriateness of health care items and services as charged under MMA 2003 Section 1013. The network comprises research-based health organizations with access to electronic health information databases and the capacity to conduct rapid turnaround research (less than 2 years duration).

The EPC reviews use a research methodology that systematically and critically appraises existing research to synthesize knowledge on a particular topic. A key component of the comparative effectiveness reviews (CERs) is the identification of research gaps and recommendations. A number of CERs are currently in progress. Additionally, 5 final reports have been issued to date.

This research involves disease states that are treated with outpatient oral medications as well as biologics. There are several high-cost disease states that the Effective Health Care Program will be addressing. Some of these disease states are included primarily because of their epidemiological impact. Others will be addressed because of the high-cost therapies available to treat them as well as the uncertain comparative effectiveness of these therapies. Still others will be addressed because they fall into both categories. One example of the latter is in the treatment of immune-mediated disease. In the area of immune-mediated disease, one can see that the current CER list includes rheumatoid arthritis (RA) or psoriatic arthritis (PsA). Some of the key points to be addressed in the RA CER include effectiveness and efficacy of the treatments relative to reducing RA symptoms, disease progression, functional improvement, and potential disease remission. A comparative analysis of the relative safety of multiple therapies will be evaluated including some of the older disease-modifying antirheumatic drugs (DMARDs) as well as the newer biologic agents (e.g., antitumor necrosis factor [TNF]-α agents).

The Effective Health Care Program’s CER on “Comparative Effectiveness of Drug Therapies for Rheumatoid Arthritis” will use existing research to address questions regarding which therapies are the most effective, have the best safety profile, and are the most cost effective.

The DEcIDE Network also currently has a number of ongoing projects. Initial research from the DEcIDE Network focuses on outcomes of prescription drug use and other interventions for which randomized controlled trials would not be feasible or timely or would raise ethical concerns that are difficult to address. Other DEcIDE Network projects may focus on electronic registries, methods for analyzing health databases, and prospective observational or interventional studies.

**Academy of Managed Care Pharmacy Position**

In April 2004, the Academy of Managed Care Pharmacy (AMCP) issued a press release regarding their position on the AHRQ Effective Health Care Program. The following is a partial listing of AMCP’s position statements:

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Introduction: Medicare Section 1013 and AHRQ’s Effective Health Care Program

• Supports research on the comparative clinical and cost effectiveness of prescription drugs;
• Believes that to generate credible information that is comprehensive in scope, it is appropriate for the federal government to be charged with the primary responsibility for conducting or sponsoring comparative effectiveness research on prescription drugs;
• Believes that only the federal government has the financial resources to support large-scale independent studies; the expertise to provide oversight to ensure the quality and integrity of the research process; and the ability to widely disseminate the research data to all interested audiences which, when completed, will be available in the public domain;
• Believes that AHRQ, as well as the National Institutes of Health (NIH), are the logical agencies to oversee comparative clinical research efforts on behalf of the federal government since conducting research and studies is part of the mission of AHRQ and NIH, and they have the scientific and management expertise to fulfill this responsibility;
• Believes that encouraging this research will help to assure positive patient outcomes through appropriate medication use and promote the prudent management of financial resources within the health care system;
• Realizes that only limited authoritative research exists that distinguishes the effectiveness and safety profiles offered by any particular drug compared with other drugs in the same or similar treatment class;
• Realizes that those entities that pay for prescription drug benefits require this type of information so that a benefit can be designed that ensures that patients receive the best value for the resources expended.

Focus on Anti-Tumor Necrosis Factor-α Biologics

Comparative Effectiveness Review

There continues to be uncertainty about optimal drug treatments for RA, including which drug to start, when and how to combine drugs, and risks and benefits in different subgroups of patients. The purpose of this CER, “Comparative Effectiveness of Drug Therapies for Rheumatoid or Psoriatic Arthritis,” is to compare the benefits and safety of RA and PsA drug therapies. This CER will focus on the comparative benefits and safety of DMARDs, corticosteroids, and various combinations of those agents compared with each other, placebo, or other comparators (such as non-steroidal anti-inflammatory drugs [NSAIDs]). Because NSAIDs do not have disease-modifying properties, they are excluded as primary drugs from this review. A prior CER compared the effectiveness and safety of analgesics for the treatment of osteoarthritis. This new CER, “Comparative Effectiveness of Drug Therapies for Rheumatoid or Psoriatic Arthritis” will build on the results of a recent AHRQ-sponsored technology assessment on biologic DMARDs for RA, “Design and Analysis of the Cost-effectiveness of Etanercept, Adalimumab and Anakinra in Comparison to Infliximab in the Treatment of Patients with RA in the Medicare Program.”

Both the older synthetic DMARDs (e.g., azathioprine, cyclosporine, gold [IM, intramuscular], hydroxychloroquine, leflunomide, methotrexate [MTX], minocycline, sulfasalazine) and the newer biologic DMARDs such as etanercept, infliximab, adalimumab, and anakinra will be included. Some of the key questions to be addressed in this research include whether the available therapies
• are able to reduce symptoms or prevent progression of radiographic joint damage,
• differ in the ability to improve functional capacity or quality of life,
• differ in their effect on maintaining remission, and
• differ in safety, tolerability, adherence, or adverse effects.

Also to be included are the comparative benefits and safety of drug therapies for inflammatory arthritis in subgroups of patients based on disease stage, history of prior therapy, demographics, concomitant therapies, and/or comorbidities.

The DEcIDE Project

The current DEcIDE project pertaining to the use of anti-TNFs for RA treatment is titled “Assessment of Factors Modulating Treatment Outcomes of Rheumatoid Arthritis.” Since RA is a lifelong disease affecting a small percentage of the general population, population-based studies are needed to assist in quantifying beneficial and adverse clinical outcomes associated with RA treatments. This project proposes a series of epidemiologic studies aimed at addressing knowledge gaps in the effectiveness and safety of specific DMARDs. The project will examine the comparative effectiveness and safety of older DMARDs versus newer biologic agents, including the anti-TNF agents. The following are also goals of this DEcIDE project:

1. To define a cohort of patients with RA among state Medicaid enrollees to determine the prevalence of use of selected DMARDs.
2. To explore several outcomes as measures of relative effectiveness of specific agents/combinations such as prevalence of cotherapy with corticosteroids, NSAIDs and narcotics, and adherence to standard regimens and continuation of use
3. To determine the incidence of congestive heart failure (CHF) in the RA cohort and test whether RA patients receiving anti-TNF-α therapy (etanercept, infliximab, and adalimumab) are at increased risk of developing CHF versus patients receiving traditional synthetic DMARDs
4. To determine the incidence of selected infection outcomes in the RA cohort and test whether RA patients receiving anti-TNF-α (etanercept, infliximab, and adalimumab) or anti-interleukin-1 (anakinra) are at increased risk of serious infections versus patients receiving traditional synthetic DMARDs

Summary

The MMA is not just about drugs for seniors. Section 1013 of the MMA includes the AHRQ Effective Health Care Program to identify knowledge gaps and study highly utilized, high-cost (or both)
treatments (drugs and other) for many diseases. Translation of the knowledge will occur, and dissemination of the knowledge will be reported to all stakeholders. Stakeholders include health plans, physicians, and patients/consumers. The information identified through this program, although not meant to be a “benchmark,” may well turn out to be the government standard.

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DISCLOSURES

This article is based on a presentation given by the authors 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. Author Schumarry H. Chao discloses that she is a consultant for Johnson & Johnson, sanofi-aventis, and Novartis. She has received an honorarium from PRIME, Inc. for participation in this supplement. Author Frank L. Urbano discloses that he is the medical director at PRIME; he discloses no other potential bias or conflicts of interest relating to this article.

Chao served as principal author of the study. Study concept and design were contributed by both authors.

REFERENCES


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

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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 tried 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. There are 13 National Agency for Healthcare Research and Quality (AHRQ) Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) centers. 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, then the early cyclooxygenase-2 inhibitors (celecoxib in 1998 and rofecoxib in 1999). The first anti-TNF-α agent, etanercept, was approved in late 1998, followed by infliximab in late 1999 (infliximab was already on the U.S. market, having received FDA approval for treatment of Crohn’s disease in mid-1998). Adalimumab was approved in late 2002, followed by anakinra, valdecoxib, abatacept, and, most recently, rituximab, 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). 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).
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. Forty-four patients (50%) in the groups 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. 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 +

### TABLE 1: Comparison of TNF Antagonists

<table>
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<th>Adalimumab</th>
<th>Etanercept</th>
<th>Infliximab</th>
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<tr>
<td>Human MAb</td>
<td>Fusion protein (P75Fc of IgG)</td>
<td>Chimeric MAb</td>
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<tr>
<td>Half-life</td>
<td>12-14 days</td>
<td>4-5 days</td>
<td>8-10 days</td>
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<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 ATTRACT (A-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 at least a 20% improvement in 3 of the 5 following objective or subjective measures in RA:
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).13 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
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>
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<tr>
<td>20% (ACR 20)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>12 weeks</td>
<td>33</td>
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<td>24 weeks</td>
<td>27</td>
<td>71</td>
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<td>50% (ACR 50)</td>
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<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>
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<td>12 weeks</td>
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<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.

The study: 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 (intra-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. 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 proMMP-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 rhiinitis, 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 asthma), 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.

The anti-TNF-α agents adalimumab, etanercept, and infliximab at the appropriate dosages are effective in managing late RA, yet their comparative effectiveness is not known at this time.

### 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

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### TABLE 4

<table>
<thead>
<tr>
<th>Adalimumab Dosage (Every Other Week)</th>
<th>Placebo</th>
<th>20 mg</th>
<th>40 mg</th>
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<tr>
<td>ACR 20, n (%)</td>
<td>9 (14.5)</td>
<td>33 (47.8)</td>
<td>45 (67.2)</td>
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<tr>
<td>P≤0.001</td>
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<tr>
<td>ACR 50, n (%)</td>
<td>5 (8.1)</td>
<td>22 (31.9)</td>
<td>37 (55.2)</td>
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<tr>
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<td>&lt;0.001</td>
</tr>
<tr>
<td>ACR70, n (%)</td>
<td>3 (4.8)</td>
<td>7 (10.1)</td>
<td>18 (26.9)</td>
<td>14 (19.2)</td>
</tr>
<tr>
<td>P≤0.020</td>
<td></td>
<td>NS</td>
<td>&lt;0.001</td>
<td>0.020</td>
</tr>
</tbody>
</table>

* Values are the number (%) of patients who met the American College of Rheumatology (ACR) criteria for 20%, 50%, 70% improvement (ACR20, ACR50, ACR70, respectively) at week 24. Patients who did not complete the 24-week study were defined as nonresponders.

† Adalimumab versus placebo, by Dunnett’s test; statistical significance was set at P ≤ 0.05.

‡ Adalimumab versus placebo, by unadjusted t test; statistical significance was set at P ≤ 0.05.

NS = not significant.
The Conclusion of this study is that use of DMARDs early after RA disease onset stopped erosions in 72% of etanercept-treated patients.
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 (QW), 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). 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 ≥ 6 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.22 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.23 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.\textsuperscript{21-25}

**Mycobacterium Tuberculosis**

Infliximab was approved by the FDA in August 1998 for the treatment of Crohn’s disease and fistulizing Crohn’s disease.\textsuperscript{26} It was approved in November 1999 for the treatment of RA.\textsuperscript{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.\textsuperscript{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 (TNFRe55). 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.\textsuperscript{29} 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.\textsuperscript{30} 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.\textsuperscript{31} 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.\textsuperscript{21} 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.\textsuperscript{63} 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 clinical 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.\textsuperscript{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.\textsuperscript{21} 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 lymphoprolifer-
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. 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.

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<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>No. of Lymphomas</th>
<th>No. of Patients at Risk</th>
<th>Incidence Rate</th>
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<tr>
<td>All patients/treatments</td>
<td>29</td>
<td>15.5</td>
<td>1.9</td>
</tr>
<tr>
<td>All biologics</td>
<td>14</td>
<td>4.9</td>
<td>2.9</td>
</tr>
<tr>
<td>Infliximab + etanercept</td>
<td>9</td>
<td>3.4</td>
<td>2.6</td>
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<tr>
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<td>8</td>
<td>2.1</td>
<td>3.8</td>
</tr>
<tr>
<td>Infliximab</td>
<td>6</td>
<td>2.7</td>
<td>2.2</td>
</tr>
<tr>
<td>Eta nercept</td>
<td>5</td>
<td>1.4</td>
<td>3.5</td>
</tr>
<tr>
<td>Infliximab + etanercept</td>
<td>3</td>
<td>0.7</td>
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<td>Anakinra</td>
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<td>0</td>
<td>0.9</td>
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<tr>
<td>MTX only (switched)</td>
<td>10</td>
<td>5.8</td>
<td>1.7</td>
</tr>
</tbody>
</table>

* Time at risk is expressed in years. Incidence rates are expressed per 100,000 patient-years of exposure. For leflunomide, “switched” means that patients in the leflunomide-only group who did not receive leflunomide during National Data Bank (NDB) follow-up were counted as being in the no methotrexate (MTX)/no biologics group. For MTX, switched means patients in the MTX-only group who did not receive MTX during NDB follow-up were counted as being in the no MTX/no biologics group.

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.  

**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. 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. 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. 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.

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. 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. Any history of MS must also first be ascertained from the patient. 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 infection rates, but etanercept was not included in this analysis. Infliximab may be associated with higher rates of typical or atypical (extrapulmonary) MTB. It is unclear whether biologic or nonbiologic DMARDs are associated with higher infection rates, so extra caution is prudent. In addition, etanercept may be associated with a higher risk for demyelination.

**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.

**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 Savent Pharmaceuticals. He has received an honorarium from PRIME, Inc. for participation in this supplement.

**REFERENCES**

The Comparative Safety and Effectiveness of TNF-α Antagonists


ABSTRACT

OBJECTIVE: To describe some of the managed care perspectives regarding the data development and coverage issues.

BACKGROUND: Section 1013 of the Medicare Modernization Act of 2003 has initiated the formation of the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program, which is evaluating the treatments for rheumatoid arthritis (RA) in the Medicare population. The results of these studies have the potential to impact future drug utilization. It is not known whether this data could be applied to the commercial population.

SUMMARY: Payers (e.g., managed care organizations, pharmacy benefit managers) make decisions about which drugs will be covered and to which formulary “tier” the drug will be assigned. These decisions are made by evaluating current evidence based on safety, effectiveness, outcomes, and cost. Patients believe in a “warranty” of care, meaning that there will always be a treatment option whether they are compliant with their treatment regimen or not. All treatments are measured by a “value,” and each stakeholder may see this value differently. A return on medical investment is one way to assess this value.

CONCLUSIONS: Different stakeholders view treatment value in different ways. The evidence that will be identified through AHRQ’s Effective Health Care Program will partially define this value. If this model succeeds, it has the potential to significantly affect health care.

KEYWORDS: AHRQ, Effective health care, Medicare, Rheumatoid arthritis, Relative value, Pharmacy benefit managers, Payers

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WILLIAM K. FLEMING, PharmD

The Medicare Modernization Act (MMA) of 2003 has changed the lives of seniors by providing them with access to medications that many have never had. Additionally, it has given them access to quality programs such as medical therapy management (MTM) that, for the most part, did not previously exist. However, the real question is whether the coverage and programs for seniors can be applied to the commercial population as well as to the Medicare population. Access to the Web site www.medicare.gov has provided managed care providers and the general public with a tremendous amount of information regarding drug costs, insurance premiums, what pharmacies charge, and what the manufacturers charge. Section 1013 provides data around outcomes that produce another level of transparency, whether good or bad, as seniors and other payers make decisions.

AHRQ’s Effective Health Care Program will be evaluating the safety and effectiveness of anti-TNF-α therapies in rheumatoid arthritis. The manner in which health plans and other payers may eventually cover or “tier” these agents is discussed, including some information on potential cost sharing.

Medication Coverage Based on Cost-Effectiveness Data

Today, drug benefits are tiered, based on whether an agent is generic or brand and whether it is on the formulary or not. One possibility for a future method of placing drugs on tiers could include checking whether there is data that demonstrate a tradeoff of savings on other health care costs; if so, then the drug would have more value. Reimbursement for health care services holds the patient responsible for a portion or percentage of the charge, with an attending strategy to serve as a means of reducing utilization if the health care service appears too costly to the individual patient. Cost sharing normally includes an annual deductible amount that would make patients more accountable for their medication use.

For example, is there a return on medical investments within a year? The most ideal model would include expenditures in one year and a return of the money in that same year. A model still suitable but not exceptional would be if the dollars are spent one year but the return is not for 5, 10, or 20 years; since there is still a return on medical investment, the model is still acceptable. Perhaps, however, the return on medical investment acts a little differently, wherein the return of that money expended takes a number of years to occur, such as in terms of the cost sharing and how an employer or the government may want to fund that medication. Some questions to ponder could include: Is there a return on work-place productivity? Is there a return on quality of life or activities of daily living? The formulary tiering, perhaps, ought to be based on these points of view, with a return on medical investment being the cost sharing to the consumer, and it ought to
be zero. On the other hand, when considering improvement in quality of life, perhaps that is the highest cost sharing because the consumer has the most vested interest in seeing that come to fruition for himself or herself. While this may be so for the affective component of quality of life, it may also be so for the functional component since both impact work productivity. Much of this remains to be seen as the results of this research gets transcribed.

Consider the following list (also see the information below about the "choices/decisions"):

- Physician counseling for smokers
- Total hip replacement for arthritis
- Outreach for flu and pneumonia vaccine
- Treatment for major depression
- Screening for colon cancer
- Implantable cardioverter-defibrillators to prevent sudden death
- Tight control of diabetes
- Resuscitation after in-hospital cardiac arrest
- Left ventricular assist devices for patients with severe heart failure
- Treating elevated cholesterol levels in people without heart disease
- Treatment for osteoporosis

After reviewing the list, you are then told that you have a choice of (a) covering these items, (b) possibly covering these items, or, (c) not covering these items. Then take another look at the list and decide, based on the fact that you can only have 3 a’s, 3 b’s, and 5 c’s, “Which would you choose? What 3 items from this list would you definitely cover? What 3 items from this list might you cover, and what 5 from this list would you deny?” These are the decisions that lie ahead for payers, health care providers, managed care organizations, and pharmacy benefit managers, etc. in talking about cost-effectiveness analysis. From both an employer's and a payer's points of view, ethical decisions need to be made.

- Are payer groups ready to take a position on covering or not covering potential benefits based on cost-effectiveness data?
- Are employers ready to present this type of model to their employees to decide on which services or products to cover?

Other models to review would be that of the National Institute for Health and Clinical Excellence (NICE) program in the United Kingdom.1 If one payer follows this paradigm change, will that company be able to compete in the marketplace? Will employers buy the product—or won’t they?

A cost-effectiveness model suggests that, if it is not cost effective, then there may be no coverage or there may be more lengthy coverage such as through a step protocol or through a “criteria for use” protocol. There are a lot of social issues that need to be considered such as workplace productivity, activities of daily living improvement, quality-of-life improvement, end-of-life issues, and cancer care issues, all with regard to different payment models for products and services. As previously mentioned, there are many stakeholders, including payers, the Centers for Medicare & Medicaid Services, health plans, employers, consumers, physicians, pharmacists, hospitals, pharmaceutical manufacturers, distributors (e.g., sales, consultants, brokers), and other health care professionals. Payers either from the government or the private sector want this type of information. Consumers also want this type of information for areas such as end-of-life issues, cancer-related issues, and transplant issues.

## Summary

The data is compelling, but better systems are needed to mine the data. The various stakeholders are going to view the data provided by Section 1013 and use the results in many different ways. Among other things, these stakeholders will need to think about the impacts of coverage, noncoverage, ethical issues, and societal issues, on how they do their work and/or how they run their businesses. This model, if it succeeds in getting into the marketplace, is going to change this in a very material way. This program and the data development are first steps on a journey. The work of AHRQ related to Section 1013 is a great next step for the United States, but it is still in the early phases of the journey. This is really going to be a lifetime’s worth of work as we watch it play out.

## 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 has received an honorarium from PRIME, Inc. for participation in this supplement. He discloses no potential bias or conflict of interest relating to this article.

## REFERENCE

Modernization Versus Limitation: Cross-Firing the Impact of the AHRQ Effective Health Care Program on Access to Biologic Therapies

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In order to receive CE credit for this program, you must complete the following forms online:
1. Posttest form for this program, “Modernization Versus Limitation: Cross-Firing the Impact of the AHRQ Effective Health Care Program on Access to Biologic Therapies,” on the AMCP.org Online Learning Center site—to receive CE credit, you must receive a score of at least 70%. You will have 2 opportunities to pass the posttest.
2. Program Evaluation form

Upon successful completion of this program, you will automatically receive your CE statement. Your CE credits will be automatically archived and tracked for you on the AMCP.org Online Learning Center site. All information is kept confidential.

Note: There will be a $10 processing fee for nonmembers. (See payment instructions on site.)

Posttest Worksheet: Modernization Versus Limitation: Cross-Firing the Impact of the AHRQ Effective Health Care Program on Access to Biologic Therapies

1. Which of the following is not provided for in the Medicare Modernization Act of 2003?
   a. Funding for a study and report on concierge care
   b. Grants to physicians to implement electronic prescribing
   c. Funding for case management services for chronically ill elderly patients
   d. Coverage for an initial preventive physical examination

2. All of the following are components of the Effective Health Care Program except
   a. translate knowledge.
   b. analyze available research.
   c. synthesize existing scientific literature.
   d. generate new knowledge where gaps have been identified.
3. Which of the following is true regarding the use of anti-TNF drugs in the treatment of rheumatoid arthritis?
   a. Patients who do not respond to one anti-TNF drug usually do not respond to others.
   b. The rate of infections is higher with anti-TNF drugs than with older, traditional DMARDs.
   c. Etanercept is associated with higher rates of malignancy than other anti-TNF drugs.
   d. Tuberculosis in patients treated with anti-TNF drugs is more likely to be extrapulmonary.

4. Which of the following is true regarding combination therapy with anti-TNF and DMARDs?
   a. Treatment with infliximab + DMARDs is equally as effective as DMARDs alone for controlling joint erosion progression.
   b. Combination therapy with etanercept + DMARDs is more effective than infliximab + DMARDs in controlling joint erosion progression.
   c. Treatment with etanercept + DMARDs is more effective than DMARDs or combination therapy with infliximab + DMARDs in controlling progressive joint space narrowing.
   d. Combination therapy with infliximab or etanercept + DMARDs is more effective than etanercept alone for controlling joint erosion progression.

5. Which of the following agents has not been evaluated in a rheumatoid arthritis effectiveness study?
   a. Infliximab
   b. Alefacept
   c. Etanercept
   d. Methotrexate

6. Which of the following statements is not true regarding anti-TNF-α therapies?
   a. Screening for tuberculin with purified protein derivative is not always recommended before starting therapy with anti-TNF agents.
   b. Their safety should be continually evaluated.
   c. They can be administered subcutaneously or intravenously depending on the therapy.
   d. There is no specific lab monitoring recommended for these agents.

7. Which of the following statements about biologic agents for RA therapy is false?
   a. They are derived from proteins or protein fragments.
   b. Some are recombinant monoclonal antibodies.
   c. They may be administered intramuscularly.
   d. Some target proinflammatory cytokines.

8. Which of the following is not considered a stakeholder of AHRQ’s Effective Health Care Program?
   a. Pharmaceutical manufacturers
   b. Managed care organizations or pharmacy benefit managers
   c. Patients
   d. All of the above are stakeholders of the AHRQ Effective Health Care Program

9. Which of the following is not used in measuring outcomes in rheumatoid arthritis?
   a. ACR 90
   b. HAQ
   c. CRP
   d. PASI 50

10. Which of the following agents has not been evaluated in a rheumatoid arthritis safety study?
    a. Alefacept
    b. Rituximab
    c. Methotrexate
    d. Etanercept

11. Which of the following adverse effects have not been identified in rheumatoid arthritis safety studies reviewed herein?
    a. Liver function test elevations
    b. Extrapulmonary tuberculosis in the joint leading to septic arthritis
    c. Lower respiratory tract infection
    d. Otitis media

12. The ACR 70 does not include
    a. swollen and tender joint count.
    b. focused assessment of extraarticular manifestations.
    c. physician or patient global assessment.
    d. visual analog scale for evaluation of pain.

13. Adalimumab, etanercept, and infliximab are ______ effective when combined with methotrexate?
    a. not
    b. most
    c. more
    d. less

14. Sequential effectiveness of anti-TNF-α therapies was demonstrated by which authors?
    a. Nikas et al.
    b. Weinblatt et al.
    c. Finckh et al.
    d. Schiff et al.
15. Which of the following databases have not been utilized in comparative safety studies for anti-TNF-α therapies?
   a. Dutch Register
   b. British Society for Rheumatology Biologics Register
   c. Surveillance Epidemiology and End Results
   d. Swedish Register

16. Which of the following ideas may be related to health care coverage issues?
   a. Tiering of pharmaceuticals based on outcomes
   b. Return on medical investment
   c. Coverage of pharmaceuticals based on cost-effectiveness
   d. a, b, and c are all ideas related to health care coverage issues

17. One goal of the AHRQ Effective Health Care Program is to set a national benchmark:
   a. True
   b. False

18. Which of the following is true regarding the Medicare Modernization Act (MMA) Section 1013:
   a. MMA Section 1013 instructs the Secretary of Health and Human Services to conduct and support research focusing on outcomes and comparative clinical effectiveness.
   b. The mission of the Agency for Healthcare Research and Quality is to improve quality, safety, and effectiveness of health care in the world.
   c. It is designed to assist CMS in determining the most effective therapies for a number of low-utilization disease states.
   d. AHRQ will identify gaps in existing research but will not have to conduct any new research.

19. The Academy of Managed Care Pharmacy’s position on the Effective Health Care Program includes all of the following except
   a. that the federal government has the resources to conduct these types of large-scale studies.
   b. that it supports research on the comparative clinical and cost-effectiveness of prescription drugs.
   c. that it believes that encouraging this research will help to assure positive patient outcomes through appropriate medication use.
   d. All of the above are true

20. Which of the following agents is not a DMARD used to treat rheumatoid arthritis?
   a. Infliximab
   b. Celecoxib
   c. Cyclosporine
   d. Anakinra
Evaluation Questions (not scored)

1. This activity met/did not meet (circle one) the learning objectives and, consequently,
   a. I require more advanced information on this topic.
   b. I am satisfied with the amount of information I now possess on this topic.

2. What is your preferred learning method for CME?
   a. Local dinner meeting
   b. Symposium at national meeting
   c. Online program
   d. Webconference
   e. Printed material or CD ROM
   f. Lunch program at work

3. As a result of this educational activity, I will most likely encourage my organization to (choose all that apply)
   a. review available data on the comparative effectiveness and safety of anti-TNF drugs.
   b. visit the AHRQ Web site to obtain further information about the Effective Health Care program.
   c. review the formulary status of therapies for rheumatoid arthritis.
   d. conduct a financial analysis of our costs associated with treatment for rheumatoid arthritis.

4. Based upon the information presented in this educational program, what is your opinion of the comparative effectiveness and safety of anti-TNF drugs, and what action will you take based upon that opinion?
   a. All anti-TNF drugs are equally safe and efficacious, and I would support coverage based upon cost alone.
   b. All anti-TNF drugs are equally safe and efficacious, and I would support coverage based upon individual patient response.
   c. One specific anti-TNF drug is safer and/or more efficacious than the other ones, and I would support inclusion of that drug on our formulary.
   d. While the anti-TNF drugs are all equally efficacious, I am concerned about their safety and would only support specific, targeted coverage of these drugs.

5. The program was presented in an unbiased and fair-balanced manner:
   Yes____   No____

To complete this activity, go to www.amcp.org (Learning Center/Online CE), where you will access the posttest and evaluation form.