

Longitudinal Analysis of the Use of Etanercept Versus Infliximab Determined From Medical Chart Audit

JACOB ABARCA, PharmD, MS; DANIEL C. MALONE, PhD;
EDWARD P. ARMSTRONG, PharmD; AMY J. GRIZZLE, PharmD; and MARC D. COHEN, MD

ABSTRACT

OBJECTIVE: To describe the dosing of etanercept and infliximab for the treatment of rheumatoid arthritis (RA).

METHODS: Adult patients with a diagnosis of RA who were treated with either etanercept or infliximab between 1999 and 2002 were selected from 16 rheumatology practices in the western and southeastern United States. Patients with a terminal illness or those receiving a tumor necrosis factor (TNF)- α inhibitor for an indication other than RA were excluded. Data were collected through a review of the patient medical records. Data collected on each patient included demographics, concurrent disease-modifying antirheumatic drug therapy, TNF- α inhibitor dose, frequency, duration of TNF- α inhibitor therapy, and discontinuation of TNF- α inhibitor therapy.

RESULTS: A total of 244 patients were included in the evaluation (etanercept only [n = 128; 52%], infliximab only [n = 89; 36%], both [n = 27; 11%]). The mean age of these patients was 55.1 \pm 13.3 years, 54.9 \pm 13.5 years, and 52.8 \pm 14.0 years, respectively; the mean duration of RA was 13.3 \pm 8.8 years, 13.4 \pm 8.0 years, and 14.0 \pm 9.9 years, respectively. Female patients constituted 70% of the sample. Health maintenance organization insurance was the most common form of medical insurance (45.8%), followed by Medicare (22.3%). The mean duration of follow-up for etanercept and infliximab treatment was 29.3 \pm 14.1 months and 14.8 \pm 6.9 months, respectively. Among patients who were still receiving therapy at the time of review, the mean initial and last etanercept doses were 25.0 mg versus 25.8 mg ($P=0.16$); the mean initial and last infliximab doses were 3.38 mg/kg versus 4.51 mg/kg ($P<0.001$).

CONCLUSION: The dosing of etanercept and infliximab therapy was consistent with the approved labeling of both medications.

KEYWORDS: Rheumatoid arthritis, TNF- α inhibitors, Etanercept, Infliximab

J Manag Care Pharm. 2004;10(6):538-42

Authors

JACOB ABARCA, PharmD, MS, is assistant research scientist, DANIEL C. MALONE, PhD, is associate professor, EDWARD P. ARMSTRONG, PharmD, is associate professor, and AMY J. GRIZZLE, PharmD, is assistant director, the University of Arizona College of Pharmacy and the Center for Health Outcomes & PharmacoEconomic Research, Tucson, Arizona. MARC D. COHEN, MD, is professor of medicine, Division of Rheumatology, Mayo Clinic, Jacksonville, Florida.

AUTHOR CORRESPONDENCE: Jacob Abarca, PharmD, MS, Assistant Research Scientist, University of Arizona College of Pharmacy, Center for Health Outcomes & PharmacoEconomic Research, 1703 E. Mabel, P.O. Box 210207, Tucson, AZ 85721-0207. Tel: (520) 325-6532; Fax: (520) 626-2023; E-mail: abarca@pharmacy.arizona.edu

Copyright© 2004, Academy of Managed Care Pharmacy. All rights reserved.

Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects approximately 1% of the U.S. population.¹ The disease is characterized by inflammation of synovial tissue and progressive damage of joints.² The introduction of biologic agents for the treatment of RA has revolutionized the treatment of this disease. Controlled trials of tumor necrosis factor (TNF)- α inhibitors, both as monotherapy and in combination, have demonstrated that these agents are effective in reducing symptoms, improving functionality and quality of life, and slowing the progression of the disease.^{3,4}

The biologic agents currently approved for the treatment of RA include the anti-TNF monoclonal antibodies adalimumab (Humira) and infliximab (Remicade), the TNF- α soluble receptor etanercept (Enbrel), and the IL-1 receptor antagonist, anakinra (Kineret) (Table 1).² To date, little data are available concerning how these medications are being used in actual clinical practice. Etanercept and infliximab have been U.S. Food and Drug Administration (FDA)-approved in the United States for several years and are the most frequently prescribed biologic agents for RA. The purpose of this paper is to describe dosing patterns of etanercept and infliximab among patients being treated for RA in usual care.

Methods

Subjects for this study were selected using a convenience sample from 16 rheumatology practices located in the western and southeastern United States. Subjects were included if they were at least 18 years of age and had received treatment with a TNF- α inhibitor (i.e., etanercept or infliximab) in the period of 1999-2002. Subjects were required to have a diagnosis of RA noted in their medical record or at least 1 medical claim with an ICD-9-CM code 714.0 during the 12 months prior to the

TABLE 1 FDA-Approved Dosage and Indications for Etanercept and Infliximab^{3,4}

Drug	Maintenance Dose for Adult Rheumatoid Arthritis	Route	Other Indications
Etanercept (Enbrel)	25 mg twice weekly	Subcutaneous	Juvenile rheumatoid arthritis Psoriasis Psoriatic arthritis Ankylosing spondylitis
Infliximab (Remicade)	3-10 mg/kg every 4 to 8 weeks	Intravenous	Crohn's disease

medical record review.

Eligible subjects were initially identified by their health plan by reviewing prior-authorization records and then verifying eligibility criteria through medical and pharmacy records. However, because the health plans covered large geographic areas, it became impractical, due to the travel time, to visit each rheumatology practice. Instead, rheumatology practices were contacted directly by telephone, and patients were identified by each office.

The patients were required to have complete information available in their medical record from the time of initiating TNF- α inhibitor therapy to their latest follow-up visit or until discontinuing TNF- α inhibitor treatment. Subjects were excluded from the review if they had a terminal illness or were receiving a TNF- α inhibitor treatment for an indication other than RA (e.g., Crohn's disease, psoriasis, ankylosing spondylitis). Medical records maintained by the provider (rheumatologist) responsible for prescribing and monitoring the TNF- α inhibitor therapy were reviewed retrospectively for the time period during which the subject received therapy with either etanercept, infliximab, or both. Interruptions in treatment were considered part of the treatment period and were included in the review. This study was conducted prior to the implementation of HIPAA (Health Insurance Portability and Accountability Act of 1996) rules and was approved by the Institutional Review Board at the University of Arizona.

A standardized data collection instrument was developed and pretested; slight modifications were made after the pretest to improve data capture. Demographic data collected from the medical record included age, sex, and weight. Among infliximab-treated subjects, weight was recorded at each infusion time in order to calculate the milligram per kilogram infliximab dose. The year of RA diagnosis recorded in the medical chart was collected. In cases where the diagnosis had been made many years beyond what was recorded in the medical record, an approximate year of RA diagnosis was recorded based on the available history (e.g., decade of RA diagnosis). The use of disease modifying antirheumatic drugs (DMARDs) concurrently with TNF- α inhibitor therapy was recorded as a binary variable (yes/no). Data on DMARD dose, frequency, and duration of therapy were not collected. Medical insurance coverage was classified into the following categories: health maintenance organization (HMO), preferred provider organization, traditional indemnity, Medicare, Medicaid, or other (i.e. self-pay, other insurance). Classification was based on what was reported by the patient's health plan or based on what was reported by the provider's office based on their billing history.

Anti-TNF- α therapy was recorded for each subject. For etanercept-treated subjects, the date etanercept was prescribed, the initial dose, frequency of administration, and date etanercept was discontinued (if applicable) were recorded. Changes in the dose or frequency of administration during the

TABLE 2 Baseline Demographic Information Among Treatment Groups

	Etanercept n = 128	Infliximab n = 89	Both* n = 27	P
Female (%)	99 (77.3)	52 (58.4)	21 (77.8)	0.038†
Mean age, years (SD)	55.1 (13.3)	54.9 (13.5)	52.8 (14.0)	0.71‡
Duration of RA, years (SD)	13.3 (8.8)	13.4 (8.0)	14.0 (9.9)	0.93‡
Type of insurance, n (%)				<0.01†
HMO	40 (31.3)	60 (67.4)	13 (48.2)	
PPO	39 (30.5)	5 (5.6)	2 (7.4)	
Indemnity	9 (7.0)	4 (4.5)	2 (7.4)	
Medicare	32 (25.0)	17 (19.1)	6 (22.2)	
Medicaid	5 (3.9)	1 (1.1)	2 (7.4)	
Other	3 (2.3)	2 (2.2)	2 (7.4)	

* Includes patients that were switched from etanercept to infliximab or vice versa.

† Chi-square test.

‡ One-way ANOVA test with post hoc Tukey-Kramer test.

RA = rheumatoid arthritis; SD = standard deviation;

HMO = health maintenance organization; PPO = preferred provider organization.

course of treatment were also recorded. For infliximab-treated subjects, data was collected for each infusion episode. These data included the date of infusion, dose, most current patient weight, and the administration of adjunctive medications (i.e., diphenhydramine, acetaminophen). The frequency of administration (dosing interval) was determined by calculating the number of days between each infusion episode. The dose of infliximab was reported as milligrams per kilogram and was calculated using the dose and most current weight at each infusion episode. The duration of therapy was calculated using the date of initiating therapy and the stop date. In cases where the subject was still receiving treatment at the time of follow-up, the date of the medical record review was used as the stop date.

The change in dose of either TNF- α inhibitor therapy was the primary end point in the analysis. The number of DMARDs used by patients treated with each TNF- α inhibitor was also evaluated. Continuous variables were analyzed using a one-way analysis of variance. Categorical variables were compared using a chi-square test. The alpha level for statistical significance was set at 0.05. All analyses were performed using SAS 8.2 (Cary, NC).

Results

A total of 244 medical records were identified and included in this study. Table 2 contains a description of the baseline characteristics. Females comprised 70% of the sample, which is consistent with gender distribution of this disease.¹ However, the gender distribution was not uniform across groups, with a higher proportion of males in the infliximab-only group compared with etanercept-only or etanercept/infliximab groups. Other demographic variables were similar across

TABLE 3 Mean Initial Dose, Ending Dose, and Mean Duration of Therapy of Patients Treated With Etanercept

Category	n	Duration of Therapy (Months)	Initial Dose mg (SD)	Ending Dose mg (SD)
Data for Patients Receiving Maintenance Etanercept Therapy				
<6 months	7	3.8 (2.3)	25.0 (0)	28.6 (9.4)
6 to <12 months	10	9.1 (1.6)	25.0 (0)	25.0 (0)
12 to <24 months	20	19.5 (3.2)	25.0 (0)	25.0 (0)
≥24 months	91	38.7 (6.7)	25.0 (0)	25.3 (2.6)
All	128	31.7 (13.1)	25.0 (0)*	25.4 (3.1)*
Data for Patients Who Discontinued Etanercept Therapy				
<6 months	9	4.2 (1.6)	25.0 (0)	25.0 (0)
6 to <12 months	4	9.5 (1.3)	25.0 (0)	25.0 (0)
12 to <24 months	4	17.8 (2.2)	25.0 (0)	25.0 (0)
≥24 months	10	33.2 (6.4)	25.0 (0)	32.5 (12.1)
All	27	17.7 (13.5)	25.0 (0)*	27.8 (8.0)†

* Two-sample t-test comparison of initial dose versus ending dose, $P=0.158$.

† Two-sample t-test comparison of initial dose versus ending dose, $P=0.083$.

SD=standard deviation.

TABLE 4 Mean Initial Dose, Ending Dose, and Mean Duration of Therapy of Patients Treated With Infliximab

Category	n	Duration of Therapy (Months)	Initial Dose mg (SD)	Ending Dose mg (SD)
Data for Patients Receiving Maintenance Infliximab Therapy				
<6 months	11	3.8 (1.9)	3.26 (0.42)	3.86 (1.55)
6 to <12 months	15	10.7 (1.2)	3.60 (0.85)	4.75 (1.88)
12 to <24 months	25	17.6 (3.1)	3.27 (0.62)	4.68 (2.03)
≥24 months	5	28.6 (1.5)	3.56 (0.99)	4.34 (0.90)
All	56	13.7 (7.5)	3.38 (0.69)	4.51 (1.82)*
Data for Patients Who Discontinued Infliximab Therapy				
<6 months	5	5.6 (0.9)	3.12 (0.27)	3.52 (0.87)
6 to <12 months	14	10.7 (1.3)	3.04 (0.13)	3.92 (1.51)
12 to <24 months	34	16.9 (2.5)	3.23 (0.82)	4.35 (1.49)
≥24 months	7	28.6 (1.5)	3.29 (0.68)	4.60 (1.47)
All	60	15.9 (6.3)	3.18 (0.66)	4.21 (1.45)*

* Two-sample t-test comparison of initial dose versus ending dose, $P<0.001$.

SD=standard deviation.

groups. The majority of patients were insured in an HMO-type insurance plan, followed by Medicare as the second most common.

The initial and end doses of the TNF- α inhibitors are provided in Tables 3 and 4. Among the 128 patients who were

still receiving etanercept at the time of the review, the mean dose increased 1.6 % ($P=0.16$) from their initial dose to their last follow-up. Among those who discontinued etanercept treatment, the mean dose increased 11.2% ($P=0.08$) during treatment. Among 56 infliximab-treated patients who were still receiving treatment at the time of the review, the mean dose increased 34% ($P<0.001$) from the initial dose to the last follow-up. A similar 32% increase was observed among those who discontinued infliximab therapy. Reasons for dose increases or discontinuations were not collected.

The use of concurrent DMARD therapy is shown in Table 5. The majority of patients used concurrent DMARD therapy along with TNF- α inhibitor treatment. Of those receiving DMARDs, 77% were treated with methotrexate either alone or in combination. The next most commonly used DMARDs were plaquenil (12.3%) and leflunomide (11%). A small proportion of patients used 2 or more DMARDs concurrently. The reasons for this treatment strategy were not collected.

Discussion

Overall, the dosing of etanercept and infliximab is consistent with the current FDA-approved labeling of these products. For etanercept, there was a nonsignificant 11.2% mean dose increase among those who discontinued therapy, and a 1.6% mean dose increase among those who were maintained on therapy, which indicates that some patients exceeded the FDA-approved dosage for this medication. However, on average, patients were maintained on a relatively constant dose over time. For infliximab, the mean dose increased significantly—by approximately 33%—during treatment among individuals who were maintained on infliximab and among those who discontinued therapy. The increase in dose among infliximab-treated patients was expected since it can be titrated to achieve a maximal therapeutic response. However, all patients on infliximab therapy were maintained on a dose below the FDA-approved maximum dosage (10 mg/kg every 4 to 8 weeks).⁴

Etanercept is indicated for use with or without concurrent methotrexate.³ Infliximab is indicated for use in combination with methotrexate.⁴ The use of DMARDs among both groups in our study appeared to be consistent with the FDA-approved labeling of these products since more than 70% of patients treated with either TNF- α inhibitor received concurrent DMARD therapy. Most frequently, the DMARD was methotrexate, but other DMARDs, such as hydroxychloroquine and leflunomide, were concurrently prescribed. In addition, 10% of patients were receiving more than one DMARD concurrently with TNF- α inhibitor therapy. To date, no clinical studies have demonstrated the efficacy or safety with DMARDs other than methotrexate or with more than one DMARD.

Determining the reason for increased DMARD therapy was not within the scope of this study. However, there are at least 2 plausible explanations for this observation. First, patients

receiving more than one DMARD therapy could represent a group of patients that is not responding adequately to treatment with a TNF- α inhibitor plus methotrexate.² Another potential explanation is that these patients receive adequate control but continue experiencing residual symptoms from their disease, prompting the provider to augment their regimen with an additional DMARD in order to attain complete control of the disease.² It is likely that both scenarios are represented in the patient population studied.

The results of this evaluation are consistent with previously published studies.⁵⁻⁷ A retrospective analysis using claims data from a large U.S. health plan evaluated dosage administration of etanercept or infliximab in patients with RA.⁵ Over a 1-year period, the mean dose of infliximab and etanercept increased by 37.4% and 7.4%, respectively. Data from the Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT) demonstrated greater improvements in the signs and symptoms of the disease based on the ACR20 (American College of Rheumatology response criteria), ACR50, and ACR70 scores in patients who received higher doses of infliximab.⁶ In addition, recent data shows that dosing of infliximab at 8-week intervals may result in insufficient concentrations to maintain an adequate therapeutic effect and may require more frequent administration.⁷ Stockl, et al. conducted a similar evaluation to this study and found subsequent dosing following initiation of infliximab and etanercept was 4.2 ± 1.4 mg/kg and 25.7 ± 13.9 mg, respectively, among patients with RA.⁸

Biologics are increasingly prescribed for the treatment of RA in clinical practice. Erkan et al. evaluated rheumatologists' treatment preferences for the treatment of RA based on disease severity.⁹ Hydroxychloroquine and methotrexate were the most commonly cited medications for first-line treatment of mild or moderate RA, respectively. For severe RA, TNF- α inhibitors were in 66% of the regimens that were listed by rheumatologists when cost was not a consideration. However, they were only in 14% of the regimens listed by rheumatologists when cost was taken into account. It is important to note that these data were collected before the publication of the results of randomized clinical trials comparing the use of etanercept and methotrexate in the treatment of early RA.¹⁰ Thus, it is likely that biologic agents would be listed more commonly if a more recent evaluation was conducted.

The preference for more expensive biologic agents in the treatment of RA is creating increased pressure on health care systems to provide coverage for these medications.^{2,11} Although the biologic agents significantly reduce RA-related disability and help patients maintain productive lifestyles, there are concerns about how much the health care system can afford to expand coverage for innovative, but costly therapies.¹¹⁻¹³ This concern is clearly demonstrated in the dramatic shift in rheumatologists' treatment preferences, particularly for biologics, when asked to take cost into consideration.⁹ Other issues, such as whether to

TABLE 5 Frequency of Concurrent DMARD Therapy by Treatment Group*

Number of DMARDs	Etanercept n (%)	Infliximab n (%)	Both† n (%)	P Value
0	55 (43.0)	11 (12.4)	5 (18.5)	
1	61 (47.7)	69 (77.5)	18 (66.7)	
2 or more	12 (9.4)	9 (10.1)	4 (14.8)	
Total	128 (100)	89 (100)	27 (100)	0.01‡

* DMARDs (disease-modifying antirheumatic drugs) included azathioprine, gold, hydroxychloroquine, leflunomide, methotrexate, and sulfasalazine.

† Includes patients that were switched from etanercept to infliximab or vice versa.

‡ Chi-square test.

consider biologics a medical or pharmacy benefit, have created new challenges for health care payers. Traditionally, injectables are more likely to be covered as a medical benefit; self-administered medications are more likely to be covered as a pharmacy benefit. In the case of etanercept and infliximab, this has created inconsistencies in how coverage is provided by some health care systems.^{14,15} In addition, how the financial cost of these agents should be tracked under the pharmacy or medical benefit has become an issue for some health plans.^{15,16}

As the availability of biologic agents to treat RA has expanded, the selection of the most cost-effective agent has become a pressing issue. Several factors contribute to the difficulty of identifying the most cost-effective agent. Perhaps the biggest limitation is the lack of direct head-to-head comparison data on efficacy and safety. Yet, resolving this issue does not necessarily resolve the entire cost-effectiveness question. Credible data regarding resource utilization associated with TNF- α inhibitor treatment are still required.^{11,14}

In the United States, there is a preference by many health care systems to use actual data obtained from patients treated in routine clinical practice to answer these types of questions.¹¹ This is particularly challenging for the current TNF- α inhibitors for several reasons. First, clinical measures of disease severity are usually not calculated and recorded in the patient's medical record, thus precluding a reliable measure of effectiveness. Second, obtaining data on resource utilization requires accessing a variety of data sources (e.g., medical record, medical claims, pharmacy claims, home health record) in order to obtain comprehensive resource utilization data. With the concerns over patient privacy, this usually requires obtaining individual patient consent, which is time-consuming, and may not be possible.

Contributing to the magnitude of the problem of measuring complete health care resource utilization, it is apparent that health care systems and third-party payers manage the use of etanercept and infliximab differently. For example, because etanercept is self-administered and can be dispensed from a pharmacy, it is more often covered as a pharmaceutical benefit,

but it also appears in medical claims. Infliximab is administered as an infusion and is therefore more likely to be covered as a medical benefit, but it may also appear in pharmacy claims.^{14,15} One solution is to analyze total costs of care (i.e., not just disease-specific costs) for patients receiving a TNF- α inhibitor.^{15,16} This approach captures all utilization, but it makes it difficult to identify specific practice patterns that may be driving the cost of treatment. Another approach is to coordinate all the available data sources (i.e., medical records, electronic claims, hospital records) and conduct a comprehensive economic evaluation.¹⁶ However, the challenges involved in getting access to the necessary data sources make this option difficult to achieve. Nevertheless, comparative cost-effectiveness data are necessary and will become more important as more RA treatment options are introduced and compete with traditional therapies for first-line treatment and standard of care.

Limitations

There are several limitations to this study. First, the design of this study was descriptive and was intended to describe the dosage patterns and DMARD use of patients treated with TNF- α inhibitors. Clinical information related to efficacy was not collected since this is usually not recorded in a consistent manner in the medical record. In addition, the reasons for changes in dose or discontinuation of therapy were not collected. Thus, it is not possible to make inferences about the comparative efficacy of either medication or comment about potential clinical outcomes associated with treatment.

Second, the data collected for this study came from medical records maintained by the prescribing rheumatologist. It is assumed that the pertinent information concerning the administration of each TNF- α inhibitor was documented correctly and completely in the medical record. It is possible that other clinical information concerning TNF- α therapy may have been maintained by a provider other than the rheumatologist and was not captured by this review.

Third, the duration of follow-up was twice as long for patients treated with etanercept compared with those treated with infliximab, which further precludes any type of comparison. Finally, the sample was not randomly selected from the population of RA patients treated with etanercept or infliximab. Thus, it is possible that characteristics of the patients (e.g., disease severity) were different from the average patient population and could reflect an extreme segment of this patient population by disease severity or other factor. However, the results of our study are similar to other published reports.

Conclusion

The results of this study of the actual practice of rheumatologists indicate that TNF- α inhibitors are being dosed according to their FDA-approved labeling. Further research on comparative effectiveness of these agents is needed.

DISCLOSURES

Funding for this research was provided by Wyeth Pharmaceuticals and was obtained by author Daniel C. Malone. Malone is a consultant to Amgen, and author Marc D. Cohen is a consultant to Wyeth, Abbott, Amgen, Centicore, Merck, and TAP pharmaceutical companies. Authors Jacob Abarca, Edward P. Armstrong, and Amy J. Grizzle disclose no potential bias or conflict of interest relating to this article. Abarca served as principal author of the study. Study concept and design were contributed by Abarca, Malone, Armstrong, and Grizzle. Analysis and interpretation of data were contributed by all authors. Drafting of the manuscript was primarily the work of Abarca and Malone, and its critical revision was the work of Armstrong, Grizzle, and Cohen. Statistical expertise was contributed by Abarca and Malone.

REFERENCES

1. Hochberg MC. Adult and juvenile rheumatoid arthritis: current epidemiologic concepts. *Epidemiol Rev*. 1981;3:27-44.
2. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 Update. *Arthritis Rheum*. 2002;46:328-46.
3. Etanercept Prescribing Information. Available at: <http://www.wyeth.com/content/ShowLabeling.asp?id=101>. 2003. Accessed September 9, 2004.
4. Infliximab [prescribing Information]. Available at: <http://www.remicade.com/pdf/prescribing.pdf>. 2003. Accessed September 9, 2004.
5. Harley CR, Frytak JR, Tandon N. Treatment compliance and dosage administration among rheumatoid arthritis patients receiving infliximab, etanercept, or methotrexate. *Am J Manag Care*. 2003;9:S136-S144.
6. Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. *Lancet*. 1999;354:1932-39.
7. St Clair EW, Wagner CL, Fasanmade AA, Wang B, Schaible T, Kavanaugh A, et al. The relationship of serum infliximab concentrations to clinical improvement in rheumatoid arthritis: results from ATTRACT, a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum*. 2002;46:1451-59.
8. Stockl K, Jarrar M, Tandon N. Dosing patterns of anti-TNF therapy in patients with rheumatoid arthritis in a managed care setting. *Disease Manage Health Outcomes* 2004;12:189-96.
9. Erkan D, Yazici Y, Harrison MJ, Paget SA. Physician treatment preferences in rheumatoid arthritis of differing disease severity and activity: the impact of cost on first-line therapy. *Arthritis Rheum*. 2002;47:285-90.
10. Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med*. 2000;343:1586-93.
11. Lubeck DP. A review of the direct costs of rheumatoid arthritis: managed care versus fee-for-service settings. *Pharmacoeconomics*. 2001;19:811-18.
12. Jenkins JK, Hardy KJ. Biological modifier therapy for the treatment of rheumatoid arthritis. *Am J Med Sci*. 2002;323:197-205.
13. Kosinski M, Kujawski SC, Martin R, Wanke LA, Buatti MC, Ware JE, Jr., et al. Health-related quality of life in early rheumatoid arthritis: impact of disease and treatment response. *Am J Manag Care*. 2002;8:231-40.
14. Gallup E. Coverage inequalities of new therapies for rheumatoid arthritis in a managed care setting. *Manag Care Interface*. 2001;14:52-69.
15. Morrow TJ. Designing and implementing an effective specialty pharmacy service program. *Manag Care Interface*. 2003;16:50-53.
16. Johnson KA. Managing the cost drivers of medical injectables. *Manag Care Interface*. 2003;16:37-40.