

Impact of Leflunomide Versus Biologic Agents on the Costs of Care for Rheumatoid Arthritis in a Managed Care Population

Daniel A. Ollendorf, MPH; Anna N. Peterson, BA; Joseph Doyle, RPh, MBA; and Daniel M. Huse, MA

Abstract

Objective: To compare the impact of leflunomide on resource utilization and costs relative to that of etanercept and infliximab among patients with rheumatoid arthritis (RA) in a managed care setting.

Methods: Data were obtained from the PharMetrics Integrated Outcomes Database for all patients newly starting 1 of the 3 medications of interest in 1999 or 2000. Claims were compiled for 180 days prior to the first prescription for study therapy and for a minimum of 90 days thereafter. Measures of interest during follow-up included the incidence of significant interventions (eg, joint injection, synovectomy), 1-year utilization of study therapy, other RA-related medications, inpatient and outpatient services, and total costs of RA-related care. Data were adjusted for variable follow-up using survival techniques. Multivariate analyses were conducted on total costs, controlling for between-group differences in demographic, clinical, and pretreatment characteristics.

Results: A total of 4069 patients were included in the study cohort (n = 2217, 1547, and 305 for leflunomide, etanercept, and infliximab, respectively). Three quarters of the cohort were female; etanercept patients were somewhat younger than leflunomide or infliximab recipients. Severity of illness (as measured by the Charlson index) was highest among infliximab patients. The incidence of significant interventions was high in all patients, but did not differ by treatment group. Use of nonsteroidal anti-inflammatory drugs (8.1 versus 8.9 claims) and narcotic analgesics (7.8 versus 8.5) was substantially lower for leflunomide than for etanercept. Costs of RA-related care were 42% to 53% lower among leflunomide patients for biologic medications (\$9618 versus \$16,534 and \$20,263 for etanercept and infliximab, respectively), primarily as a result of lower medication costs. Findings persisted in multivariate analyses of cost.

Conclusions: Leflunomide is associated with reduced costs of medications and other healthcare services relative to biologic medications among managed care patients with RA.

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Rheumatoid arthritis (RA) is a costly and debilitating autoimmune disorder characterized by joint pain, stiffness, and impaired functionality. Symptoms arise from inflammation and degradation of the synovial membrane. As synovial tissue is attacked, joint function degrades, causing progressive disability.¹ As a result, conduct of normal activities, work, and health-related quality of life are seriously impaired in patients with RA. The economic costs of RA are also considerable; as the disease progresses, patients require frequent invasive procedures (eg, joint injections, synovectomy) and sometimes eventual replacement of affected joints. It is estimated that the direct and indirect costs of RA in the United States total \$19 billion annually.²

Because RA has no known cure, the goals of therapy are to treat the disease's symptomology and attempt to slow or halt disease progression. Pharmacotherapy is the cornerstone of treatment; symptoms may be treated with combinations of nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and narcotic analgesics. In addition, disease-modifying antirheumatic drugs (DMARDs) are used to influence disease progression; these medications, which range from antimalarial agents (eg, hydroxychloroquine) to gold salts to chemotherapeutic agents (eg, methotrexate) are effective in slowing the rate of disease progression. Each formulation has limited effectiveness, however, and the sometimes high levels of toxicity experienced by patients taking these medications are problematic for long-term therapy.³

Several new agents have recently been introduced for the treatment of RA, and all have been shown to exhibit disease-modifying activity. Leflunomide is an oral medication that inhibits an enzyme (dihydroorotate dehydrogenase) that mediates lymphocyte proliferation, thereby reducing the intensity of the hyperinflammatory response characteristic of RA. In addition, 2 biologic medications, etanercept and infliximab, provide antirheumatic activity by inhibiting tumor necrosis factor (TNF), another important mediator of inflammatory response. Use of these agents in combination with methotrexate have been shown to be clinically superior to methotrexate alone in controlled clinical trials.⁴⁻¹²

Although all of these new agents are clinically promising for patients who are not responding well to other DMARDs such as methotrexate, the associated costs of therapy range widely. In 2000, the estimated daily cost of therapy was \$33.98 for etanercept, \$28.50 for infliximab, and \$7.66 for leflunomide.¹³ In the absence of comparative clinical studies to assess whether any of these agents has superior efficacy, economic considerations would suggest that a course of leflunomide be tried before resorting to the more expensive biologic agents. This study addressed the issue by comparing total costs of RA treatment during 1 year after initiation of therapy with etanercept, infliximab, or leflunomide.

Methods

Data Source. Data were obtained from the PharMetrics (Watertown, MA) Integrated Outcomes Database, which comprises fully adjudicated medical and pharmaceutical claims for more than 24 million unique patients from 40 health plans across the United States. The database included inpatient and outpatient diagnoses (in *International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] format) and procedures (in Current Procedural Terminology-4 and Health Care Procedure Coding System [HCPCS] formats), as well as standard and mail-order prescription records; available data on prescription records included the

National Drug Code and days supplied and quantity dispensed (for a subgroup of datasets). Both paid and charged amounts were available for all services rendered, as well as dates of service for all claims. Additional data elements included demographic variables (age, sex, geographic region), product type (eg, health maintenance organization [HMO], preferred provider organization [PPO]), payer type (eg, commercial, self-pay), provider specialty, and start and stop dates for plan enrollment.

To create its episode-based database, PharMetrics uses Symmetry Health Data Systems' Episode Treatment Group (ETGTM) analytical methodology. The ETG "grouping" software allows for the merging of patient-specific diagnostic, procedural, and demographic information generated by medical claims systems with prescription drug claims. Claims are grouped into episodes based on diagnosis; matching of drug and medical claims as well as definitions of the appropriate initiation and termination dates of each type of episode are attained through a series of clinically based algorithms.

All patients from the PharMetrics database who met the sample-selection criteria set forth below were included in these analyses.

Sample Selection. Patients included in this study must have had at least 1 claim with a listed diagnosis of RA (ICD-9-CM 714.xx), and at least 1 pharmacy or medical claim for leflunomide, etanercept, or infliximab between January 1, 1999, and December 31, 2000. Attention was focused on patients newly starting these medications; accordingly, patients with any evidence of use of leflunomide, etanercept, or infliximab during the 180-day pretreatment period were excluded from the sample. Patients aged 65 years and older at the time of index drug use were included only if they were a member of a Medicare risk plan, because full utilization and cost data were not available for those enrolled in a supplemental Medicare plan. Finally, patients who were not enrolled in the database during the entire pretreat-

ment period and for a period of at least 90 days subsequent to the index date were excluded from the study sample.

Patients were assigned an index date equivalent to the date of the first-observed use of 1 of the 3 medications of interest, and were assigned to relevant treatment groups accordingly. If the first-observed drug of interest was either infliximab or etanercept, then an additional search was conducted for claims with miscellaneous HCPCS codes (J9999 and J3490) that preceded the index date, because these codes were used before the introduction of drug-specific codes for these medications. The distribution of charges for these claims was examined; patterns of charges beyond the first quartile of each distribution were comparable to charges observed with the actual drug-specific HCPCS codes. Those charges that exceeded the first quartile of charges among etanercept patients (\$504) but were less than the first quartile for infliximab users (\$1283) were assumed to be likely related to etanercept claims; those that were greater than or equal to \$1283 were assumed to be likely related to infliximab claims. For etanercept, 94 patients (6.1%) included imputed charges as described above, and for infliximab, 8 patients (2.6%) had imputed charges.

Measures. Measures of interest included selected demographic and clinical characteristics of the study sample, utilization of RA-related pharmacotherapy and other services during follow-up, and the total costs of RA-related care. Demographic and clinical characteristics included age (as of the index date), sex, geographic region (ie, Northeast, South, Midwest, West), type of plan (eg, HMO, PPO), provider specialty (as of the index date), use of rheumatologist services during the pretreatment period, use of methotrexate, sulfasalazine, hydroxychloroquine, or other DMARDs (ie, gold salts, D-penicillamine, azathioprine, cyclosporine, cyclophosphamide) during pretreatment, severity of illness, and total (ie, RA-related and unrelated) charges during pretreatment. Overall health status during the year prior to the index date was meas-

ured using the Charlson comorbidity index, a widely used measure of comorbidity that is represented by a single numeric value and has been adapted for use with administrative data.¹⁴

The use of clinically significant interventions during the follow-up period also was assessed. Significant interventions included joint aspiration/injection, arthrodesis, arthroscopy, synovectomy, and joint arthroplasty. The time to the first significant intervention was calculated based on the interval between the index date and the claim for the first observed intervention.

The total number of claims for RA-related medications, which included study therapy, methotrexate, sulfasalazine, hydroxychloroquine, other DMARDs, oral corticosteroids, NSAIDs, and narcotic analgesics, also were calculated and compared across treatment groups. Other measures included the number of inpatient admissions and corresponding days in hospital, and the number of management (ie, physician office) and emergency-department visits and ancillary services (eg, laboratory). Medical services were classified as RA related based on their inclusion in an ETG for RA (ETGs 712 to 714).

Estimates of cost were based on billed charges, and included the costs of RA-related inpatient care, outpatient care, and pharmacy as described above. Charges were expressed in 2001 US dollars, and were adjusted as necessary using the medical-care component of the US consumer price index (unpublished data, US Bureau of Labor Statistics, 2002).

Analyses. Primary analyses were conducted on an intent-to-treat basis; therefore, all patients meeting study entry criteria were included in these analyses. Data were reported by treatment group (ie, leflunomide, etanercept, or infliximab); in addition, because use of more than 1 of these agents was common only among leflunomide patients, this group was further stratified into those who used etanercept, infliximab, or no biologic agent during follow-up. All analyses were descriptive in nature, because the level of power to detect important differences

between groups was unknown. We presented findings as overall group means and percentages, along with appropriate measures of variability and precision (ie, standard deviations, 95% confidence intervals [CI]). Differences in baseline and pretreatment characteristics, however, were evaluated using a chi-square test or *t* test for categorical and continuous variables, respectively. All analyses were conducted using Statistical Analysis Software (SAS®), version 8.1 (SAS Institute, Cary, NC).

Because the duration of follow-up was expected to vary by patient, and to preserve as much data as possible for infliximab patients (because this medication was introduced later than leflunomide and etanercept), techniques of survival analysis were used to estimate 1-year measures of utilization and cost. Patients with less than 1 year of follow-up were flagged as “censored,” but nevertheless were included in the model for the available duration of follow-up. Specifically, the LIFEREG procedure, which produces estimates of parametric regression models with censored survival data using the maximum likelihood method, was used to estimate 1-year measures of utilization and cost.¹⁵

Finally, because differences in selected baseline and pretreatment measures between treatment groups may have affected estimates of cost independent of the effects of treatment, statistical significance of between-treatment differences in survival-adjusted estimates was tested using generalized log-linear regression modeling techniques (GLM); GLM is based on the exponential family of distributions, a direct extension of traditional regression techniques and analysis of variance. Covariates included age, sex, Charlson index score, geographic region, physician specialty, plan type, use of rheumatologist services in the pretreatment period, pretreatment methotrexate, sulfasalazine, hydroxychloroquine, and other DMARD use, and total pretreatment charges.

Results

Patient Characteristics. Demographic and clinical characteristics of the study

sample are presented in **Table 1**. A total of 4069 patients were included in the study cohort (n = 2217, 1547, and 305 for leflunomide, etanercept, and infliximab, respectively). Not surprisingly, because of its later introduction to the marketplace, the duration of follow-up among infliximab patients was significantly shorter than that among patients receiving leflunomide or etanercept (225 versus 289 and 296 days, respectively, $P < .0001$). A total of 371 leflunomide patients (16.7%) used a biologic agent during follow-up (primarily etanercept). Significant differences ($P < .0001$) were noted between treatment groups in terms of age; overall, etanercept patients were somewhat younger than patients who started on leflunomide or infliximab. Approximately three quarters of the cohort were female; this proportion did not differ by treatment group. Nearly one half of patients were seen by a rheumatologist at the index date; this proportion was somewhat higher among etanercept and infliximab recipients. Significant differences also were observed between groups for plan type and geographic region; use of infliximab was less likely to occur in a stringently managed (ie, HMO) environment than use of leflunomide or etanercept.

Table 1 also presents selected pretreatment measures by treatment group. The mean Charlson index score did not differ significantly among the treatment groups; 80% to 90% of patients had at least 1 rheumatologist visit during pretreatment. Use of methotrexate and other DMARDs during pretreatment was common in all groups, and did not significantly differ by index therapy; in contrast, use of pretreatment sulfasalazine was infrequent. Pretreatment use of hydroxychloroquine varied significantly among the treatment groups (leflunomide, 23.3%; etanercept, 22.1%; infliximab, 16.7%; $P = .0348$). Mean total (ie, RA-related and unrelated) pretreatment costs also varied significantly ($P < .0001$); costs were more than 20% higher for patients receiving biologic medications compared with those receiving leflunomide.

Table 1. Demographic, Clinical, and Pretreatment Characteristics of the Study Sample

Characteristic	Leflunomide			All (N = 2217)	Etanercept (N = 1547)	Infliximab (N = 305)	P*
	Follow-up Etanercept Use (n = 327)	Follow-up Infliximab Use (n = 44)	No Follow-up Biologic Use (n = 1846)				
Age							
<18 years (%)	1 (0.3)	0 (0.0)	6 (0.3)	7 (0.3)	54 (3.5)	1 (0.3)	<.0001
18 to 34 years (%)	16 (4.9)	2 (4.5)	79 (4.3)	97 (4.4)	147 (9.5)	21 (6.9)	
35 to 44 years (%)	84 (25.7)	4 (9.1)	328 (17.8)	416 (18.8)	302 (19.5)	58 (19.0)	
45 to 54 years (%)	123 (37.6)	14 (31.8)	654 (35.4)	791 (35.7)	484 (31.3)	93 (30.5)	
55 to 64 years (%)	100 (30.6)	20 (45.5)	658 (35.6)	778 (35.1)	478 (30.9)	114 (37.4)	
65+ years (%)	3 (0.9)	4 (9.1)	121 (6.6)	128 (5.8)	82 (5.3)	18 (5.9)	
Sex (% female)	246 (75.2)	28 (63.6)	1389 (75.2)	1663 (75.0)	1176 (76.0)	233 (76.4)	.7200
Charlson index, mean (SD)	1.28 (0.88)	1.23 (0.94)	1.37 (1.01)	1.35 (0.99)	1.33 (0.87)	1.39 (1.03)	.5042
Provider specialty							
Rheumatology (%)	151 (46.2)	17 (38.6)	803 (43.5)	971 (43.8)	717 (46.3)	152 (49.8)	.0140
Internal medicine (%)	40 (12.2)	5 (11.4)	232 (12.6)	277 (12.5)	153 (9.9)	29 (9.5)	
FP/GP (%)	47 (14.4)	6 (13.6)	250 (13.5)	303 (13.7)	209 (13.5)	24 (7.9)	
Orthopedics (%)	14 (4.3)	1 (2.3)	65 (3.5)	80 (3.6)	65 (4.2)	9 (3.0)	
Other/unknown (%)	75 (22.9)	15 (34.1)	496 (26.9)	586 (26.4)	403 (26.1)	91 (29.8)	
Plan type							
HMO (%)	107 (32.7)	10 (22.7)	640 (34.7)	757 (34.1)	679 (43.9)	84 (27.5)	<.0001
PPO (%)	110 (33.6)	29 (65.9)	704 (38.1)	843 (38.0)	466 (30.1)	161 (52.8)	
POS (%)	74 (22.6)	3 (6.8)	305 (16.5)	382 (17.2)	254 (16.4)	36 (11.8)	
Indemnity (%)	19 (5.8)	1 (2.3)	88 (4.8)	108 (4.9)	55 (3.6)	18 (5.9)	
Other (%)	17 (5.2)	1 (2.3)	109 (5.9)	127 (5.7)	93 (6.0)	6 (2.0)	
Geographic region							
Northeast (%)	41 (12.5)	2 (4.5)	229 (12.4)	272 (12.3)	317 (20.5)	11 (3.6)	<.0001
South (%)	111 (33.9)	4 (9.1)	643 (34.8)	758 (34.2)	558 (36.1)	104 (34.1)	
Midwest (%)	119 (36.4)	20 (45.5)	634 (34.3)	773 (34.9)	428 (27.7)	91 (29.8)	
West (%)	56 (17.1)	18 (40.9)	340 (18.4)	414 (18.7)	244 (15.8)	99 (32.5)	
Pretreatment measures:							
Rheumatologist use (%)	268 (82.0)	40 (90.9)	1496 (81.0)	1804 (81.4)	1232 (79.6)	262 (85.9)	.0328
Medication use:							
Methotrexate (%)	161 (49.2)	21 (47.7)	870 (47.1)	1052 (47.5)	745 (48.2)	154 (50.5)	.5954
Sulfasalazine (%)	3 (0.9)	1 (2.3)	8 (0.4)	12 (0.5)	6 (0.4)	1 (0.3)	.7413
Hydroxychloroquine (%)	73 (22.3)	10 (22.7)	433 (23.5)	516 (23.3)	342 (22.1)	51 (16.7)	.0348
Other DMARDs (%)	252 (77.1)	31 (70.5)	1305 (70.7)	1588 (71.6)	1119 (72.3)	216 (70.8)	.8219
Billed charges, mean (SD)(\$) [†]	46,240 (110,897)	35,107 (19,473)	32,840 (43,758)	34,862 (58,594)	42,838 (45,299)	42,823 (39,476)	<.0001

Values are number (percentage), unless indicated otherwise.

*P values based on comparison of leflunomide-all, etanercept, and infliximab treatment groups.

[†]RA-related and unrelated.

DMARDs = disease-modifying antirheumatic drugs; FP = family practice; GP = general practice; HMO = health maintenance organization; POS = point of service; PPO = preferred provider organization; RA = rheumatoid arthritis; SD = standard deviation.

Table 2. Incidence of Significant RA-Related Interventions

Measure	Leflunomide			All (N = 2217)	Etanercept (N = 1547)	Infliximab (N = 305)
	Follow-up Etanercept Use (n = 327)	Follow-up Infliximab Use (n = 44)	No Follow-up Biologic Use (n = 1846)			
Intervention*						
Joint aspiration/injection (%)	163 (49.8)	26 (59.1)	767 (41.5)	956 (43.1)	601 (38.8)	114 (37.4)
Arthroscopy (%)	81 (24.8)	15 (34.1)	439 (23.8)	535 (24.1)	369 (23.9)	67 (22.0)
Arthrodesis (%)	185 (56.6)	33 (75.0)	1068 (57.9)	1286 (58.0)	835 (54.0)	157 (51.5)
Synovectomy (%)	71 (21.7)	10 (22.7)	406 (22.0)	487 (22.0)	318 (20.6)	59 (19.3)
Joint arthroplasty (%)	40 (12.2)	4 (9.1)	199 (10.8)	243 (11.0)	186 (12.0)	31 (10.2)
Time to first intervention (days)						
Mean (SD)	71.1 (71.4)	62.7 (78.4)	66.7 (72.0)	72.3 (78.0)	73.7 (78.0)	60.6 (66.7)
Median	43	29	37	47	42	36
Minimum	1	3	1	1	1	1
Maximum	364	328	356	337	365	365
Interquartile range	65	51	65	83	82	67

*Values are number (percentage).
RA = rheumatoid arthritis; SD = standard deviation.

Significant Interventions. The incidence of significant RA-related interventions at 1 year of follow-up is presented in **Table 2**. Rates were generally comparable across the 3 medication cohorts, although a slightly higher percentage of leflunomide patients underwent joint aspiration/injection or arthrodesis than patients receiving biologic agents; in most instances, the leflunomide rate was influenced by higher rates in the subgroup of patients receiving follow-up biologic medications. The rate of invasive procedures was relatively high for all patients; rates for synovectomy (22.0%, 20.6%, and 19.3% for leflunomide, etanercept, and infliximab, respectively) and joint arthroplasty (11.0%, 12.0%, and 10.2%, respectively) did not differ across groups.

Rheumatoid Arthritis-Related Resource Utilization. One-year estimates of utilization of medications and healthcare services are presented in **Table 3**. The mean duration of study therapy (defined as the time between the last and first observed fill or injection dates) for leflunomide was more than 20% shorter than that for etanercept

(186.2 versus 236.2 days, respectively), but nearly 40% longer than that for infliximab (134.0 days). Leflunomide patients had more claims for oral corticosteroid agents than those receiving the biologic agents; in comparison with those receiving etanercept, the mean number of claims for NSAIDs (8.1 versus 8.9) and narcotic analgesic agents (7.8 versus 8.5) was substantially lower among leflunomide patients.

The incidence of RA-related hospitalization was relatively infrequent among all patients. On average, however, the total number of days in hospital was over 3-fold higher among infliximab patients (12.5 days versus 4.1 and 3.4 days for etanercept and leflunomide, respectively). In general, levels of outpatient utilization were lower among leflunomide patients relative to those in the biologic-agent groups.

Rheumatoid Arthritis-Related Costs. Reflecting resource utilization findings, particularly the avoidance of costly biologic agents, RA-related medication charges at 1 year were reduced among patients who initially received leflunomide com-

Table 3. Utilization of RA-Related Medications and Healthcare Services at 1 Year

Medication	Leflunomide			All (N = 2217)	Etanercept (N = 1547)	Infliximab (N = 305)
	Follow-up Etanercept Use (n = 327)	Follow-up Infliximab Use (n = 44)	No Follow-up Biologic Use (n = 1846)			
Total duration of study therapy (days)*	137.4 (123.9, 151.0)	171.9 (133.7, 210.0)	195.1 (189.0, 201.2)	186.2 (180.6, 191.7)	236.2 (229.8, 242.46)	134.0 (122.1, 145.9)
Number of medication claims						
Leflunomide	4.2 (3.8, 4.6)	5.8 (4.6, 6.9)	6.5 (6.2, 6.6)	6.2 (5.9, 6.3)	0.3 (0.2, 0.3)	0.1 (0, 0.2)
Etanercept	5.5 (5.0, 5.8)	0.1 (0, 0.3)	0.0 (0, 0)	0.8 (0.7, 0.9)	8.8 (8.5, 9.1)	0.1 (0, 0.1)
Infliximab	0.0 (0, 0)	3.8 (3.2, 4.4)	0.0 (0, 0)	0.1 (0, 0.1)	0.1 (0, 0.1)	4.9 (4.6, 5.2)
Methotrexate	1.0 (0.6, 1.4)	1.0 (0.2, 1.8)	1.4 (1.1, 1.6)	1.3 (1.1, 1.5)	1.5 (1.2, 1.8)	2.1 (1.3, 2.9)
Sulfasalazine	0.1 (0, 0.2)	0.1 (0, 0.1)	0.0 (0, 0)	0.0 (0, 0.1)	0.0 (0, 0)	0.1 (0, 0.1)
Hydroxychloroquine	0.9 (0.6, 1.2)	1.9 (0.8, 2.9)	1.2 (1.1, 1.4)	1.2 (1.1, 1.3)	1.1 (1.0, 1.3)	0.9 (0.6, 1.2)
Other DMARDs	2.2 (1.6, 2.7)	2.5 (1.3, 3.7)	2.3 (2.1, 2.6)	2.3 (2.1, 2.5)	2.2 (1.9, 2.4)	2.5 (1.9, 3.2)
Oral corticosteroids	4.8 (3.9, 5.7)	6.4 (3.9, 8.9)	6.1 (5.4, 6.6)	5.9 (5.4, 6.4)	4.5 (3.9, 5.0)	4.5 (3.6, 5.4)
NSAIDs	8.5 (7.7, 9.4)	9.3 (6.8, 11.8)	8.0 (7.6, 8.3)	8.1 (7.8, 8.4)	8.9 (8.4, 9.2)	7.6 (6.6, 8.5)
Narcotic analgesics	9.3 (8.1, 10.4)	7.6 (5.6, 9.7)	7.6 (7.0, 7.9)	7.8 (7.3, 8.2)	8.5 (8.0, 9.0)	7.7 (6.7, 8.7)
Inpatient						
Hospitalizations	0.1 (0, 0.1)	0.0 (0, 0.1)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.2 (0.1, 0.3)
Average length of stay (days)	0.7 (0.1, 1.4)	0.0 (0, 0)	3.9 (1.9, 5.9)	3.4 (1.7, 5.0)	4.1 (1.1, 7.0)	12.5 (0, 31.9)
Outpatient						
Management	6.6 (5.9, 7.3)	7.6 (5.6, 9.5)	4.7 (4.4, 4.9)	5.0 (4.8, 5.3)	5.8 (5.4, 6.1)	5.9 (4.7, 7.0)
Emergency department	0.1 (0.1, 0.2)	0.1 (0, 0.2)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.2 (0.1, 0.2)	0.1 (0, 0.2)
Ancillary	18.8 (16.8, 20.7)	27.9 (21.84, 33.98)	16.4 (15.5, 17.3)	17.0 (16.2, 17.8)	17.2 (16.1, 18.2)	18.9 (16.7, 21.0)

Values are mean (95% confidence intervals).

*Defined as (last fill or injection date for index medication) – (index date).

DMARDs = disease-modifying antirheumatic drugs; NSAIDs = nonsteroidal anti-inflammatory drugs; RA = rheumatoid arthritis.

pared with those receiving etanercept or infliximab (\$7645 versus \$14,278 and \$17,195 respectively) (Table 4). Between-group differences manifested almost entirely through the cost of RA drug therapy; total charges for all 3 medications (including those of switch or add-on therapy) averaged \$2883, \$10,210, and \$12,736 in the leflunomide, etanercept, and infliximab groups, respectively. In fact, total charges among leflunomide-treated patients who subsequently switched to or added on biologic agents were approximately \$2500 lower than those who received the latter agents initially.

Charges for RA-related inpatient and outpatient care were also reduced among patients receiving leflunomide. Mean inpatient charges were 20% to 50% lower (\$501 versus \$573 and \$940 for etanercept and infliximab, respectively), whereas those for outpatient care were reduced by 15% to 30% (\$1474 versus \$1696 and \$2117, respectively).

Mean total charges (ie, those of medications, outpatient services, and inpatient care) for all leflunomide patients at 1 year were \$9618 (95% CI, \$8923, \$9676), which is a reduction of 42% relative to etanercept (mean \$16,534, 95% CI, \$15,869, \$17,284) and 53% relative to infliximab (mean

Table 4. Estimated Costs of RA-Related Care at 1 Year (2001 Dollars)

Component	Leflunomide			All (N = 2217)	Etanercept (N = 1547)	Infliximab (N = 305)
	Follow-up Etanercept Use (n = 327)	Follow-up Infliximab Use (n = 44)	No Follow-up Biologic Use (n = 1846)			
Pharmacy						
Leflunomide	1188 (1074, 1299)	1446 (1123, 1769)	1815 (1756, 1865)	1714 (1661, 1761)	75 (56, 92)	28 (0, 55)
Etanercept	6548 (6090, 7023)	95 (0, 282)	0 (0,0)	963 (850, 1088)	9980 (9731, 10,292)	60 (0, 122)
Infliximab	34 (0, 86)	10,119 (8056, 12,181)	0 (0,0)	206 (134, 278)	155 (90, 220)	12,648 (11,651, 13,617)
Methotrexate	326 (209, 444)	277 (51, 503)	458 (365, 565)	435 (355, 526)	360 (275, 445)	382 (241, 523)
Sulfasalazine	1 (0, 1)	0 (0, 1)	0 (0, 0)	0 (0, 1)	0 (0, 0)	1 (0, 2)
Hydroxychloroquine						
Other DMARDs	67 (47, 87)	145 (58, 233)	89 (79, 99)	87 (78, 96)	79 (68, 89)	54 (36, 72)
Oral corticosteroids	1249 (723, 1776)	869 (0, 1766)	1571 (1231, 1959)	1509 (1216, 1843)	1259 (971, 1547)	1550 (906, 2193)
NSAIDs	489 (240, 738)	448 (111, 784)	821 (616, 1035)	765 (590, 947)	456 (350, 564)	743 (446, 1039)
Narcotic analgesics	828 (716, 948)	682 (476, 888)	709 (675, 747)	726 (694, 763)	779 (736, 820)	716 (604, 827)
Total pharmacy	928 (677, 1174)	733 (341, 1124)	1358 (945, 1720)	1282 (936, 1585)	1127 (943, 1320)	1010 (747, 1274)
Outpatient						
Management	655 (529, 781)	568 (427, 709)	550 (481, 619)	566 (505, 627)	616 (539, 694)	924 (553, 1296)
Emergency department	31 (0, 62)	34 (0, 92)	68 (19, 117)	62 (21, 103)	52 (24, 79)	49 (0, 99)
Ancillary	1042 (721, 1363)	2218 (1241, 3195)	779 (677, 880)	846 (747, 945)	1028 (851, 1205)	1144 (948, 1340)
Total outpatient	1727 (1379, 2076)	2820 (1824, 3816)	1397 (1257, 1536)	1474 (1344, 1603)	1696 (1470, 1922)	2117 (1692, 2543)
Inpatient						
Grand Total	777 (238, 1315)	0 (0,0)	464 (293, 636)	501 (338, 664)	573 (340, 807)	940 (242, 1638)
Grand Total	14,177 (12,665, 5,679)	17,634 (14,831, 20,438)	8609 (7835, 9545)	9618 (8923, 9676)	16,534 (15,869, 17,284)	20,263 (18,330, 22,140)

Values are mean (95% confidence intervals).

DMARDs = disease-modifying antirheumatic drugs; NSAIDs = nonsteroidal anti-inflammatory drugs; RA = rheumatoid arthritis.

§20,263, 95% CI, §18,330, §22,140). In a multivariate log-linear model (Table 5), adjusted total charges in the etanercept and infliximab groups were 122% and 168% higher, respectively, than in the leflunomide group ($P < .0001$ for both pairwise comparisons).

Discussion

To compare the impact of use of leflunomide therapy on RA-related resource utilization and costs with that among patients receiving etanercept or infliximab, we undertook a retrospective analysis of medical and pharmacy claims data among a cohort of RA patients newly starting these medications. Data on the incidence of sig-

nificant interventions were examined for these patients, as was information on the utilization and costs of RA-related medications, outpatient services, and inpatient care. The number of patients treated with leflunomide who subsequently initiated therapy with an anti-TNF biologic agent was also examined.

The results of this study indicated that 83% of patients treated with leflunomide did not switch to or add a biologic agent within 1 year after initiating therapy. Additionally, these patients did not exhibit significantly higher utilization of other pharmacotherapies or invasive procedures, and thus appeared to be adequately treated with leflunomide during the time

Table 5. Multivariate Log-Linear Model of Total RA Charges

Parameter	Coefficient	SE	P*
Intercept	8.2198	0.0948	<.0001
Study treatment			
Etanercept versus leflunomide	0.7993	0.0287	<.0001
Infliximab versus leflunomide	0.9844	0.0526	<.0001
Age (years)	-0.0004	0.0012	.7328
Plan type			
HMO versus other/unknown	0.2368	0.0642	.0002
Indemnity versus other/unknown	0.3188	0.0877	.0003
PPO versus other/unknown	0.3043	0.0636	<.0001
POS versus other/unknown	0.3586	0.0672	<.0001
Geographic region			
Midwest versus Northeast	-0.0671	0.0470	.1536
South versus Northeast	-0.2624	0.0443	<.0001
West versus Northeast	-0.3765	0.0506	<.0001
Provider specialty			
GP/FP versus other/unknown	-0.0980	0.0457	.032
Internal medicine versus other/unknown	-0.0702	0.0479	.1428
Orthopedics versus other/unknown	0.2003	0.0730	.0061
Rheumatology versus other/unknown	-0.0305	0.0358	.3948
Prior rheumatology care	-0.0457	0.0398	.251
Prior DMARD therapy			
Sulfasalazine	0.5606	0.1948	.004
Hydroxychloroquine	0.1284	0.0321	<.0001
Methotrexate	0.1439	0.0285	<.0001
Other DMARDs	0.1996	0.0312	<.0001
Charlson comorbidity index	-0.0376	0.0149	.0119
Prior RA charges (\$000)	0.0057	0.0003	<.0001

*P values were produced for each factor comparison to determine its significance in explaining differences between leflunomide-all, etanercept, and infliximab treatment groups.

DMARDs = disease-modifying antirheumatic drugs; FP = family practice; GP = general practice; HMO = health maintenance organization; POS = point of service; PPO = preferred provider organization; RA = rheumatoid arthritis; SE = standard error.

of the study. The 17% of leflunomide patients who did switch to or add etanercept or infliximab still incurred lower costs than those who initially received etanercept or infliximab. By deferring the use of costly biologic agents, the use of leflunomide (analyzed on an intention-to-treat basis) was associated with reduced RA-related utilization and costs relative to etanercept and infliximab. These findings

persisted after multivariate analyses controlling for baseline and pretreatment differences between treatment groups.

These findings confirm and extend the results of a previous analysis using the PharMetrics Integrated Outcomes Database.¹⁶ In that study, total RA charges over 6 months were \$3302 for patients receiving leflunomide and \$7722 for patients treated with etanercept. As in the

present study, the difference in total charges was driven mainly by the differential cost of study treatment (etanercept versus leflunomide). Sufficient data on infliximab were not available at the time to include it in the study.

In this study, estimates of RA-related costs at 1 year after initiation of these medications were higher than those previously reported for patients with RA. For example, Gabriel et al¹⁷ estimated the costs of RA for a 25-year period after diagnosis to range between \$61,000 and \$122,000. Newhall-Perry et al¹⁸ estimated that the direct costs of RA after initial seropositive diagnosis totaled \$200 per month. These differences are not surprising, however, as most patients who received the 3 medications that were the focus of our analysis had severe or advanced forms of RA that could not be treated successfully with older medications alone. Our estimates are nonetheless important for managed care organizations to consider, because aggressive use of these new medications early in the course of RA has been recommended recently.^{19,20}

In addition to the retrospective analyses described herein, the economic impact of leflunomide has been compared with that of methotrexate as well as placebo (ie, standard therapy) in a Canadian evaluation conducted in conjunction with a 1-year randomized controlled trial.²¹ Patient utilities were similar for leflunomide and methotrexate (both of which were superior to placebo); however, direct medical costs were significantly higher for leflunomide compared with the other groups when drug acquisition and monitoring costs were incorporated. Nonetheless, given the high levels of toxicity and side effects often experienced with methotrexate, leflunomide appears to be a viable treatment option for patients not able to tolerate methotrexate and for those with suboptimal outcomes.³

We note important limitations of our analysis. First, leflunomide was compared with the 2 antirheumatic biologic medications that had been available in the US market for sufficient time to accumulate a substantial history of use and outcomes in

the claims files of managed care plans. A third medication, anakinra, is currently available, but had not yet been approved by the US Food and Drug Administration during the time period for which data were available.

In addition, as with all such quasi-experimental research based on retrospective data, we cannot rule out the possibility that our findings may have been influenced by differences in disease severity or progression between treatment groups. Indeed, use of the biologic medications in managed care is often restricted through the use of precertification or prior authorization programs, in which patients must have failed methotrexate or other DMARDs before initiation of etanercept or infliximab²²; if these same types of rules are not used to restrict leflunomide use, the patients using leflunomide may in fact be at a less severe stage of disease. Although total pretreatment costs were higher for patients receiving biologic medications than for those receiving leflunomide, pretreatment use of selected RA medications and rheumatologist services were comparable among the groups, suggesting a similar level of RA severity. Also, our findings persisted after adjustment (to the extent feasible) for differences between treatment groups. In addition, to examine whether the possible impact of “drug failure” restrictions may have affected our estimates, total costs were stratified according to whether patients received pretreatment methotrexate. Not surprisingly, costs were higher among patients who did receive pretreatment methotrexate; however, mean total costs remained lower among leflunomide patients in this subgroup (\$12,506 versus \$18,330 and \$23,237 for etanercept and infliximab, respectively), and in the group of patients who did not receive pretreatment methotrexate (\$7023 versus \$14,870 and \$17,250, respectively). Finally, our estimates did not include the costs of managing or treating side effects associated with leflunomide, etanercept, or infliximab (eg, diarrhea, hypertension, opportunistic infection, sepsis); and, because our study was limited to 1 year, our estimates may

not reflect any potential longer-term benefits of therapy.

Although we included proxies for effectiveness in our analysis of treatment-related outcomes and costs, we could not measure the impact of these medications on important intermediate and qualitative outcomes such as radiographic progression, joint pain, and function. Measurement of clear differences in effectiveness will come only through the conduct of randomized, head-to-head clinical trials of these agents, in which levels of disease severity are comparable at the time of enrollment.

Despite these limitations, we believe our study has important implications. Our findings confirm that leflunomide is a lower-cost alternative to biologic therapy when total RA treatment costs are considered. Although some leflunomide-treated patients may subsequently require a biologic agent to control the progression of their disease, a delay in initiating such costly therapy nevertheless represents a significant economic benefit. Our results are therefore likely to be of interest to healthcare payers and others concerned with identifying optimal treatment guidelines for advanced RA.

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