

# Cost of Biologic Treatment Persistence or Switching in Rheumatoid Arthritis

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Approximately 1.48 million adults in the United States have rheumatoid arthritis (RA),<sup>1</sup> a chronic inflammatory joint disease leading to severe disability and premature mortality.<sup>2</sup> Treatment guidelines for RA recommend methotrexate—or another conventional synthetic disease-modifying antirheumatic drug (DMARD), such as hydroxychloroquine, leflunomide, or sulfasalazine—alone for a patient with early RA and no prior DMARD therapy.<sup>3,4</sup> Patients with an inadequate response to conventional synthetic DMARDs may benefit from initiation of biologic therapy, consisting of either a tumor necrosis factor inhibitor (TNFi), such as adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab, or a non-TNFi biologic, such as abatacept, rituximab, or tocilizumab.<sup>3,4</sup>

Many studies have examined treatment patterns for biologic therapy in clinical practice, such as persistence, switching to another biologic, restarting the same biologic after a gap in therapy, or discontinuation of biologic therapy.<sup>5-14</sup> Nonpersistence on biologic therapy may occur due to medical reasons, such as inadequate response or medication intolerance,<sup>15-17</sup> or due to payer policies or changes in coverage<sup>18</sup> that lead to nonmedical switching to another biologic.<sup>19,20</sup> Systematic reviews have concluded that interventions to improve adherence and persistence need to be identified<sup>6,8</sup> and that large studies are needed to draw consistent conclusions about predictive factors for biologic treatment adherence and persistence.<sup>13</sup>

Several studies have compared medication costs or total healthcare costs across biologics<sup>21-33</sup> or the cost-effectiveness of biologics<sup>34-45</sup> in patients with RA. There is limited information comparing healthcare costs between patients with RA who switch biologics and those who persist on biologic therapy.<sup>46</sup> The objective of this study was to estimate total healthcare costs among patients with RA in the first year after they initiated biologic therapy, according to biologic treatment patterns and the index biologic.

## ABSTRACT

**OBJECTIVES:** To estimate total costs among patients with rheumatoid arthritis (RA) who persisted on or switched from newly initiated biologic therapy.

**STUDY DESIGN:** A retrospective claims database analysis.

**METHODS:** This analysis included adults in the HealthCore Integrated Research Database with RA who initiated treatment with a biologic for RA (abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, or tocilizumab) between January 2009 and November 2014. Total healthcare costs (plan- and patient-paid) were estimated for 1 year post index. Treatment persistence was defined as no discontinuation (ie, no refill gap >45 days) and no biologic switch.

**RESULTS:** Of 7468 patients, 45.2% persisted on the index biologic for at least 1 year without a refill gap and 16.7% switched to another biologic in the first year; other patients discontinued the index biologic (23.2%) or restarted after a refill gap (15.0%). Mean 1-year total healthcare costs per patient were \$41,901 [95% CI, \$40,855-\$42,947] among persistent patients and \$44,244 [95% CI, \$40,820-\$47,668] among switchers. In a multivariable analysis of all patients, switchers had 5% higher postindex costs on average than persistent patients ( $\exp(\beta) = 1.05$ ; 95% CI, 1.01-1.08), and etanercept had the lowest postindex costs ( $\exp(\beta)$  ranged from 1.03 to 1.51 for other biologics relative to etanercept).

**CONCLUSIONS:** Patients with RA who switched biologic therapy incurred higher 1-year total postswitch healthcare costs compared with patients who were persistent on the index biologic. Healthcare costs were lowest for patients who started on etanercept, particularly those who persisted on etanercept.

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## METHODS

### Study Design

This was a retrospective cohort study of administrative claims data from the HealthCore Integrated Research Database (HIRD). HIRD contains a broad and geographically diverse spectrum of longitudinal claims data that represents the largest commercially insured population in the United States. HIRD is comparable with US Census data (American Community Survey) by age and gender, with slight underrepresentation of adults 65 years and older.<sup>47</sup>

### Eligibility Criteria

To be included in the analysis, a patient needed to have at least 1 claim for a biologic of interest (abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, or tocilizumab), with an index date (the first biologic claim) between January 1, 2009, and November 30, 2014. Other key inclusion criteria were continuous enrollment in the health plan for at least 180 days preindex and at least 365 days post index, age of 18 to 63 years on the index date, at least 1 diagnosis for RA (based on *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnosis codes) in the preindex period, and an index claim after FDA approval for RA treatment for that biologic.

Patients could not receive more than 1 biologic of interest on the index date or any biologic dose greater than twice the approved maximum dose. To limit the analysis to patients newly initiating biologic therapy, patients were required to have no claim for any biologic of interest in the 180-day preindex period (ie, before the first claim for their index biologic). Patients were excluded from the analysis if during the preindex period they had any of the following conditions that are indications for at least 1 biologic of interest: psoriasis, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, ulcerative colitis, Crohn disease, non-Hodgkin lymphoma, or chronic lymphocytic leukemia. Patients were excluded from the analysis if they had either no cost in the claims line for a biologic of interest or an inappropriate source of claims (eg, J-code for a self-administered biologic or a prescription claim for an intravenously administered biologic).

Study approval by an institutional review board and collection of informed consent from patients were not necessary for this retrospective claims-based analysis. No identifiable protected health information was collected or used in this study.

### Treatment Patterns

Patients were considered persistent on the index biologic if they had no refill gap of more than 45 days and did not switch to another biologic. This refill gap was selected based on the most common

## TAKEAWAY POINTS

We examined treatment persistence (no refill gap >45 days) and total healthcare costs among nearly 7500 commercially insured patients in the United States who initiated treatment with a biologic for rheumatoid arthritis (abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, or tocilizumab) between January 2009 and November 2014. Mean 1-year total healthcare costs per patient were \$41,901 among persistent patients and \$44,244 among switchers. Switchers had 5% higher postindex costs on average than persistent patients.

- ▶ Patients with rheumatoid arthritis often switch from one biologic to another for either medical or nonmedical reasons.
- ▶ Switching biologics is associated with higher costs than persistence on treatment.

prescription period (30 days) plus 15 days, to avoid misclassification of patients who had a break in therapy but were persistent on treatment. The refill gap began at the end of the expected benefit of the prior dose. Thus, for a subcutaneous biologic, a refill gap started at the end of the reported days of supply in the most recent pharmacy claim. For an infusible biologic, the days of coverage for the most recent medical claim were calculated from the approved dosing schedule, and the refill gap started after the days of coverage ended. Patients were considered to have switched treatment if a nonindex biologic was initiated within 1 year post index. To be included in the postswitch analysis, patients needed to be continuously enrolled for at least 365 days after the switch. Patients with a refill gap of more than 45 days could either restart the same biologic after the treatment gap or discontinue the biologic without restarting the same biologic or switching to another biologic within 1 year post index.

### Costs

Total healthcare costs were reported as the sum of plan-paid and patient-paid costs (ie, coinsurance, deductible, and co-payment) for inpatient hospitalizations, emergency department (ED) visits, outpatient services, and pharmacy costs. Costs for inpatient stays, ED visits, and outpatient services were identified from medical claims and could include costs incurred in these settings for infusion or administration of infusible biologics (eg, abatacept, infliximab, rituximab, and tocilizumab). Pharmacy costs included prescription fills from pharmacy claims, including subcutaneous biologics (eg, adalimumab, certolizumab pegol, etanercept, and golimumab) and medications for other conditions in pharmacy claims. Total healthcare costs and biologic costs were adjusted to 2015 US\$ based on Consumer Price Index information provided by the Bureau of Labor Statistics.<sup>48</sup>

### Statistical Methods

Analyses of 1-year total healthcare costs were performed post index among all patients and post switch among switchers. A nonparametric Wilcoxon test was conducted to compare postindex costs for persistent patients with postswitch costs for switchers. A multivariable analysis of factors associated with 1-year postindex total healthcare costs was performed using a generalized linear

**TABLE 1.** Patient Attrition

Reason for Attrition	Patients Remaining	
	n	%
Inclusion criteria		
≥1 RA-related biologic <sup>a</sup> claims during identification period	105,325	
Continuously enrolled ≥180 days preindex	94,862	90.1%
Aged 18-63 years on index date	73,446	69.7%
Continuously enrolled ≥365 days post index <sup>b</sup>	53,789	51.1%
≥1 diagnosis claims for RA ≤180 days preindex <sup>b</sup>	21,183	20.1%
Biologic claim date after FDA approval date	21,183	20.1%
Exclusion criteria		
>1 RA-related biologic claim on index date	21,182	20.1%
Any RA-related biologic exposure preindex	9677	9.2%
Another biologic indication <sup>c</sup> preindex	7906	7.5%
Inappropriate source of claims <sup>d</sup>	7669	7.3%
More than twice the approved maximum dose for any indication	7529	7.1%
Zero cost in claims line for a biologic of interest	7468	7.1%

RA indicates rheumatoid arthritis.

<sup>a</sup>Abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, or tocilizumab.

<sup>b</sup>Including the index date.

<sup>c</sup>Psoriasis, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, ulcerative colitis, Crohn disease, non-Hodgkin lymphoma, or chronic lymphocytic leukemia.

<sup>d</sup>A Healthcare Common Procedure Coding System J-code for a self-administered biologic or a prescription claim for an intravenously administered biologic.

model with gamma distribution and log link. Covariates were treatment pattern, index biologic, age, sex, insurance plan type, geographic region, comorbidities, preindex total healthcare costs (all-cause and RA-related), and physician specialty. A separate multivariable analysis of factors associated with 1-year postswitch total healthcare costs used the same methods, but only in the patients who switched biologics.

## RESULTS

### Study Population

Overall, 7468 eligible patients were identified from a sample of 105,325 patients who received at least 1 biologic during the identification period (Table 1). Patient eligibility criteria that resulted in attrition of more than 50% of possible patients were the absence of any diagnosis claim for RA in the preindex period (an inclusion criterion to identify use of the biologic for RA) and any biologic use in the preindex period (an exclusion criterion to identify new biologic use). The mean (SD) age of the study population was 48.8 (10.1) years, and 76.0% of patients were women. Other demographic characteristics, including health plan type, geographic region, and prescribing physician specialty, are summarized in Table 1.

During the 1-year postindex period, 45.2% of patients were persistent on the index biologic, 23.2% discontinued the index

biologic, 16.7% switched to another biologic, and 15.0% restarted the index biologic after a refill gap of more than 45 days ( $P < .001$  across treatment patterns). Statistically significant differences across the cohorts of patients by treatment pattern were observed for each of the demographic characteristics (Table 2).

### Costs

Mean postindex total healthcare costs per switcher were \$43,204 (95% CI, \$41,572-\$44,835). Mean 1-year total healthcare costs per patient were \$41,901 (95% CI, \$40,855-\$42,947) for the first year post index among persistent patients and \$44,244 (95% CI, \$40,820-\$47,668) for the first year post switch among switchers ( $P = .006$ ) (Figure). Among persistent patients, mean 1-year total healthcare costs post index per patient ranged from \$37,638 (95% CI, \$36,783-\$38,494) for etanercept to \$73,202 (95% CI, \$37,950-\$108,455) for tocilizumab. Among switchers, mean 1-year postswitch total healthcare costs per patient ranged from \$41,183 (95% CI, \$38,807-\$43,558) for etanercept to \$57,080 (95% CI, \$35,310-\$78,849) for certolizumab pegol.

In the multivariable analysis of postindex 1-year total healthcare costs that adjusted for other factors (Table 3), patients who switched to another biologic had 5% higher costs, on average, than persistent patients ( $\exp(\beta) = 1.05$ ; 95% CI, 1.01-1.08;  $P = .015$ ). Compared with etanercept, other biologics were associated with 3% to 51% higher postindex costs. Patients in the southern United States had 5% lower postindex costs than patients in the western United States. Compared with patients with RA without a comorbid condition, postindex costs were higher among patients with comorbid hypertension (11% higher;  $P < .001$ ), asthma (10% higher;  $P < .001$ ), neutropenia (27% higher;  $P = .010$ ), or depression (15% higher;  $P < .001$ ). Patients who were treated by a nonrheumatologist had 5% lower postindex costs than those who were treated by a rheumatologist.

A separate multivariable analysis was conducted in the subset of biologic switchers to examine baseline predictors for 1-year total healthcare costs after the switch (Table 4). After adjusting for other factors, starting on etanercept was associated with significantly lower postswitch costs than starting on abatacept (23% higher postswitch costs;  $P = .036$ ), certolizumab pegol (39% higher;  $P = .025$ ), or infliximab (21% higher;  $P = .009$ ). Men had 20% higher postswitch costs than women ( $P < .001$ ). Patients in the northeastern United States had 18% higher postswitch costs than patients in the western United States ( $P = .018$ ). Patients treated by a nonrheumatologist had 11% higher postswitch costs than patients who were treated by a rheumatologist ( $P = .034$ ).

**TABLE 2.** Demographic Characteristics

Characteristics	Total	Discontinued	Persistent	Switched	Restarted	P <sup>a</sup>
Total patients, n (%)	7468	1731 [23.2%]	3372 [45.2%]	1246 [16.7%]	1119 [15.0%]	<.001
Age (years), mean ± SD	48.8 ± 10.1	48.8 ± 10.3	49.5 ± 9.7	48.1 ± 10.2	47.8 ± 10.5	<.001
Sex, female, n (%)	5679 [76.0%]	1352 [78.1%]	2474 [73.4%]	986 [79.1%]	867 [77.5%]	<.001
Plan type, n (%)						
HMO	1644 [22.0%]	401 [23.2%]	731 [21.7%]	274 [22.0%]	238 [21.3%]	<.001
PPO	5042 [67.5%]	1146 [66.2%]	2288 [67.9%]	836 [67.1%]	772 [69.0%]	
Other	782 [10.5%]	184 [10.6%]	353 [10.5%]	136 [10.9%]	109 [9.7%]	
Geographic region, n (%)						
Northeast	1063 [14.2%]	260 [15.0%]	463 [13.7%]	172 [13.8%]	168 [15.0%]	<.001
Midwest	2210 [29.6%]	521 [30.1%]	1059 [31.4%]	342 [27.4%]	288 [25.7%]	
South	2554 [34.2%]	576 [33.3%]	1142 [33.9%]	450 [36.1%]	386 [34.5%]	
West	1641 [22.0%]	374 [21.6%]	708 [21.0%]	282 [22.6%]	277 [24.8%]	
Prescribing physician, n (%)						
Rheumatology	5412 [72.5%]	1173 [67.8%]	2488 [73.8%]	968 [77.7%]	783 [70.0%]	<.001
Family/general practice	40 [0.5%]	17 [1.0%]	11 [0.3%]	4 [0.3%]	8 [0.7%]	
Internal medicine	182 [2.4%]	43 [2.5%]	83 [2.5%]	25 [2.0%]	31 [2.8%]	
Dermatology	2 [0.0%]	1 [0.1%]	1 [0.0%]	0 [0.0%]	0 [0.0%]	
Other	678 [9.1%]	215 [12.4%]	261 [7.7%]	75 [6.0%]	127 [11.3%]	
Unknown	1154 [15.5%]	282 [16.3%]	528 [15.7%]	174 [14.0%]	170 [15.2%]	

HMO indicates health maintenance organization; PPO, preferred provider organization.

<sup>a</sup>P value for the comparison across treatment patterns.

**Discussion**

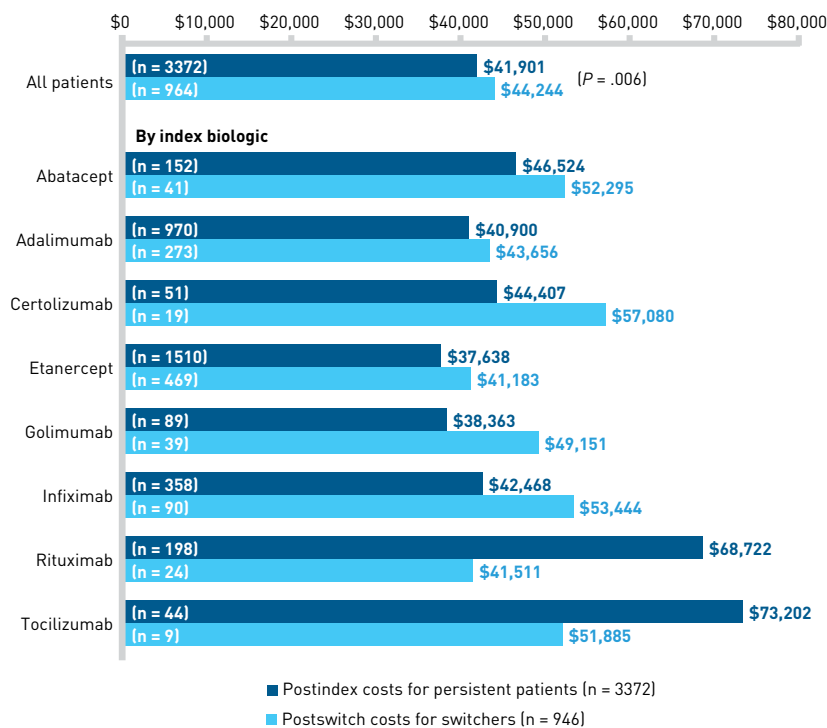
In this analysis of treatment patterns and costs among nearly 7500 commercially insured patients with RA in the United States who initiated biologic therapy, 1 in 6 patients (16.7%) switched to a different biologic within the first year. Nearly half of the patients (45.2%) were persistent on their newly initiated biologic therapy without a refill gap of more than 45 days in the first year. For all index biologics combined, 1-year total healthcare costs were lower for the first year after treatment initiation among patients who were persistent on therapy compared with the 1-year total healthcare costs for the first year after patients switched biologic therapy. Patients who switch treatment may have higher costs both because they must visit a prescriber to switch the medication and because the new medication may require loading doses.

Previous studies examining biologic treatment persistence in patients with RA have used a variety of methods, which may explain why a systematic review of 52 studies reported rates of treatment persistence at 12 months ranging from 32% to 91%.<sup>8</sup> Moreover, limited data are available specifically comparing costs between patients who were persistent on the index biologic therapy and those who switched biologic therapy. One study examined a smaller cohort of 474 patients with RA in Italy who received TNFi therapy with adalimumab, etanercept, or infliximab.<sup>46</sup> Biologic use in the last 3 months of the first year post index was used to identify patients

who were persistent (the same biologic at baseline) or switched (a different biologic at baseline). Rates of biologic switching in that study (18% for adalimumab, 15% for infliximab, and 11% for etanercept) were similar to the biologic switching rate in our study, despite the use of a different method to analyze switching, and treatment costs were higher for patients who switched biologics in the first year than for patients who did not switch (€12,710 vs €11,332). Notably, 47% of patients in the Italian cohort received another biologic in the preindex period. In our study, we included only patients with no biologic use in the preindex period to examine treatment patterns and costs in the first year after starting biologic therapy. Our analysis also examined treatment patterns and 1-year total healthcare costs associated with other biologics that are approved for the treatment of RA, including both TNFi and non-TNFi biologics.

Three studies compared costs between persistent and nonpersistent patients but did not examine costs separately among biologic switchers. In the first study, after initiation of a subcutaneous TNFi (adalimumab, etanercept, certolizumab pegol, or golimumab), 55% to 58% of patients were persistent on the TNFi at 12 months, and nonbiologic healthcare costs in the first year after initiation were significantly lower among persistent patients than nonpersistent patients.<sup>49</sup> In the second study, patients who received TNFi therapy with adalimumab, etanercept, or infliximab reported lower costs among persistent patients than nonpersistent patients.<sup>50</sup> In the

**FIGURE.** Mean 1-Year Total Healthcare Costs Per Patient Among Persistent Patients (postindex costs) and Those Who Switched Biologics (postswitch costs)<sup>a</sup>



<sup>a</sup>Costs were adjusted to 2015 US\$. The number of switchers decreased from 1119 to 964, because some switchers did not have 12 months of continuous enrollment after the switch date. A nonparametric Wilcoxon test was conducted to compare postindex total costs of persistent patients with postswitch total costs of switchers. Postswitch costs did not include the cost of the index biologic before the switch.

third study, greater persistence on TNFi therapy with adalimumab, etanercept, or infliximab was associated with lower nonmedication costs.<sup>51</sup> Because these studies did not examine costs among patients who switched to another biologic, it is not possible to compare the results of our study directly with those of the previous studies, but they support the finding in our study that treatment nonpersistence is associated with higher healthcare costs than treatment persistence in RA.

Among both persistent patients and switchers in this study, patients who initiated biologic therapy with etanercept had lower 1-year total healthcare costs than patients who initiated therapy with another biologic. Several previous studies have also found that in the treatment of RA or other inflammatory conditions, etanercept was associated with lower medication or total healthcare costs than other biologics, particularly when compared with infused biologics,<sup>21-30,43,52-57</sup> but other studies have reported conflicting findings.<sup>11,32,33,58</sup> These studies varied widely in the methods used to assess costs. Some studies examined only medication costs,<sup>11,26-30,43,52-56</sup> whereas others examined total healthcare costs.<sup>21-25,57</sup> Our study included all patient-paid and plan-paid amounts to examine total healthcare costs,

inclusive of biologics, to assess the overall economic impact of initiating, persisting, and switching biologic treatment in RA.

This was a retrospective, claims-based analysis that did not randomize patients to treatment or stratify patients by baseline characteristics. Patients who switched biologic therapy were younger, more likely to be women, and more likely to be treated by a rheumatologist than the patients who were persistent on the index biologic. To adjust for these baseline differences, multivariable analyses of costs were conducted that included age, sex, and physician specialty among the variables. In the multivariable analysis of postindex costs among all patients, switching therapy was associated with significantly higher healthcare costs in the first year than persistence on the index biologic. Patients who initiated biologic therapy with etanercept continued to have lower healthcare costs in the first year compared with patients who initiated therapy with another biologic. Patients in the southern United States had lower healthcare costs than patients in the western United States, which may reflect differences in healthcare utilization in these regions. Patients treated by nonrheumatologists had lower healthcare costs than patients treated by rheumatologists, which may be attributable to increased referral of more severe cases from nonrheumatologists

to rheumatologists.<sup>59</sup> This hypothesis is supported by the finding that patients with greater comorbidity at baseline also had higher costs than patients with isolated RA in this study.

The multivariable analysis of 1-year total healthcare costs after switching biologic therapy was conducted in the subset of 964 patients who switched biologics and provided 12 additional months of data after the switch. Starting with etanercept as the index biologic was associated with significantly lower postswitch costs than starting biologic therapy with abatacept, certolizumab pegol, or infliximab. After adjustment for other variables, patients whose index biologic was adalimumab, golimumab, tocilizumab, or rituximab did not have significantly different postswitch costs compared with patients whose index biologic was etanercept. The total healthcare costs included the drug costs for biologic therapy after the switch but did not include costs before the switch date. This led to potentially confusing results for predicting postswitch costs based on the index biologic. In the multivariable analysis of postindex costs, rituximab and tocilizumab were associated with 51% and 17% higher postindex healthcare costs, respectively, than etanercept. In the multivariable analysis of postswitch costs,

**TABLE 3.** Postindex Costs: Generalized Linear Model for 1-Year Total Healthcare Costs

Variable	Exp(β)	95% CI	P
Treatment pattern (ref: persistence)			
Discontinued	0.76	0.74-0.79	<.001
Switch	1.05	1.01-1.08	.015
Restart	0.83	0.80-0.86	<.001
Index biologic (ref: etanercept)			
Abatacept	1.15	1.08-1.23	<.001
Adalimumab	1.03	1.00-1.06	.096
Certolizumab pegol	1.09	1.00-1.20	.054
Golimumab	1.07	1.00-1.16	.054
Infliximab	1.16	1.11-1.22	<.001
Rituximab	1.51	1.43-1.59	<.001
Tocilizumab	1.17	1.05-1.31	.004
Age	1.01	1.01-1.01	<.001
Sex, male (ref: female)	1.02	0.99-1.05	.111
Plan type (ref: other)			
HMO	0.98	0.93-1.03	.391
PPO	0.98	0.94-1.03	.473
Region (ref: West)			
Northeast	0.99	0.95-1.04	.704
Midwest	0.98	0.95-1.02	.395
South	0.95	0.92-0.99	.007
Comorbidities (ref: none)			
Cardiovascular disease	1.07	0.98-1.16	.116
Hypertension	1.11	1.08-1.15	<.001
Asthma	1.10	1.05-1.16	<.001
Neutropenia	1.27	1.06-1.53	.010
Depression	1.15	1.10-1.20	<.001
Anxiety	0.99	0.94-1.04	.696
Preindex total healthcare costs (\$1000)	1.01	1.01-1.01	<.001
Physician specialty (ref: nonrheumatology)	0.95	0.93-0.98	.002

HMO indicates health maintenance organization; PPO, preferred provider organization; ref, reference.

switching from rituximab or tocilizumab to another biologic was not associated with significantly higher costs after the switch as compared with switching from etanercept to another biologic. A likely explanation is that patients who initiated costly treatment with rituximab or tocilizumab switched to a less costly biologic, resulting in lower postswitch costs, but this study was not designed to examine costs across all possible combinations of biologic switching. Additionally, the small number of analyzed patients who switched from rituximab (n = 24) or tocilizumab (n = 9) to another biologic complicated the interpretation of these results.

**TABLE 4.** Postswitch Costs: Generalized Linear Model for 1-Year Total Healthcare Costs

Variable	Exp(β)	95% CI	P
Index biologic (ref: etanercept)			
Abatacept	1.23	1.01-1.50	.036
Adalimumab	1.06	0.97-1.17	.180
Certolizumab pegol	1.39	1.04-1.84	.025
Golimumab	1.18	0.96-1.45	.116
Infliximab	1.21	1.05-1.39	.009
Rituximab	0.77	0.59-1.00	.052
Tocilizumab	0.79	0.52-1.20	.274
Age	1.01	1.00-1.01	<.001
Sex, male (ref: female)	1.20	1.09-1.33	<.001
Plan type (ref: other)			
HMO	0.85	0.73-0.99	.040
PPO	0.80	0.71-0.92	.001
Region (ref: West)			
Northeast	1.18	1.03-1.36	.018
Midwest	1.00	0.89-1.12	.986
South	0.92	0.82-1.02	.114
Comorbidities (ref: none)			
Cardiovascular disease	0.83	0.60-1.15	.273
Hypertension	1.08	0.98-1.18	.126
Asthma	1.06	0.90-1.24	.484
Neutropenia	1.03	0.31-3.42	.967
Depression	0.94	0.83-1.07	.365
Anxiety	0.96	0.84-1.11	.597
Preindex total healthcare costs (\$1000)	1.01	1.01-1.02	<.001
Physician specialty (ref: nonrheumatology)	1.11	1.01-1.23	.034

HMO indicates health maintenance organization; PPO, preferred provider organization; ref, reference.

Several previous analyses also reported substantially greater use of etanercept, adalimumab, or infliximab compared with other biologics for the treatment of RA during the period covered by this analysis,<sup>11,33,54,58</sup> so the smaller sample sizes for other biologics in this analysis were expected, which suggests that the results were applicable to typical clinical practice.

**Limitations**

This analysis included only commercially insured patients, and the results might not be applicable to patients with Medicare or Medicaid

coverage. Administrative claims data may not reflect treatment adherence, particularly if a subcutaneous biologic is dispensed but not administered.<sup>60</sup> Claims data do not include information on the reason for a change in therapy, which may include both medical and nonmedical reasons. For example, formularies may influence biologic therapy choices for nonmedical reasons, but the administrative claims database did not include information about formularies. Among the medical reasons, disease progression was a likely contributor to switching therapy, but administrative claims also do not include direct measures of disease severity. Patients with more severe disease at baseline probably were more likely to fail the initial therapy and require a switch in biologic therapy post index. Thus, patient characteristics that were not available from the administrative claims database may have contributed to the higher costs among patients who switched biologic therapy. However, the significant association between switching biologic therapy and healthcare costs was maintained in generalized linear models that adjusted for other significant differences at baseline. Healthcare costs and treatment persistence were measured for 1 year, which is a standard approach for economic analyses of commercially insured patients, but differences in treatment persistence across biologics may not be evident until more than 12 months after initiation of therapy.<sup>49</sup> Treatment persistence was based on a 45-day treatment gap from the end of the expected benefit for the prior dose, which accounted for different dosing schedules for biologic therapy. However, a 45-day gap could be more meaningful for a once-weekly medication (6 doses missed) than for a medication that is administered every 2 weeks (3 doses missed) or once monthly (1 dose missed). Treatment patterns after the initial switch were not analyzed among biologic switchers and may be an area for additional research. This analysis did not examine the effect of biologic dose escalation on costs; a patient whose dose was escalated during the first year but had no treatment gaps and did not switch to another biologic was considered persistent on the initial biologic. Previous studies have established that dose escalation differs among biologics,<sup>61-64</sup> contributing to higher costs for biologics that require dose escalation.<sup>22,25,27</sup>

## CONCLUSIONS

Patients who switched biologic therapy incurred higher 1-year total healthcare costs compared with patients who were persistent on the newly initiated biologic for at least 1 year. Of all biologics approved for RA, starting on etanercept and persisting on etanercept were associated with the lowest costs. ■

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