Impact of Switching From an Initial Tumor Necrosis Factor Inhibitor on Health Care Resource Utilization and Costs Among Patients With Rheumatoid Arthritis

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ABSTRACT

Purpose: Despite improved clinical outcomes for the majority of patients, nearly 30% of patients with rheumatoid arthritis (RA) who initiate tumor necrosis factor antagonist (anti-TNF) biologic agents fail to respond to their first-line anti-TNF and switch to another anti-TNF or a non-TNF biologic. How this change affects health care costs and resource utilization is unknown. We therefore compared RA patients taking first-line anti-TNFs who switched to a second anti-TNF versus those patients who switched to an alternate biologic.

Methods: Health care claims data were obtained from a large US database for eligible adults with confirmed RA diagnoses who initiated anti-TNF treatment and switched to another biologic. Health care costs and utilization during the first 12 months' postswitch were compared. Generalized linear models were used to adjust for differences in demographic and clinical characteristics before switching.

Findings: Patients who switched to a second anti-TNF rather than a non-TNF biologic were generally younger (53.0 vs. 55.3 years; $P < 0.0001$) and less likely to be female (79.7% vs. 82.7%; $P = 0.0490$). Of the 3497 eligible patients who switched from first-line anti-TNFs, 2563 (73.3%) switched to another anti-TNF and 934 (26.7%) switched to a non-TNF. Adalimumab was the most frequently prescribed (43.4%) second-line anti-TNF, and abatacept was the most common non–anti-TNF (71.4%). Patients who switched to a second anti-TNF remained on their first medication for a significantly shorter period (342.5 vs 420.6 days; $P < 0.0001$) and had lower comorbidity indices and higher disease severity at baseline than those who switched to a non–anti-TNF. After adjusting for baseline differences, patients who switched to second anti-TNFs versus a non-TNF incurred lower RA-related costs ($20,938.9 vs $22,645.2; $P = 0.0010$) and total health care costs ($34,894.6 vs $38,437.2; $P = 0.0010$) 1 year postswitch. These differences were driven by increased physician office visit costs among the non-TNF group.

Implications: Among the anti-TNF initiators who switched therapy, more patients switched to a second anti-TNF than to a non-TNF. Switching to a second anti-TNF treatment was associated with lower all-cause and RA-related health care costs and resource utilization than switching to a non-TNF. Because switching therapy may be unavoidable, finding a treatment algorithm mitigating this increase to any extent should be considered. These data are limited by their retrospective design. Additional confounding variables that could not be controlled for may affect results. (*Clin Ther*. 2015;37:1454–1465)

Key words: health care costs, health care utilization, rheumatoid arthritis, real-world data analysis.

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disorder causing joint pain and swelling that progresses to joint tissue and bone destruction.[1] The prevalence of RA is estimated at 1.5 million adults in the United States, which has significant economic implications for both individual patients and society.[2] Each year, RA is

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responsible for >250,000 hospitalizations and >9 million physician visits in addition to a decrease in life expectancy of 3 to 10 years.[3,4] Moreover, excess health care costs for patients with RA in the United States have been estimated at $8.4 billion annually, with an additional $10.9 billion lost due to functional and work limitations (prices in 2005 US dollars).[5] Appropriate pharmacy and medical policies for the management of patients with RA based on clinical and economic data are imperative for improving patient outcomes while controlling health care costs at the population level.

In the past decade, tumor necrosis factor antagonist (anti-TNF) use has changed the treatment paradigm, with improved clinical outcomes for RA patients with moderate to severe disease.[6] Anti-TNF combination therapy with methotrexate (MTX) has been shown to be a cost benefit, compared with conventional disease-modifying antirheumatic drug therapy, and has demonstrated slowing of radiographic progression.[7] However, nearly 30% of patients with RA fail to respond to their first anti-TNF agent or experience adverse events by 2 years of therapy.[8] Subsequent therapeutic options include switching to another anti-TNF or to a non-TNF biologic agent.

The availability of multiple biologic agents has engendered the question of whether switching to a different TNF inhibitor versus switching to a non-TNF biologic will lead to different clinical and economic outcomes after failure to respond to the initial anti-TNF. Several managed-care medical policies require treatment with at least 2 TNF inhibitors before switching to an alternate biologic agent.[9] These policies are based on the results of controlled clinical trials and observational studies that have shown benefit for a number of patients who failed to respond to initial anti-TNF therapy and who switched to another TNF inhibitor.[10–13] In these studies, patients were more likely to respond to a subsequent anti-TNF agent if previous anti-TNF treatment was discontinued because of adverse reactions.[14,15] Although there are controlled clinical trials evaluating the efficacy and safety of non-TNF biologic agents in patients who have failed to respond to anti-TNF therapy, there are few head-to-head studies that directly compare switching to a second anti-TNF versus switching to a non-TNF biologic agent.[16–18]

A recent study of observational data from the Consortium of Rheumatology Researchers of North America, Inc. (CORRONA) RA registry, which enrolls RA patients from private and academic institutions across the United States, found that clinical outcomes after a switch from one TNF inhibitor to a second TNF inhibitor were similar to those observed when switching to abatacept (ABA).[19] Although this study evaluated clinical outcomes in an observational setting, an economic evaluation was not conducted. The latter is an important issue because the cost-effectiveness associated with switching to a second-line biologic agent is poorly defined, although studies have shown that, after a switch in treatment, patients incur higher costs compared with those who do not switch.[20,21] It is possible that both clinical and economic evaluation of biologic switching may guide policy development to ensure this disabling disease is controlled at the population level while managing overall health care costs.

The objective of the present study, therefore, was to evaluate the impact on health care costs and resource utilization of switching from a first-line anti-TNF therapy to a second biologic agent. We also examined whether there was a differential impact on cost and resource utilization associated with switching to a second anti-TNF agent compared with switching to a non-TNF antagonist.

PATIENTS AND METHODS

Data Source

The Truven Health MarketScan Commercial Claims and Encounters Database and the Medicare Supplemental and Coordination of Benefits database from January 2004 through December 2010 were used in this retrospective study. These databases capture the full continuum of care in all settings, including physician office visits, inpatient stay, emergency department (ED) visits, and retail, mail order, and specialty pharmacy claims, as well as patient demographic and enrollment information.

Study Sample

Adult patients at least 18 years of age with at least 2 physician-confirmed diagnoses of RA (*International Classification of Diseases, Ninth Revision, Clinical Modification*, code: 714.0X) at least 2 months apart during the identification period (January 2005–December 2009) were selected.[22] Patients were required to have an initial prescription claim for an anti-TNF biologic (etanercept [ETN], adalimumab [ADA], or infliximab [IFX]) after RA diagnosis and a subsequent switch to another anti-TNF (ETN, ADA, IFX, golimumab, or certolizumab) or non-TNF biologic (ABA, anakinra [ANK], or rituximab). Tocilizumab,

approved in January 2010, was not included in this study.

Patients were considered to have switched therapy if they had been prescribed another anti-TNF or non-TNF biologic agent without successive claims of the initial biologic agent. A minimum 12-month biologic-free period was required before the first anti-TNF agent. In addition, all patients in this study were required to have at least 12 months of continuous medical and pharmacy benefits before the first anti-TNF claim date and for 12 months after the switch date. The switch date was designated as the index date. All baseline variables were calculated for the 12 months before the index date (baseline period), and outcome variables were calculated for the 12 months after the index date (follow-up period).

Informed Consent

No patient identity or medical records were disclosed for the purposes of this study except in compliance with applicable law. Because the core study proposed herein does not involve the collection, use, or transmittal of individual identifiable data, patient approval/consent to conduct this study was not required.

Cohort Assignments

To compare patients who switched to another anti-TNF biologic versus those who switched to a non–anti-TNF biologic, 2 cohorts were created. The anti-TNF biologic switcher cohort consisted of patients who initiated ETN, ADA, or IFX and later switched to ETN, ADA, IFX, golimumab, or certolizumab. The non-TNF biologic switcher cohort was composed of patients who initiated ETN, ADA, or IFX and later switched to ABA, anakinra, or rituximab.

Baseline Covariates

Demographic variables included age, sex, geographic region, index year, and health plan type. Baseline comorbidity measures included the Charlson Comorbidity Index (CCI) score,[23,24] Chronic Disease Score,[25] binary indicator of Elixhauser index score >2,[26] individual comorbidities such as scleroderma, fibromyalgia, Crohn's disease, respiratory disease, respiratory infection, and baseline Severity Index for Rheumatoid Arthritis (SIFRA; STATinMED Research, Ann Arbor, MI) score.[27] SIFRA was developed by calculating a weighted sum of 34 RA-related indicators, including clinical and functional status, extra-articular manifestations, surgical history, and medications, assessed by an expert Delphi panel of 6 rheumatologists.[28] Higher SIFRA scores indicate increased disease severity, and the Elixhauser index has shown evidence of being a significant determinant of total and RA-related health care costs for patients with RA.[26]

Other baseline measures included RA-related treatments such as NSAIDs, corticosteroids, xenobiotics, MTX, and cytotoxic therapy. Baseline health care costs (including total all-cause pharmacy, knee and hip replacement surgery, laboratory tests, hospitalization, and ED and physician office visit costs) were also measured. Physician prescribing patterns were calculated as the percentage of times the first-line anti-TNF biologic agent was prescribed. Days from the first anti-TNF claim to the index date were calculated to determine the time to therapy switch.

Outcome Variables

Total all-cause health care costs, in addition to those associated with pharmacy, knee and hip replacement surgery, laboratory tests, hospitalization, and ED and physician office visits, were calculated for the 12-month follow-up period. Total RA-related health care costs were calculated by using medical claims with an RA diagnosis claim in any position. RA-related pharmacy costs were calculated for anti-TNF, NSAIDs, corticosteroid, xenobiotic, cytotoxic therapy, and MTX pharmacy claims. Health care costs were calculated on the basis of the amount paid by the health care plan for relevant claims and the net cost of any patient contribution (eg, copayment). Costs are expressed in 2012 US dollars and were adjusted by using the medical care component of the US Consumer Price Index. For health care utilization estimates, the number and binary indicator of hospitalizations, ED visits, and physician office visits were calculated for the follow-up period. The follow-up period SIFRA score, which was validated by using a large claims database,[27] was used to measure disease severity.

Statistical Analysis

Descriptive and bivariate analyses were performed for the anti-TNF and non-TNF switcher cohorts for baseline and outcome variables. Percentages and SDs were calculated for dichotomous variables, and means and SDs were calculated for continuous variables.

P values were generated by using the χ^2 test and Student *t* test for dichotomous and continuous variables, respectively.

Multivariate analysis was performed by using a generalized linear model, in which log link and gamma distributions were used for cost outcomes, negative binomial distribution was used for count variables (eg, number of health care utilization visits), and logistic distribution was used for binary outcomes (eg, having at least 1 visit). Variables included in the model were age, sex, geographic region, health care plan type, index year, index copay, baseline CCI score, Chronic Disease Score, Elixhauser index score, other individual comorbidities, physician prescribing patterns, baseline RA therapies, and health care utilizations and costs. Descriptive and multivariate results were compared between the anti-TNF biologic switcher cohort and the non-TNF biologic switcher cohort.

RESULTS

A total of 234,483 patients were identified for inclusion in the study during the identification period (January 2005–December 2009). Of these, 3497 patients met inclusion criteria for the final study sample, with 44.0% (n = 1540) initiating treatment with ETN, 36.2% (n = 1265) with ADA, and 19.8% (n = 692) with IFX. Within this population, 2563 patients (73.3%) switched to a second anti-TNF biologic, and 934 patients (26.7%) switched to a non-TNF biologic (Figure 1).

Among the 1540 patients who initiated ETN, 81.6% (n = 1257) switched to another anti-TNF biologic, most commonly ADA (74.9% [n = 942]). Similarly, 77.2% (n = 976) of the 1265 patients who initiated therapy with ADA switched to another anti-TNF biologic, of which ETN (67.1% [n = 655]) was the most common. Patients who initiated therapy with IFX (n = 692) were more likely to switch to a non-TNF biologic (52.3% [n = 362]). ADA was the most frequently prescribed second anti-TNF agent (43.4% [n = 1111]) among patients switched to an anti-TNF (n = 2563). ABA was the most common non-TNF biologic prescribed (71.4% [n = 667]) among patients switched to a non-TNF biologic (n = 934) (Figure 2).

Baseline Demographic and Clinical Characteristics

Patients who switched to a second anti-TNF rather than a non-TNF biologic were generally younger (53.0 vs 55.3 years; $P < 0.0001$) and less likely to be female (79.7% vs 82.7%; $P = 0.0490$) (Table I). The time to switch from one anti-TNF to another was shorter compared with switching to a non-TNF biologic (342.5 vs 420.6 days; $P < 0.0001$). In addition, patients who switched to a second anti-TNF were more likely to have an initial prescription for ETN (49.0% vs 30.3%; $P < 0.0001$) or ADA (38.1% vs 30.9%; $P = 0.0001$) than IFX (12.9% vs 38.8%; $P < 0.0001$), compared with those who switched to a non-TNF biologic (Table II).

During the baseline period, patients who switched to a second anti-TNF compared with a non-TNF biologic had higher SIFRA scores (4.5 vs 4.3; $P = 0.0004$), lower CCI scores (2.0 vs 2.5; $P < 0.0001$), and a lower percentage with Elixhauser index scores >2 (14.6% vs 20.9%; $P < 0.0001$) (Table II). In terms of RA-related medication and therapies, anti-TNF switchers were less likely to be prescribed corticosteroids (73.5% vs 76.9%; $P = 0.0436$) but more likely to be prescribed MTX (64.1% vs 57.4%; $P = 0.0003$) compared with non-TNF switchers.

The initial route of administration also played a significant role in the switching methods. Those who were initially taking a subcutaneous anti-TNF biologic (eg, ETN, ADA) were more likely to receive a subsequent anti-TNF agent. In contrast, those who were initially treated with an infused anti-TNF (IFX) were more likely to be treated with a non-TNF versus a second anti-TNF biologic (25.4% vs 23.7%; $P = 0.004$).

Baseline Health Care Costs

During the 12 months before switching therapy, anti-TNF biologic switchers incurred lower total health care costs than non-TNF biologic switchers ($23,088.4 vs $31,108.0; $P < 0.0001$). Of the cost categories evaluated, hospitalization ($2788.4 vs $6229.1; $P = 0.0003$), laboratory tests ($543.1 vs $656.6; $P = 0.0050$), pharmacy ($12,652.5 vs $13,747.7; $P = 0.0036$), and physician office visits ($1480.9 vs $1798.0; $P < 0.0001$) costs were lower in the anti-TNF group (Table III).

Risk-Adjusted Outcomes

After controlling for baseline demographic and clinical differences by using a generalized linear model, anti-TNF biologic switchers incurred significantly lower all-cause costs ($34,894.6 vs $38,437.2;

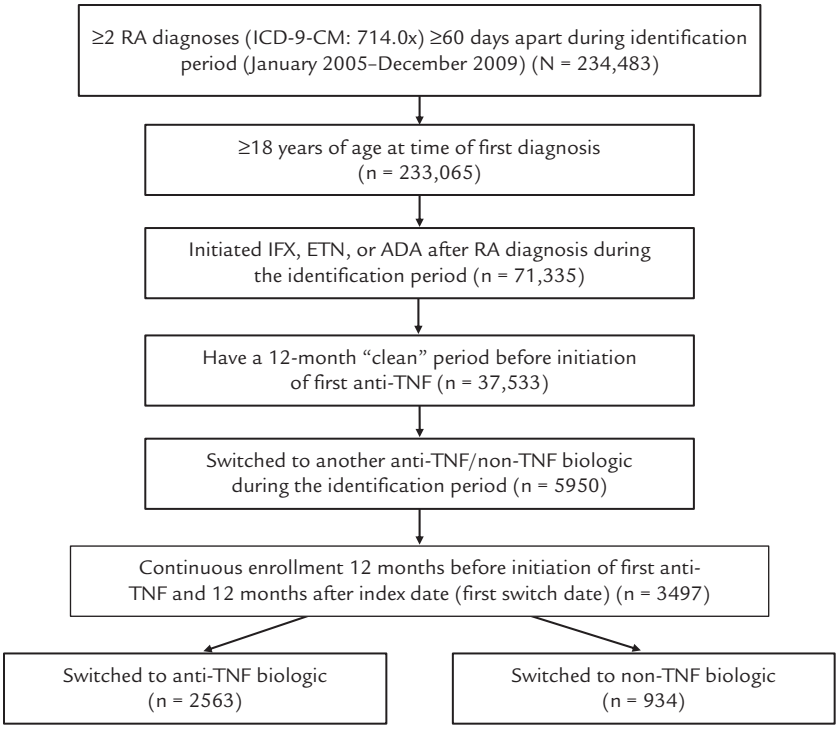

Figure 1. Subject identification. RA = rheumatoid arthritis; ICD-9-CM = *International Classification of Diseases, Ninth Revision, Clinical Modification*; IFX = infliximab; ETN = etanercept; ADA = adalimumab; TNF = tumor necrosis factor.

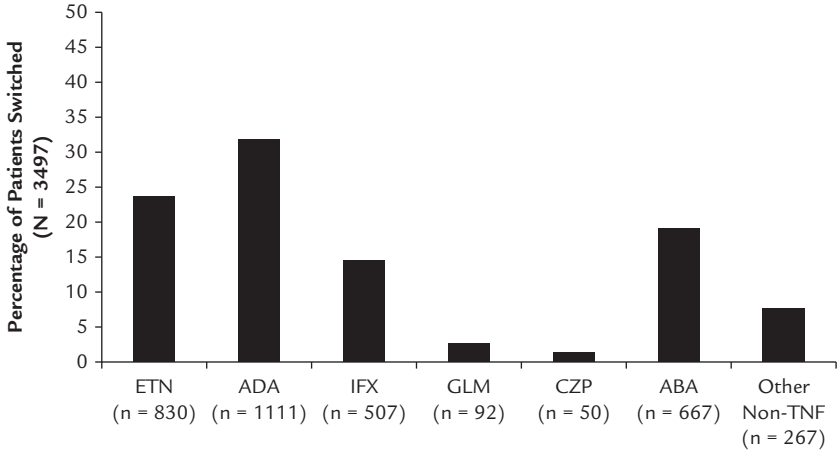

Figure 2. Patient switching pattern from first tumor necrosis factor antagonist (anti-TNF). ETN = etanercept; ADA = adalimumab; IFX = infliximab; GLM = golimumab; CZP = certolizumab pegol; ABA = abatacept.

Table I. Baseline demographic characteristics of tumor necrosis factor antagonist (anti-TNF) biologic switcher and non-TNF biologic switcher cohorts.

Characteristic	Anti-TNF Switcher Cohort (n = 2563)	Non-TNF Switcher Cohort (n = 934)	*P*
Age, y*	53.0 (12.1)	55.3 (12.7)	<0.0001
Female sex	2042 (79.7%)	772 (82.7%)	0.0490
Geographic region			
Northeast	237 (9.3%)	65 (7.0%)	0.0331
North-central	635 (24.8%)	251 (26.9%)	0.2069
South	1146 (44.7%)	438 (46.9%)	0.2515
West	533 (20.8%)	176 (18.8%)	0.2039
Unknown	12 (0.5%)	4 (0.4%)	0.8770
Years of trigger			
2005	99 (3.9%)	6 (0.6%)	<0.0001
2006	334 (13.0%)	96 (10.3%)	0.0283
2007	556 (21.7%)	177 (19.0%)	0.0779
2008	781 (30.5%)	358 (38.3%)	<0.0001
2009	793 (30.9%)	297 (31.8%)	0.6278
Time to switch, d*	342.5 (291.1)	420.6 (311.0)	<0.0001

*Mean (SD).

$P = 0.0010$) and RA-related health care costs ($20,938.9 vs $22,645.2; $P = 0.0010$) compared with non-TNF biologic switchers during the follow-up period (Figure 3).

Total pharmacy (including non-TNF, anti-TNF, and all outpatient pharmacy costs), knee and hip replacement surgery, hospitalization, laboratory tests, and ED visit costs were similar for anti-TNF biologic switchers and non-TNF biologic switchers. However, anti-TNF biologic switchers had fewer physician office visits (15.0 vs 19.3; $P < 0.0010$), which translated into lower associated costs ($1535.1 vs $1993.6; $P < 0.0010$) (Table IV). In addition, anti-TNF biologic switchers incurred significantly lower RA-related costs compared with non-TNF biologic switchers during the follow-up period.

DISCUSSION

Several studies have found that patients with RA who switch to a second biologic agent of any mechanism incur higher medical costs both before and after the switch compared with patients who continue treatment with their initial biologic agent.[20,21,29] One large retrospective claims analysis reported that baseline monthly health care costs were 27% higher for patients who switched first-line biologic therapy compared with nonswitchers.[21] This study also found that postswitching costs were increased by 35% for first-line biologic switchers versus nonswitchers, after controlling for potential confounders. Together, these data indicate that switching biologic therapy is associated with increased costs.

The present study found that numeric costs were higher in the 12 months after a switch from a TNF inhibitor to a non-TNF compared with a second anti-TNF. Although specific reasons for the switch were not evaluable in this study, switching patterns seemed to be based on the initial prescription. Of patients who were initiated on a self-injectable biologic (ADA or ETN), approximately three quarters were switched to another subcutaneously administered anti-TNF. However, 50% of those initiated on IFX were switched to an agent with an alternate mechanism of action. The difference in costs could not be explained by differences in patient characteristics at the time of the switch. Those switched to a non-TNF were more likely to be female, to be older, and to have more comorbidities than those who did not switch.

Table II. Clinical characteristics at point of switch of tumor necrosis factor antagonist (anti-TNF) and non-TNF biologic switcher cohorts.

Characteristic	Anti-TNF Switcher Cohort (n = 2563)	Non-TNF Switcher Cohort (n = 934)	*P*
Initial TNF			
ETN	1257 (49.0%)	283 (18.4%)	<0.0001
ADA	976 (38.1%)	289 (22.8%)	0.0001
IFX	330 (12.9%)	362 (52.3%)	<0.0001
SIFRA score*	4.5 (1.2)	4.3 (1.2)	0.0004
Baseline comorbidities			
Charlson Comorbidity Index score*	2.0 (1.4)	2.5 (1.9)	<0.0001
Elixhauser index score >2	375 (14.6%)	195 (20.9%)	<0.0001
Chronic Disease Score*	7.2 (3.6)	7.4 (3.7)	0.1178
Baseline comorbidities			
Scleroderma	4 (0.2%)	2 (0.2%)	0.7136
Fibromyalgia	221 (8.6%)	75 (8.0%)	0.5774
Crohn's disease	34 (1.3%)	6 (0.6%)	0.0923
Respiratory disease	1232 (48.1%)	513 (54.9%)	0.0003
Respiratory infection	890 (34.7%)	350 (37.5%)	0.1328
Baseline RA-related therapies			
NSAIDs	2058 (80.3%)	762 (81.6%)	0.3937
Corticosteroids	1884 (73.5%)	718 (76.9%)	0.0436
Xenobiotics	724 (28.3%)	252 (27.0%)	0.4597
Methotrexate	1644 (64.1%)	536 (57.4%)	0.0003
Cytotoxic therapy	559 (21.8%)	230 (24.6%)	0.0781
% Physician-prescribing patterns*			
ETN	19.4 (29.7)	7.9 (19.4)	<0.0001
ADA	18.8 (29.2)	8.2 (19.7)	<0.0001
IFX	9.8 (23.7)	12.6 (25.4)	0.0040

ETN = etanercept; ADA = adalimumab; IFX = infliximab; SIFRA = Severity Index for Rheumatoid Arthritis; RA = rheumatoid arthritis.
*Mean (SD).

Interestingly, the degree of RA disease severity was lower in those who switched to a non-TNF. The increased cost of switching to a non-TNF biologic remained after controlling for these differences. At the time of our analysis, ABA was available as an intravenous infusion administered monthly. Because 70% of non-TNF switches were to ABA, it is possible that the increased office visit costs and number of visits in the non-TNF group may be related to the increased frequency of infusions for ABA compared with IFX (monthly vs every 8 weeks). As of July 2011, ABA became available for subcutaneous administration[30]; the 2 administration methods may influence future studies evaluating switching from an anti-TNF biologic to a non-TNF biologic.

Few other studies have directly compared anti-TNF versus non-TNF biologic agents after failure of an initial biologic. Available data demonstrate that the reason for switching biologic agents is important in predicting the chance of treatment success for the second-line agent.[31–34] Efficacy of TNF sequencing is highest among patients who discontinue their anti-

Table III. Baseline descriptive health care costs* (mean [SD]) of tumor necrosis factor antagonist (anti-TNF) biologic switcher and non-TNF biologic switcher cohorts.

Variable	Anti-TNF Biologic Switcher Cohort, $ (n = 2563)		Non-TNF Biologic Switcher Cohort, $ (n = 934)		P
Total health care	23,088.4	20,069.3	31,108.0	40,832.0	<0.0001
Pharmacy†	12,652.5	8912.3	13,747.7	10,132.9	0.0036
Surgery (knee and hip replacement)	421.9	3778.9	380.6	3640.7	0.7727
Laboratory	543.1	762.4	656.6	1145.2	0.0050
Hospitalization	2788.4	11,913.9	6229.1	28,345.0	0.0003
Emergency department visits	314.9	1240.0	342.5	1058.0	0.5153
Physician office visits	1480.9	1310.6	1798.0	2200.1	<0.0001

*Subcategories are those of interest and do not include all costs.
†Costs include all anti-TNF, non-TNF, and outpatient pharmacy costs.

TNF agent (owing to tolerability or waning efficacy) and lower among patients who switch primarily due to an inadequate response to ≥1 agent.[8,13,18,35–38]

A meta-analysis of 31 studies (incorporating 5306 patients) was conducted; the majority (77%) of the studies were prospective cohort studies and 1 was a randomized controlled trial. These studies demonstrated that efficacy after switching between TNF inhibitors is lowest after a primary inadequate response and an inadequate response to >2 agents.[39]

Evidence from randomized controlled trials also showed that anti-TNF nonresponders can attain an efficacious response by switching to a second anti-TNF agent.[11,16,17,40–44] Using data from the CORRONA registry, Harrold et al[19] directly evaluated the impact on clinical outcomes of switching to a second anti-TNF compared with switching to ABA. After adjusting for a number of previous anti-TNF therapies, baseline disease activity, RA disease severity, and concomitant medications, clinical outcomes were

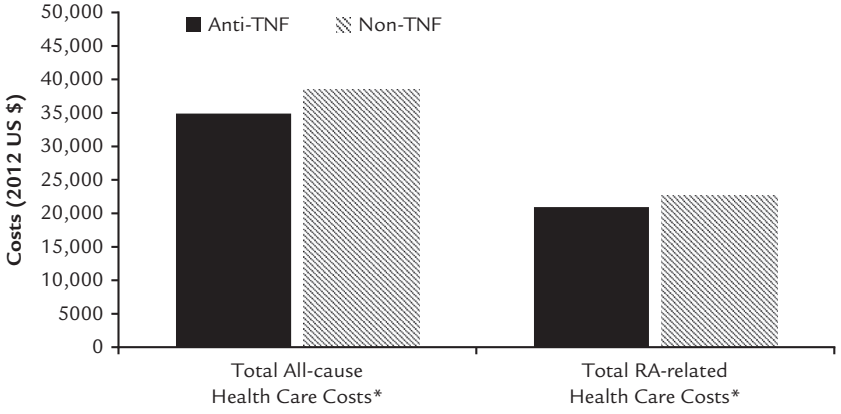

Figure 3. Risk-adjusted all-cause and rheumatoid arthritis (RA)-related health care costs of tumor necrosis factor antagonist (anti-TNF) versus non-TNF biologic switcher cohorts during the follow-up period. *$P = 0.0010$.

Table IV. Risk-adjusted outcomes for tumor necrosis factor antagonist (anti-TNF) biologic switcher and non-TNF biologic switcher cohorts.

12-Month Follow-up After Switch	Anti-TNF Biologic Switcher Cohort	Non-TNF Biologic Switcher Cohort	*P*
Follow-up health care costs, $			
Total health care	34,894.6	38,437.2	0.001
Total pharmacy*	21,627.6	21,909.5	0.565
Total surgery (knee and hip replacement)	550.6	494.6	0.827
Total laboratory	516.6	503.4	0.684
Hospitalization	3522.5	3119.4	0.505
Emergency department visits	297.2	320.5	0.582
Physician office visits	1535.1	1993.6	<0.001
Total RA-related	20,938.9	22,645.2	0.001
Total RA-related pharmacy†	18,195.2	18,167.4	0.951
Total RA-related nonpharmacy	2587.0	4341.4	<0.001
Follow-up health care utilizations			
No. of hospitalizations	0.3	0.3	0.058
No. of emergency department visits	0.5	0.6	0.174
No. of physician office visits	15.0	19.3	<0.001
Hospitalization, %	14.5	17.3	0.147
Emergency department visits, %	28.2	28.9	0.798
Physician office visits, %	100.0	100.0	0.999

RA = rheumatoid arthritis.
*Costs include all anti-TNF, non-TNF, and all outpatient pharmacy costs.
†Costs include anti-TNF, non-TNF, corticosteroids, xenobiotics, cytotoxic therapy, and methotrexate.

similar. Schabert et al[45] used a health insurance claims database and a published claims-based algorithm as a proxy to estimate treatment effectiveness for low disease activity or remission among RA patients switching from an anti-TNF to a subsequent anti-TNF or ABA. Although ABA was slightly more effective as a second-line biologic than a second anti-TNF (25% for ABA, 22% for ETN, 21% for ADA, and 11% for INF), the cost per responder was lower for both ETN and ADA compared with ABA ($66,449, $71,877, and $87,563, respectively). These results by Schabert et al may explain the current finding of lower all-cause and RA-related health care costs in the 12 months after a switch to a second TNF inhibitor compared with a non-TNF biologic.

One strength of the present study is that we controlled for baseline differences in disease severity. SIFRA is a more robust measurement of RA severity than other comorbidity indices, such as the CCI, the Elixhauser index, or the Chronic Disease Score.[27] The inclusion of SIFRA improved the strength of our study and controlled for the important observed bias for which previous research had not controlled.[26] Second, the present study evaluated the route of administration for the initial anti-TNF and how this affected what agent patients received as second-line therapy. The administration route was found to be strongly related to the anti-TNF or non-TNF biologic agents to which patients were switched. In addition, this retrospective study used a large commercial US claims database and a 7-year observation period, which made it more nationally representative than some previous studies.[46–50]

There are some limitations to this study, however. First, because of the retrospective study design, it is

difficult to be certain of causal relationships, and only the association between the noted variables and outcomes could be calculated. Second, due to the time frame in which the study was conducted, all biologic agents that are currently available for the treatment of RA were not included in the analysis. There are additional non-TNF biologic agents available for subcutaneous administration. Third, due to the nature of the claims database, the presence of a claim for a filled prescription does not indicate whether the medication was actually used as prescribed. Fourth, unmeasured confounding variables may have affected results of the multivariate analysis. For example, clinical data are not provided in the databases; therefore, the reason for treatment failure is unknown. Patients may switch from an initial anti-TNF biologic agent because of a lack of efficacy, adverse event/toxicity, or nonmedical reasons such as cost/insurance, but adjusting for these differences was not possible in this study. Another important variable to note is the different approval dates of the biologic agents, which may influence prescribing patterns.

CONCLUSIONS

The results from the present study indicate that in the real world, switching to a second anti-TNF was associated with reduced cost compared with switching to a non-TNF biologic. Because head-to-head data directly comparing the clinical efficacy of switching to a second-line biologic do not consistently support 1 agent over another, using the strategy that results in the lowest overall cost to the system maybe a prudent approach in mitigating health care costs. Further studies are warranted to evaluate biologic switching and should include reasons for the switch, clinical outcomes, and cost. This information can assist policy makers in developing appropriate clinical pathways that will ensure appropriate disease control while managing total health care costs.

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O. Baser had full access to all of the data in the study and had taken responsibility for the integrity of the data and the accuracy of the data analysis. Study concepts and design have been carried out by O. Baser, A. Ganguli, S. Roy, L. Xie and M. Cifaldi. Data interpretation was carried out by O. Baser, A. Ganguli and S. Roy. O. Baser and L. Xie drafted the paper. Statistical programming was done by L. Xie. A. Ganguli, S. Roy and M. Cifaldi made a critical revision of the manuscript for intellectual content. O. Baser was responsible for the study's supervision.

CONFLICTS OF INTEREST

Dr. Ganguli and Dr. Cifaldi are employees of AbbVie and own company stock; Mr. Roy is a former AbbVie employee; and Dr. Baser and Ms. Xie are employees of STATinMED Research, a paid consultant of AbbVie in the development of this manuscript.

AbbVie participated in the interpretation of data and the review and approval of the manuscript.

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