Health Care Resource Utilization and Costs Associated With Switching Biologics in Rheumatoid Arthritis

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ABSTRACT

Purpose: Although biologics are effective in managing rheumatoid arthritis (RA), many patients experience at least one biologic switch during treatment. A switch in biologic treatment can occur for medical or nonmedical reasons. Changes to treatment regimens, even in patients previously stable on therapy, can have clinical and cost implications. This study examined health care resource use and costs incurred with switching from an anti–tumor necrosis factor (TNF) medication in a population of patients with RA.

Methods: A retrospective analysis of patients with RA identified in Truven Commercial Claims and Encounters database (January 1, 2009, to December 13, 2013) was conducted. Patients were required to show evidence of new initiation of treatment with a biologic medication (index date) and continuous eligibility from 6 months before to 12 months after index. Patients were segmented into a continuous biologic group and a biologic switch group, the latter being further divided into switch from anti-TNF to anti-TNF (A-A subgroup) and switch from anti-TNF to a treatment with other mechanism of action (A-O subgroup). Means (SD) and medians of resource use and cost outcomes were calculated over the 12-month postindex period; multivariate models controlling for demographics, biologic switch, and preindex health, resource use, and costs were constructed.

Findings: The total sample comprised 18,070 patients, with 16,643 qualifying for the continuous group and 1427 qualifying for the overall switch group. The overall switch group was more likely to utilize physician office, emergency department, and pharmacy services compared to the continuous group. Consequently, the overall switch group incurred greater total health care costs compared to the continuous group ($41,482 vs $36,557 per patient per annum; $p < 0.05$). Within the switch group, the A-O subgroup had significantly greater outpatient, medical, and total health care expenditures compared to those in the A-A subgroup. Regression analyses revealed that increased baseline utilization and costs, worse health, and older age were associated with increased utilization and costs over the follow-up period. Switching of biologics was associated with an approximate increase of US $4000 per patient per annum in total health care costs.

Implications: These findings suggest that switching biologic agents in patients with RA may be accompanied by increased total health care costs. Efforts to optimize patient response to initial biologic therapy and to reduce unnecessary switching, such as for nonmedical reasons, may help to mitigate these costs. (*Clin Ther*. 2019;41:1080–1089) © 2019 Published by Elsevier Inc.

Key words: anti-TNF, biologic switching, health care costs, resource use, rheumatoid arthritis.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, inflammatory disorder that affects ~1.5 million people in the United States.[1] Early and aggressive treatment is essential in the slowing of disease progression. While no cure exists, current treatments provide patients with an excellent likelihood of maintaining normal daily functioning.[1,2] Most patients initiate treatment with a

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disease-modifying antirheumatic drug (DMARD) to help control inflammation and joint damage.[3] Patients who do not respond to, or who lose treatment effectiveness with, DMARDs are typically placed on a second-line therapy.

Anti–tumor necrosis factor (TNF) agents are the largest class of biologics indicated for the treatment of RA and are generally employed as a secondary treatment once nonbiologic DMARDs are no longer effective.[4] Despite the effectiveness of anti-TNF biologics in many patients, some patients may require a switch to another biologic for medical reasons. For example, a switch may be medically indicated due to nonresponse or reduced response to the initial anti-TNF therapy.[4,5] These switches in treatment can be to either another anti-TNF or to a biologic with another mechanism of action (MOA). In addition to switching for medical reasons, nonmedical switching may also occur. Nonmedical switches occur when changes are made to treatment that are not dictated by health reasons.[6,7] These types of treatment switches are often cost-motived due to health plan or health policy alterations. Such cost-driven treatment decisions contradict a recent guideline from the American College of Rheumatology, which recommends that patients with established low disease activity continue on their respective RA treatment.[3]

Prior research regarding the switching of biologics among patients with RA found that health care costs were higher among patients who switched compared to nonswitchers.[8] In addition, research focused specifically on nonmedical switching concluded that nonmedical switching is associated with not only increased health care resource use and costs, but also with worse clinical outcomes and a higher risk for additional switches in treatment.[9–11] Results of a clinician survey indicated that, following a nonmedical switch, 77% of patients experienced a decrease in effectiveness and almost half of patients reported an increase in side effects.[12] Clinicians reported commonly being asked to prescribe additional medications to compound new side effects following a nonmedical switch.[12] While switching to a less expensive treatment may reduce initial drug costs, the downstream nondrug costs have been found to increase.[10] The purpose of the current study was to examine the economic impact of switching within a population of patients with RA. Health care resource use and costs were examined over the course of a year in an overall switch group as well as in subgroups of patients who switched from anti-TNF treatment to either another anti-TNF or to other MOA treatment.

PATIENTS AND METHODS

Data Source

This study used the Truven Commercial Claims and Encounters MarketScan Research Database (Truven Health Analytics Inc, Ann Arbor, MI) to assess health care costs within a population of patients with RA who were being treated with biologic agents. The extraction included medical claims, pharmacy claims, and detailed enrollment from members with any diagnosis of RA between January 1, 2009, and December 31, 2013.

Study Population

To be eligible for the current study, patients were required to meet the following study inclusion criteria. The earliest fill/infusion of the biologic served as the cycle-of-treatment *index date*.

Eligible patients had a primary diagnosis of RA (*International Classification of Diseases, Ninth Edition—Clinical Modification* code 714.x) and at least 1 inpatient (IP) visit or 2 outpatient (OP) visits within 1 year of the index date (6 months before and 6 months after the index date).

Initiation of treatment was defined as the first date of treatment with any of the following 10 approved biologic agents: abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab, tocilizumab, or tofacitinib. *Full and continuous* eligibility was defined as eligibility from 6 months before to 12 months after a patient's index date. Eligible patients were aged ≥18 years as of the index date.

Patients were excluded if they had a diagnosis code for any of the following within 18 months before the index date: psoriatic arthritis, inflammatory bowel disease, psoriasis, ankylosing spondylitis, juvenile chronic polyarthritis, or any cancer. The purpose of this criterion was to control for patients prescribed biologics indicated for multiple inflammatory diseases. Patients evidencing pregnancy within 18 months before the index date were also excluded. Patients initiating or switching to a biologic agent not listed in the inclusion criteria were excluded, as were those who discontinued therapy with no evidence of a switch in treatment. Additionally, patients were

excluded if they exhibited overlapping use of biologics for ≥30 days. Lastly, patients with zero health care costs were excluded from cost analyses.

Study Groups

Patients were assigned to either a continuous biologic group or a biologic switch group based on whether they were switched between biologic agents within their first year of treatment. The criteria for each of the study groups were as follows.

Continuous Group

The continuous biologic group consisted of patients who were treated with a single biologic therapy persisting for at least 1 year. Patients were categorized into groups based on either continuous use of an anti-TNF or of other MOA biologics.

Switch Group

Patients with a direct switch from one biologic to another during the first 12 months of treatment comprised the biologic switch group. From the overall switch group, 2 subgroups were identified: switch from one anti-TNF to another anti-TNF (A-A); or switch from an anti-TNF to other MOA treatment (A-O).

Two additional switch subgroups were also identified: switch from other MOA to anti-TNF (O-A) and switch from other MOA to other MOA (O-O). However, since the other MOA subgroups collectively comprised <20% of the switch group sample, the current study focused only on the anti-TNF switch subgroups.

Patients in either of the switch subgroups were required to have a minimum of 2 cycles of treatment with a biologic agent. The first cycle of treatment on record was categorized as the *primary biologic* agent; the biologic agent the patient was switched to was classified as the *secondary biologic*. To qualify as a *direct switch*, there was a period of no more than 60 days between discontinuation of the primary biologic and initiation of the secondary biologic. Additionally, a minimum amount of time on therapy of 30 days (~1 administration) was imposed on switch patients' secondary biologic cycle. Patients could not have a claim for a biologic other than the primary or secondary biologic during this time.

In both study groups, all patients were required to persist on biologic therapy for 1 year. In the continuous group, this required persistence for the 1-year requirement; in the switch group, 1-year persistence was allowed to be split between the primary and secondary agents.

Measures

Health Care Resource Use

Resource use outcomes over the 12-month follow-up period were calculated. These outcomes were grouped in accordance with the place of service, and included annualized office visits, prescription fills (30-day adjusted values), percentage of patients with an ED visit, and percentage of patients with an IP visit.

Health Care Costs

Cost outcomes were not inflated and are representative of the actual cost data obtained from the administrative claims. Cost outcomes were calculated over the 12-month follow-up period. Cost outcomes included physician office costs, ED costs, IP costs, total OP costs (OP and office costs), total medical costs, pharmacy costs, and total health care costs. *Total medical costs* were the sum of IP and OP costs. *Total health care costs* were the sum of total medical costs and pharmacy costs. *Pharmacy costs* were calculated as the allowed amount and were summed by patient.

Statistical Analysis

Data on demographic and treatment characteristics were calculated in both study groups. Frequencies and percentages are presented for categorical variables, and means (SD) are presented for continuous variables. Patient characteristics included age, sex, plan type, region of residence, time to switch (in the switch group), and primary biologic agent. For significance testing, the χ^2 test of equality percentages was utilized for categorical variables and the *t* test for independent samples was used for continuous variables.

Bivariate Analyses

Means (SD) and medians of resource use and cost outcomes were calculated in both the continuous and switch groups, as well as in the 2 switch subgroups. Cost comparisons were derived from the first year of treatment. Per-annum cost comparisons were conducted between the continuous biologic group versus biologic switch group, and between the continuous group versus the A-A switch subgroup versus the A-O switch subgroup.

For significance testing, the $\chi 2$ test of equality of percentages was used for categorical variables (dichotomized ED and IP resource use). The Kruskal–Wallis test was used for continuous variables, as both resource use and cost metrics were skewed.

Multivariate Analyses

To further assess the impact of biologic switching on outcomes, multivariate models of resource use and costs were constructed. All models contained the following vector of covariates: biologic group (continuous vs switch), sex, plan type (preferred provider organization vs other), age, preindex Charlson comorbidity index, and the preindex value of the dependent variable of interest. For physician office visits and OP hospital visits, negative binomial models were fitted. Dichotomous indicators of IP and ED use (any vs none) were regressed onto predictors via logistic regression. Thirty days' supply–adjusted prescription fills were square root–transformed and regressed onto predictors via ordinary least squares models.

Total pharmacy costs, total medical costs, and total health care costs were estimated using γ models with a log link. Model parameter estimates (SE) are presented. Additionally, marginal means (SE) from γ models were run for total pharmacy, total medical, and total health care costs.

All data management and analyses were conducted with IBM SPSS Statistics version 24 (IBM, Armonk, NY). For all statistical tests, an α level of <0.05 was used to determine statistically significant differences.

RESULTS

Demographics

Using the Truven database, a total of 16,643 patients were identified as eligible for the continuous group, and 1427 patients qualified for the switch group. Data on demographic and treatment characteristics in each group are presented in Table I. Overall, patients in the continuous and switch groups were mostly female (77.7% vs 81.1%, respectively), with a mean age of 50 years. Patients resided primarily in the South or North Central regions of the United States. In the switch group, most switches from the primary biologic occurred after 90 days, with 37.4% of the sample being switched between biologics at between 91 and 180 days, and 32.9% of the sample evidencing a switch between 181 and 275 days. Few biologic switches (14.3%) were observed beyond 275 days. Interestingly, the frequencies of biologic utilization were strikingly similar between the continuous and switch groups across all 10 biologics included in the study. Of the biologics, etanercept was the most frequently used in the continuous and switch groups (35.0% and 34.3%, respectively), followed by adalimumab (28.3% and 29.4%).

Health Care Resource Utilization and Health Care–Related Expenditures

Full Sample

Examination of the levels of resource utilization in the continuous and switch groups revealed significant differences between the 2 patient populations. The mean numbers of office visits and prescription fills, and the percentages of patients with an ED visit, were greater in the switch group compared to those in the continuous group. Specifically, the mean number of office visits was 21.4% higher in the switch group versus the continuous group (23.3 vs 19.2), while the number of prescription fills and the percentage of patients with an ED visit were 16.7% higher (69.1 vs 59.2) and 30.4% higher (31.3% vs 24.0%), respectively (all, $P < 0.001$). The overall comparisons of the continuous and switch groups are presented in Table II.

Higher resource utilization in the switch group also led to increased health care–related expenditures (Table II). The switch group incurred greater office-visit costs ($15,017 vs $11,805), ED costs ($611 vs $486), total OP costs ($17,133 vs $13,469), and total medical costs ($19,070 vs $15,649) (all, $P < 0.001$). Overall, the total health care costs in the switch group exceeded those in the continuous group by nearly $5000 per patient per annum.

Continuous, TNF Switch, Other MOA Switch

Table III presents the resource utilization and health care–related expenditures in the continuous group and both anti-TNF subgroups (A-A and A-O). *Post hoc* analysis revealed that both switch groups incurred more office visits (A-A, $P < 0.05$; A-O, $P < 0.001$) and prescription fills (both, $P < 0.001$) and a greater percentage of patients with an ED visit (both, $P < 0.001$) compared to those in the continuous group (Table III). Of the switch groups, the A-O group demonstrated the largest differences compared to the continuous group, including 33% more office

Table I. Patient characteristics at index.

Characteristic	Continuous Group (n = 16,643)	Switch Group (n = 1427)	P*
Age, mean (SD), y	50.6 (9.4)	50.0 (9.5)	**0.014**
Female, no. (%)	12,933 (77.7)	1,158 (81.1)	**0.003**
PPO plan, no. (%)	10,226 (61.4)	877 (61.5)	0.991
Region, no. (%)			
South	6,883 (41.4)	543 (38.1)	**0.015**
North Central	3,841 (23.1)	324 (22.7)	0.748
West	2,992 (18.0)	305 (21.4)	**0.001**
Northeast	2,701 (16.2)	243 (17.0)	0.432
Unknown	226 (1.4)	12 (0.8)	0.100
Time to switch			
Mean (SD)	—	178 (78)	—
0—90 d, no. (%)	—	220 (15.4)	—
91—180 d, no. (%)	—	534 (37.4)	—
181—275 d, no. (%)	—	469 (32.9)	—
276+ d, no. (%)	—	204 (14.3)	—
Primary biologic			
Etanercept	5823 (35.0)	490 (34.3)	—
Adalimumab	4715 (28.3)	420 (29.4)	
Infliximab	1774 (10.7)	106 (7.4)	
Abatacept	1710 (10.3)	164 (11.5)	
Golimumab	724 (4.4)	103 (7.2)	
Rituximab	708 (4.3)	5 (0.4)	
Certolizumab	574 (3.4)	71 (5.0)	
Tocilizumab	460 (2.8)	58 (4.1)	
Tofacitinib	140 (0.8)	9 (0.6)	
Anakinra	15 (0.1)	1 (0.1)	

* For significance testing, the χ^2 test of equality of percentages was used for categorical variables, while the *t* test and 1-way ANOVA were used for continuous variables. Statistically significant *P* values are shown in boldface.

visits (mean [SD], 25.7 [15.2] vs 19.2 [14.3]), 17.2% more prescription fills (69.4 [43.7] vs 59.2 [39.2]), and 35.4% more patients with ED visits (32.5% vs 24.0%) (all, $P < 0.001$).

When comparing health care—related costs of the 3 groups, it was found that switching to other MAO treatment (A-O) was associated with higher costs in nearly every category, with the exception of pharmacy costs (Table III). Interestingly, the A-A subgroup had statistically significant lower office-visit costs ($8684 vs $11,805; $P < 0.001$), OP costs ($10,621 vs $13,469; $P < 0.01$), and total medical costs ($12,540 vs $15,649; $P < 0.01$) relative to the continuous group. Pharmacy-related costs in the A-A group, however, were significantly higher than those in the continuous group, by nearly 25% ($26,046 vs $20,908; $P < 0.001$), which resulted in both the mean and median total health care costs being slightly elevated in the A-A group. Taken together, these results indicate that switching elevates the costs of care, with greater costs associated with switching to a non-TNF biologic.

Findings From Multivariate Analysis

Multivariate results from the full sample are presented in Table IV. Baseline cost values were

Table II. Health care resource utilization and costs during the follow-up period (full sample).* Data are given as mean (SD) [median, IQR] unless otherwise noted.

Variable	Continuous Group (n = 16,643)	Switch Group (n = 1427)	*P*
Resource utilization, mean (SD)			
Office visits	19.2 (14.3) [15.0]	23.3 (14.8) [20.0]	<0.001
Prescription fills	59.2 (39.2) [50.8]	69.1 (41.9) [60.7]	<0.001
Any ED visit, no. (%)	3992 (24.0)	447 (31.3)	<0.001
Any inpatient visit, no. (%)	1344 (8.1)	121 (8.5)	0.592
Expenditure, US $			
Office visits	11,805 (17,667) [3713, 15,894]	15,017 (20,111) [7763, 19,145]	<0.001
ED visits	486 (4191) [0, 0]	611 (2106) [0, 290]	<0.001
Inpatient hospital	2180 (14,229) [0, 0]	1937 (10,568) [0, 0]	0.627
Total outpatient	13,469 (19,521) [4864, 28,962]	17,133 (23,840) [9793, 21,296]	<0.001
Total medical	15,649 (25,670) [5228, 21,757]	19,070 (29,434) [10,694, 23,350]	<0.001
Pharmacy	20,908 (14,467) [23,242, 18,524]	22,412 (12,458) [23,705, 15,870]	0.225
Total health care	36,557 (25,103) [31,588, 14,866]	41,482 (28,903) [36,143, 16,321]	<0.001

ED = emergency department; IQR = interquartile range.
* For significance testing, the χ^2 test of equality of percentages was used for categorical variables, and the Kruskal–Wallis test was used for continuous variables.

significant in all models, with most results indicating a marginal, yet positive, relationship between preindex resource use and costs and postindex resource use and costs. Although significant, some β weight values for the preindex outcomes were small, and are abbreviated in Table IV (eg, 2.069 E−5). Worse overall baseline health, as measured by the Charlson comorbidity index, was associated with greater health care costs in all models. Older age was associated with greater values for all outcomes. Men were less likely to have a physician's office visit and incurred fewer total medical costs than did women, but men did incur greater pharmacy costs. Regarding the main predictor of interest, continuous biologic users were less likely to visit a physician's office or an ED, although continuous biologic users were more likely to use the pharmacy compared to the switch group. Additionally, continuous biologic use was associated with reduced medical costs and overall health care costs. Table V displays marginal means specific to cost outcomes derived from multivariate models. These adjusted means indicate that those in the switch group incurred >$4000 more per patient per annum in total health care expenditures compared to continuous users.

DISCUSSION

Biologics are a typical second-line treatment in patients who fail to respond to DMARDs or whose DMARDs lose effectiveness.[1–3] Switching within the biologic class is common; however, it has been associated with various economic and clinical consequences.[5–7] This study focused on potential resource use and cost differences between patients who experienced continuous biologic treatment and patients who were switched between treatments. The subgroup analysis of data from patients who switched provides a more granular evaluation of resource use and cost differences.

The results of the present analysis indicate that patients with a switch in biologic treatment incur greater resource use and medical expenses compared to patients who experience consistency with biologic treatment. Specifically, patients who were switched had more physician and ED visits and incurred ~$4000 more per patient per annum in total health care costs compared to patients who were not switched. This was the case even after control for a variety of variables such as preindex costs and comorbidities. These findings are consistent with those from prior research and highlight the

Table III. Health care resource utilization and costs during the follow-up period (switch subgroups).* Data are expressed as mean (SD) [median, IQR] unless otherwise noted.

Variable	Continuous (n = 16,643)	Anti-TNF to Anti-TNF (A-A) (n = 805)		Anti-TNF to Other MOA (n = 385)		
		Value	*P* vs Continuous	Value	*P* vs Continuous	*P* vs A-A
Resource utilization						
Office visits	19.2 (14.3) [15.0]	20.9 (14.3) [17.0]	<0.05	25.7 (15.2) [22.0]	<0.001	<0.001
Prescription fills	59.2 (39.2) [50.8]	69.3 (40.5) [61.7]	<0.001	69.4 (43.7) [60.5]	NS	NS
Any ED visit, no. (%)	3992 (24.0)	237 (29.4)		125 (32.5)		<0.001
Any inpatient visit, no. (%)	1344 (8.1)	66 (8.2)		36 (9.4)		0.759
Expenditures, US $						
Office visits	11,805 (17,667) [3713, 15,894]	8684 (12,326) [4,40, 8348]	<0.001	19,781 (18,202) [16,057, 22,721]	<0.001	<0.001
ED visits	486 (4191) [0, 0]	536 (1737) [0, 185]		776 (2975) [0, 390]		<0.001
Inpatient hospital	2180 (14,229) [0, 0]	1919 (11,505) [0, 0]		2,193 (9955) [0, 0]		0.759
Total outpatient	13,469 (19,521) [4864, 18,962]	10,621 (20,554) [5233, 10,235]	<0.01	22,140 (19,112) [17,838 25,361]	<0.001	<0.001
Total medical	15,649 (25,670) [5228, 21,757]	12,540 (29,309) [5407, 11,944]	<0.01	24,334 (22,270) [19,548, 27,154]	<0.001	<0.001
Pharmacy	20,908 (14,467) [23,242, 18,525]	26,046 (9780) [25,947, 10,005]	<0.001	19,574 (13,218) [18,371, 20,635]	NS	<0.001
Total health care	36,557 (25,103) [31,588, 14,866]	38,586 (30,699) [33,428, 14,647]	NS	43,908 (20,162) [38,248, 15,958]	<0.001	<0.01

ED = emergency department; IQR = interquartile range; MAO = mechanism of action; TNF = tumor necrosis factor.

* For significance testing, the χ^2 test of equality of percentages was used for categorical variables, and the Kruskal–Wallis test was used for continuous variables.

Table IV. Multivariate models of health care resource utilization and costs during the follow-up period.* Data are given as marginal effect estimates (SE).

Variable	Office and Clinic Visits	ED Visits	Inpatient Admissions	Prescription Fills	Total Prescription Costs	Total Medical Costs	Total Health Care Costs
Continuous biologic use	**−0.15** (0.03)	**−0.33** (0.06)	−0.05 (0.10)	**0.27** (0.04)	−0.04 (0.02)	**−0.21** (0.03)	**−0.10** (0.01)
Male	**−0.15** (0.19)	−0.06 (0.04)	0.05 (0.07)	**0.05** (0.02)	**0.07** (0.02)	**−0.13** (0.02)	0.00 (0.01)
Non-PPO plan	0.01 (0.02)	**0.10** (0.04)	0.03 (0.06)	**0.09** (0.02)	**−0.05** (0.01)	0.03 (0.02)	0.00 (0.01)
Age	**0.01** (0.00)	0.00 (0.00)	**0.03** (0.00)	**0.02** (0.00)	**0.00** (0.00)	**0.01** (0.00)	**0.01** (0.00)
Preindex Charlson	**0.05** (0.01)	**0.19** (0.02)	**0.27** (0.03)	**0.16** (0.01)	**0.02** (0.01)	**0.11** (0.01)	**0.05** (0.00)
Preindex outcome value	**0.04** (0.00)	**−1.03** (0.04)	**−0.90** (0.09)	**1.04** (0.01)	**2.069 E−5** (1.53 E−6)	**3.11 E−5** (1.039 E−6)	**1.37 E−5** (2.85 E−7)
Intercept	**2.20** (0.05)	0.04 (0.12)	**−3.14** (0.22)	**1.24** (0.06)	**9.85** (0.04)	**8.96** (0.06)	**10.17** (0.02)

ED = emergency department; PPO = preferred provider organization.
* Statistically significant effects are shown in boldface.

Table V. Marginal means for cost outcomes during the follow−up period. Data are given as marginal mean (SE) US $.

Parameter	Continuous	Switch
Total pharmacy costs	21,622 (184)	22,459 (550)
Total medical costs	13,885 (155)	17,040 (549)
Total health care costs	35,736 (115)	39,569 (462)

unfavorable cost implications of biologic switching among patients with RA.[8]

Among patients who were switched in the present study, those who were switched from an anti-TNF to a different MOA treatment incurred the most physician office visits, as well as the highest total health care costs. In contrast, patients who were switched to another anti-TNF treatment incurred the greatest pharmacy costs; however, the total health care costs in these patients were less than those in patients who were switched to other MOA treatment and were not statistically different from those in patients receiving continuous treatment. This finding corroborates those from previous research that also found higher health care costs among patients who were switched to other MOA treatment compared to patients who were switched to an anti-TNF biologic.[9,13]

The findings from the present study may be of interest to managed care organizations and health care system administrators concerned about managing total health care costs in patients whose disease requires more costly therapies for optimal management. In some patients, switching between biologic medications is medically indicated for reasons such as suboptimal response or adverse events. While biologics can be effective in managing disease severity, biologic treatments can be associated with adverse reactions ranging from mild to severe.[14,15] These reactions related to biologic switching can lead to increased resource utilization, and therefore costs, since additional physician visits, and in severe cases ED visits, may be required to address side effects such as allergic reactions, nausea, fever, and infection.[11,14] Such switching can be an appropriate part of patient care.[16]

In contrast, nonmedical switching is not driven by clinical considerations, but rather is driven by other factors such as cost. Managed care organizations and health care systems often employ switching practices as a means of managing formulary spending and can impose medication-switch mandates for nonmedical reasons. However, previous research has found associations between nonmedical switching and adverse clinical consequences, in addition to higher health care resource utilization.[6,8,10–13] Recognizing that some switching is clinically indicated, efforts to mitigate switching among patients with RA may be most effective when focused on nonmedical switching that is not driven by clinical considerations, but rather is driven by other factors such as cost or profitability for the payer.

LIMITATIONS

While informative on a broad level, administrative claims data provide limited clinical or causal information, making it difficult to ascertain specifics related to why patients utilized a particular service or the progression, longevity, and severity of RA. Certain information is not available within claims data, such as information on patient death; therefore, these cases cannot be excluded from the study sample. No information regarding the reasoning behind switching is available, making it difficult to definitively provide comparisons between patients who switch for medical reasons and those who switch for nonmedical reasons. Additionally, relevant biosimilars were not available during the study period and therefore no biosimilars were included in the present analysis.

The data used herein are representative of the US population and therefore may not be generalizable to other countries that have different prescription and utilization costs as well as different treatment guidelines. Lastly, the generalizability of the results may be affected over time due to changing variables such as new treatment options, changes to treatment guidelines, and cost changes.

To help address the limitation related to disease severity, exploratory analyses were run on a subgroup of continuous and switch patients who were considered naïve to biologics (see **Supplemental Methods** in the online version at https://doi.org/10.1016/j.clinthera.2019.04.032). Results mirrored those of the overall sample presented herein, suggesting that disease severity alone may not have been the primary driver of treatment switches in this sample of patients with RA.

CONCLUSIONS

This study underscores the potential economic consequences of increased health care costs associated with switching between biologics. Switching biologic treatments, and especially switching from an anti-TNF to other MOA therapy, was associated with greater health care costs. Although this study was not able to determine the reasons for medication switching, the findings of this study indicate that switching biologic medications increases not only pharmacy costs but also overall total costs of care. Additional studies are needed to better understand how medical verses nonmedical switching affects the components underlying total health care costs.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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L.E. and J.V. conceived of the presented idea. J.T. and B.L.B. developed the research design and study methodology, as well as the analytic plan. L.E. and J.V. provided necessary feedback at all iterations of study design. J.T. extracted, processed, and analyzed the data. B.L.B. took the lead in the written presentation of study findings, with assistance from L.E. and J.V. All of the authors were heavily involved in the interpretation of the results and contributed to the final manuscript. This study was sponsored by Janssen Scientific Affairs, LLC.

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APPENDIX A. SUPPLEMENTARY DATA

The following is the Supplementary data to this article:

Clinical Therapeutics

Submission number: CLINTHER-D-18-00299R1

Supplementary material: Outline of methods and results for exploratory analyses reported in discussion section regarding a biologic naïve subsample.

1. METHODS

1.1. Data source

This study used the Truven MarketScan® commercial claims and encounter database to assess healthcare costs within a population of patients with RA who were being treated with biologic agents. The extraction includes medical claims, pharmacy claims, and detailed enrollment for members with any diagnosis of RA between January 1, 2009 and December 31, 2013.

1.2. Study population

To be eligible for the current study, patients were required to meet the following study inclusion criteria. The earliest fill/infusion of the biologic served as the cycle of treatment index date.

1. Primary diagnosis of RA (ICD-9-CM 714.x) for at least one inpatient (IP) visit or two outpatient (OP) visits within one year of the index date (6 months prior to, and 6 months following, the index date).
2. Initiation of treatment with any of the following 10 approved biologic agents: abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab, tocilizumab, or tofacitinib.
3. Full and continuous eligibility 6 months prior to, and 12 months following, a patient's index date.
4. .Age $\geq$18 years as of index date.

Patients were excluded if they had a diagnosis code for any of the following: psoriatic arthritis, inflammatory bowel disease, psoriasis, ankylosing spondylitis, juvenile chronic polyarthritis, any cancer, or pregnancy within 18 months of the index date. Additionally, patients were excluded if they exhibited overlapping biologic use for $\geq$30 days.

1.2.1. Biologic Naive

Patients were considered to be biologic naïve if they had a 12-month biologic naïve period preceding the earliest biologic episode.

1.2.2. Continuous group

The continuous biologic group consisted of patients who were treated with a single biologic therapy persisting for at least one year. Patients were categorized into groups based upon either continuous use of an anti-TNF or of other MOA biologics.

1.2.3. Switch group

Patients with a direct switch from one biologic to another during the first 12 months of treatment comprised the biologic switch group. From the overall switch group, two subgroups were identified:

1 Anti-TNF → Anti-TNF
2 Anti-TNF → Other MOA

Two additional switch groups, Other MOA to Anti-TNF; Other MOA to Other MOA, were also identified. Since the Other MOA subgroups collectively comprised <3% of the switch group sample, the current study only focused on the Anti-TNF switch subgroups.

Patients in either of the switch subgroups were required to have a minimum of two cycles of treatment for different biologic agents. The first cycle of treatment on record was categorized as the primary biologic agent; the biologic agent the patient switched to was classified as the secondary biologic. To qualify as a direct switch there was no more than a 60-day period between discontinuation of the primary biologic and initiation of the secondary biologic. Additionally, a minimum amount of time on therapy of 30 days (approximately one administration) was imposed on switch patients' secondary biologic cycle. Patients could not have a claim for a biologic other than the primary or secondary biologic during this time.

For both study groups, all patients were required to persist on biologic therapy for one year. For the continuous group this naturally required persistence for the one-year requirement, but for the switch group one-year persistence was allowed to be split between the primary and secondary agents.

1.3. Analyses

1.3.1. Outcomes

Healthcare service use outcomes were categorized in accordance with the place of service, and included annual office visits, prescription fills (raw values and 30-day supply adjusted values), proportion of members with an ER visit, and proportion of members with an IP visit. Similarly, cost outcomes included office/outpatient costs, ER costs, IP hospital costs, total medical costs, total pharmacy costs, and total healthcare costs.

1.3.2. Service utilization and cost analyses

Means, medians, and standard deviations of service utilization and cost outcomes are presented for all possible subgroups within the biologic naïve sample over the first year of treatment. Annual cost comparisons were conducted between the following groups:

1 .continuous biologic group *vs.* biologic switch group
2. anti-TNF → anti-TNF switch group *vs.* anti-TNF → other MOA switch group *vs.* continuous group

For significance testing, chi-square tests of equality of proportions were used for categorical variables (dichotomized ER and IP utilization), and Kruskal–Wallis tests were used for continuous variables, as healthcare service utilization and cost metrics were skewed.

2. RESULTS

2.1. Patient Characteristics

From the overall RA sample 8,612 patients met criteria to be identified as biologic naïve. Patient characteristics between the Continuous and Switch group can be viewed in Table 3.1. The majority of the biologic naïve patients qualified for the Continuous group (92%). The average age of both the Continuous and Switch group was 50 years, and the majority of patients were female (75% and 80%, respectively). The most common primary biologic for both groups was etanercept (43–46.5%), followed by adalimumab (31–33%).

2.2. Service utilization and cost: Continuous and Switch groups

Continuous and Switch group comparisons are presented in Table 3.2. In general, results were similar to those achieved in the overall RA sample. The Switch group incurred greater office visits (22.5 vs. 18.7; $p < 0.001$) compared to the Continuous group. The Switch group also filled more prescriptions (69.7 vs. 59.6; $p < 0.001$) and were more likely to visit the ER (29.1% vs. 22.9%; $p < 0.001$) compared to the Continuous group. Regarding costs, the Switch group incurred significantly greater office ($11,539 vs. $9,504), ER ($523 vs. $418), total outpatient ($13,109 vs. $11,037), total medical ($14,955 vs. $13,067), and total healthcare costs ($40,040 vs. $36,321; $p's < 0.001$) compared to the Continuous group. The Switch group also incurred greater pharmacy costs compared to the Continuous group ($25,084 vs. $23,254; $p < 0.05$).

2.3. Service utilization and costs: Continuous and Switch subgroups

Table 3.3 contains the service utilization and cost results with the Switch group segmented into the Anti-TNF to Anti-TNF Switch group and the Anti-TNF to Other MOA Switch group within the biologic naïve cohort. The Anti-TNF to Other MOA group incurred more office visits compared to both the Continuous (26.5 vs. 18.7) and Anti-TNF to Anti-TNF groups (26.5 vs. 20.8; $p's < 0.001$). The Continuous group had fewer prescription fills compared to both Switch groups (Continuous: 59.6; Anti-TNF to Anti-TNF: 68.3; Anti-TNF to Other MOA: 75.1; $p's < 0.001$). With regard to costs, the Anti-TNF to Other MOA group incurred greater office costs compared to the other two groups (Anti-TNF to Other MOA: $18,878; Anti-TNF to Anti-TNF: $8,143; Continuous: $9,504; $p's < 0.001$). The Anti-TNF to Other MOA group also incurred the highest outpatient costs (Anti-TNF to Other MOA: $20,925; Anti-TNF to Anti-TNF: $9,586; Continuous: $11,037; $p's < 0.001$) and the highest medical costs (Anti-TNF to Other MOA: $22,926; Anti-TNF to Anti-TNF: $11,240; Continuous: $13,067; $p's < 0.001$). The Anti-TNF to Anti-TNF group incurred higher pharmacy costs compared to both the Continuous group ($26,969 vs $23,254) and the Anti-TNF to Other MOA group ($26,969 vs. $21,615; $p's < 0.001$). Finally, for total healthcare spend, the Anti-TNF to Other MOA group incurred the greatest costs compared to both the Anti-TNF to Anti-TNF group ($44,540 to $38,209; $p < 0.05$) and the Continuous group ($44,540 to $36,321; $p < 0.001$).

3. APPENDIX A: RESULTS TABLES

Table 3.1. Patient Characteristics

	Continuous Group		Switch Group		p^1
	n =	7,948	n =	664	
	Mean/f	*Std. Dev/%*	*Mean/f*	*Std. Dev/%*	
Age	50.7	9.4	50.0	9.5	**0.038**
Female	5,984	75.3%	534	80.4%	**0.003**
PPO Plan	4,804	60.4%	386	58.1%	0.243
Region					
Northeast	1,233	15.5%	117	17.6%	0.151
North Central	1,930	24.3%	157	23.6%	0.712
South	3,277	41.2%	255	38.4%	0.155
West	1,426	17.9%	131	19.7%	0.250
Unknown	82	1.0%	4	0.6%	0.285
Time to Switch (days)	~	~	181	77	~
0—90 days	~	~	92	13.9%	~
91—180 days	~	~	253	38.1%	~
181—275 days	~	~	224	33.7%	~
276+ days	~	~	95	14.3%	~
Primary Biologic					
abatacept	466	5.9%	36	5.4%	~
adalimumab	2,495	31.4%	219	33.0%	~
anakinra	6	0.1%	0	0.0%	~
certolizumab	212	2.7%	21	3.2%	~
etanercept	3,408	42.9%	309	46.5%	~
golimumab	272	3.4%	33	5.0%	~
infliximab	814	10.2%	43	6.5%	~
rituximab	166	2.1%	0	0.0%	~
tocilizumab	69	0.9%	2	0.3%	~
tofacitinib	40	0.5%	1	0.2%	~

Note: For significance testing, chi-square tests of equality of proportions were used for categorical variables, while t-tests and one-way ANOVAs were used for continuous variables.

Table 3.2. Bivariate Service Utilization and Cost Outcomes: Continuous and Switch Groups

	Continuous Group			Switch Group			p[1]
	n = 7,948			n = 664			
	Mean/f	Std. Dev/%	Median	Mean/f	Std. Dev/%	Median	
Service Utilization							
Office Visits	18.7	14.1	15.0	22.5	14.8	19.0	**<0.001**
Prescription Fills	59.6	38.2	51.4	69.7	40.1	62.9	**<0.001**
Proportion with an ER Visit	1,823	22.9%	~	193	29.1%	~	**<0.001**
Proportion with an IP Visit	572	7.2%	~	56	8.4%	~	0.239
Expenditure							
Office	$9,504	$15,931	$3,120	$11,539	$15,439	$5,269	**<0.001**
Emergency Room	$418	$2,411	$0	$523	$1,767	$0	**<0.001**
Inpatient Hospital	$2,030	$16,110	$0	$1,847	$9,289	$0	0.271
Total Outpatient	$11,037	$17,070	$3,997	$13,109	$16,187	$6,710	**<0.001**
Total Medical	$13,067	$25,206	$4,152	$14,955	$20,240	$7,461	**<0.001**
Pharmacy	$23,254	$12,224	$25,194	$25,084	$11,221	$26,255	**0.048**
Total Healthcare	$36,321	$24,299	$31,798	$40,040	$18,899	$35,754	**<0.001**

bolded p values = statistical significance < 0.05

[1]: For significance testing, chi-square tests of equality of proportions were used for categorical variables, and Kruskal-Wallis tests were used for continuous variables, as healthcare service utilization and cost metrics were skewed.

Table 3.3. Bivariate Service Utilization and Cost Outcomes: Continuous and Switch subgroups

	Continuous Group[a]			Anti TNF – Anti INF[b]			Anti TNF - Other MOA[c]			p[1]
	n = 7,948			n= 495			n = 130			
	Mean/f	Std. Dev/%	Median	Mean/f	Std. Dev/%	Median	Mean/f	Std. Dev/%	Median	
Servi ce Utilization										
Office Vis its	18.7	14.1	15.0	20.8	14.3	17.0	26.5	14.6	24.0	**<0.01[ab]; <0.001[ac,bc]**
Prescription Fills	59.6	38.2	51.4	68.3	37.4	625	75.1	48.4	673	**<0.00[ab,ac]**
Proportion with an ER Visit	1,823	22.9%	~	136	27 5%	~	38	29.2%	~	**0.019**
Proportion with an IP Visit	572	7.2%	~	40	8.1%	~	10	7.7%	~	0.749
Expenditure										
Office	$9,504	$15,931	$3,120	$8,143	$10,908	$4,028	$18,878	$17,664	$12,765	**<0.001[ac,bc]**
Emergency Room	$418	$2,411	$0	$491	$1,849	$0	$642	$1,628	$0	**<0.001**
Inpatient Hospital	$2,030	$16,110	$0	$1,654	$8,353	$0	$2,001	$11,258	$0	0.759
Total Outpatient	$11,037	$17,070	$3,997	$9,586	$11,932	$4,943	$20,925	$18,210	$14,482	**<0.001[ac,bc]**
Total Medical	$13,067	$25,206	$4,152	$11,240	$15,749	$5,218	$22,926	$23^84	$14,695	**<0.001[ac,bc]**
Pharmacy	$23,254	$12,224	$25,194	$26,969	$9,579	$26,957	$21,615	$13,698	$22,174	**<0.001[ac,bc]**
Total Healthcare	$36,321	$24,299	$31,798	$38,209	$15,859	$34,578	$44,540	$20539	$38,870	**<0.05[bc]; <0.001[ac]**

bolded p values = statistical significance < 0.05

[1]: For significance testing, chi-square tests of equality of proportions were used for categorical variables, and Kruskal-Wallis tests were used for continuous variables, as healthcare service utilization and cost metrics were skewed.