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ORIGINAL RESEARCH

A Retrospective Analysis of Corticosteroid Utilization Before Initiation of Biologic DMARDs Among Patients with Rheumatoid Arthritis in the United States

Christina A. Spivey · Jenny Griffith · Cameron Kaplan · Arnold Postlethwaite · Arijit Ganguli · Junling Wang

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ABSTRACT

Introduction: Understanding the effects of corticosteroid utilization prior to initiation of biologic disease-modifying antirheumatic drugs (DMARDs) can inform decision-makers on the appropriate use of these medications. This study examined treatment patterns and associated burden of corticosteroid utilization before initiation of biologic DMARDs among rheumatoid arthritis (RA) patients.

Methods: A retrospective analysis was conducted of adult RA patients in the US MarketScan Database (2011–2015). The following patterns of corticosteroid utilization were analyzed: whether corticosteroids were used; duration of use (short/long duration defined as $<$ or $\geq$ 3 months); and dosage (low as $<$ 2.5, medium as 2.5 to $<$ 7.5 and high as $\geq$ 7.5 mg/day). Effects of corticosteroid use on time to biologic DMARD initiation were examined using Cox proportional hazards models. Likelihood and number of adverse events were examined using logistic and negative binomial regression models. Generalized linear models were used to examine healthcare costs. Independent variables in all models included patient demographics and health characteristics.

Results: A total of 25,542 patients were included (40.84% used corticosteroids). Lower hazard of biologic DMARD initiation was associated with corticosteroid use (hazard ratio = 0.89, 95% confidence interval = 0.83–0.96), long duration and lower dose. Corticosteroid users compared to non-users had higher incidence rates of various adverse events including cardiovascular events ($P < 0.05$). Higher likelihood of adverse events was associated with corticosteroid use and long duration of use, as was increased number of adverse events. Corticosteroid users had a greater annualized mean number of physician visits, hospitalizations, and emergency department (ED) visits than non-users in adjusted analysis. Corticosteroid users compared to non-users had higher mean costs for total healthcare, physician visits, hospitalizations, and ED visits.

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C. A. Spivey · J. Wang (✉)
University of Tennessee Health Science Center College of Pharmacy, Memphis, TN, USA
e-mail: jwang26@uthsc.edu

J. Griffith · A. Ganguli
Health Economics and Outcomes Research, AbbVie, North Chicago, IL, USA

C. Kaplan · A. Postlethwaite
University of Tennessee Health Science Center College of Medicine, Memphis, TN, USA

Conclusions: Among patients with RA, corticosteroid utilization is associated with delayed initiation of biologic DMARDS and higher burden of adverse events and healthcare utilization/costs before the initiation of biologic DMARDs.
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Keywords: Adverse events; Biologic disease-modifying antirheumatic drugs (DMARDs); Corticosteroids; Healthcare costs; Healthcare utilization; Rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune inflammatory disease associated with pain, stiffness, swelling, and loss of function in the joints, which can lead to poorer quality of life, and even increased mortality [1, 2]. The primary goal of RA treatment is to maximize long-term quality of life through control of symptoms, prevention of structural progression, and normalization of physical function and social participation [3]. A treat-to-target approach should be used to obtain these goals, which involves setting goals for treatment (e.g., low disease activity or remission), frequently monitoring disease status, and adjusting medication therapy as needed based on monitoring [1, 3].

DMARDs are recommended for all patients as the primary therapy in the treatment of RA as they have been shown to slow the course of the disease [1]. More specifically, the first step in treatment should be initiation of non-biologic DMARD monotherapy. If disease activity remains moderate to severe, biologic DMARDs are recommended as monotherapy or combination therapy with non-biologic DMARDs as they have substantially changed the course of disease and dramatically improved long-term outcomes in RA among patients refractory or intolerant to traditional DMARDs [1, 4].

Corticosteroids are widely used due to their quick anti-inflammatory effect and are recommended by the *American College of Rheumatology* in low doses as an effective short-term (< 3 months) therapy to 'bridge' patients until the benefits of DMARDs are observed or to manage DMARD failure or a disease flare [1]. The most recent guidelines by the European League Against Rheumatism (EULAR) have similar recommendations regarding the use of only short-term corticosteroids [2]. Harmful side effects of corticosteroid use have been reported (e.g., weight gain, worsening of diabetes, increased risk of infection), thus the decision to initiate therapy should be balanced by the lack of long-term corticosteroid safety studies in the RA population [1, 5, 6].

Many patients are not managed according to treatment guidelines, with significant delay in initiating DMARDs [7–11]. Researchers have thus explored the relationship between corticosteroid and biologic DMARD use in clinical practice [6–10]. For example, it was found that corticosteroids are often used as RA treatment prior to initiating DMARDs despite recommendations that all patients should be managed with a DMARD [6]. Another study found that median time from initiation of the traditional DMARD to the first biologic was more than 4 years [8]. Yazdany et al. found that one in ten RA patients receive corticosteroids alone without DMARDs [9]. Additionally, Kim et al. noted that corticosteroid users were more likely to initiate biologic DMARDS, and Caplan et al. found that initiation of biologic DMARDs is associated with the discontinuation of corticosteroids [10, 11].

Further exploration of the relationship between corticosteroid and biologic DMARD use in the treatment of RA is warranted. In particular, understanding corticosteroid treatment patterns and associated burden prior to biologic DMARD initiation can inform clinical and policy decision-makers on the appropriate use of these two drug classes in RA management. Santiago and da Silva noted limitations in the knowledge base regarding adverse events associated with corticosteroid use in RA treatment [6]. These investigators encourage that the "risk and benefit" of corticosteroid use in RA should be "regularly revisited [6]". Therefore, the objectives of this study were to test whether: (1) corticosteroid utilization was associated with a delay in the initiation of biologic DMARDs among patients with RA; (2) corticosteroid utilization was associated with more adverse

events before the initiation of biologic DMARDs among patients with RA; and (3) corticosteroid use was associated with higher healthcare utilization and costs before the initiation of biologic DMARDs among patients with RA.

METHODS

A retrospective analysis was conducted of the MarketScan Commercial and Medicare Supplemental Claims and Encounters Database (1/1/2011–12/31/2015) [12]. MarketScan is a de-identified, nationwide medical claims database that includes insurance claims of inpatient, outpatient, emergency department (ED), pharmacy, behavioral healthcare, and enrollment data from a wide variety of health plans. All claims in the MarketScan Database are linkable using a unique patient ID. All claims except outpatient pharmaceutical claims have diagnosis codes associated with service records. Outpatient pharmaceutical claims include National Drug Code, date service incurred, days' supply, and patient out-of-pocket expenses.

The study population was adults 18 years of age and older diagnosed with RA. To be included, a patient had to have at least two diagnoses of RA at least a week apart within a year in an ambulatory or non-acute setting [9, 13, 14]. The earliest date a patient was diagnosed with RA was identified as the index date as long as there was a six-month washout period before the date of diagnosis. A washout period was applied so there was a reasonable possibility that included patients were newly diagnosed with RA. Additionally, included patients were required to have continuous enrollment in a health insurance plan for 6 months prior to the index date, and 1 year following the index date. Patients were observed from the index date to the first initiation of a biologic DMARD, the end of the patient's continuous enrollment in health plans or the end of 2015, whichever came first.

Corticosteroids evaluated included all oral corticosteroid prescriptions filled in a pharmacy and injectable corticosteroids administered in an outpatient or inpatient setting with a corresponding HCPCS code. All corticosteroids were converted to a prednisone equivalent dose [15–17]. For the purposes of counting treatment duration, injectable corticosteroids were counted the same as a 15-day supply of oral corticosteroids. Biologic drugs evaluated included: abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab, and tocilizumab.

Corticosteroid utilization measures were as follows: having used corticosteroids or not, treatment duration, and dosage [18, 19]. Having used corticosteroids or not is defined as a dummy variable, with having not used corticosteroids as the reference group. Treatment duration was defined as short term (< 3 months) and long term (≥ 3 months) based on the 2015 American College of Rheumatology Guidelines for the Treatment of RA [1]. The dosage categories were defined based on average daily dosages of prednisone as low (> 0 to < 2.5 mg/day), medium (2.5 to < 7.5 mg/day), and high (≥ 7.5 mg per day) [18, 19].

The study outcomes were time to initiation of biologic DMARD, diagnosis of adverse events, and health services utilization (physician visits, ED visits, hospitalizations, and medications) and costs (pharmacy and medical). The adverse events include cardiovascular, gastrointestinal, and skin conditions, infection, lipodystrophy, metabolic/endocrinologic, neuropsychiatric, and ophthalmologic conditions, and osteoporotic fractures (refer to Supplementary material: Table S1 for full list of adverse events) [11, 20–24].

The Andersen's Behavioral Model of Health Services Utilization (Andersen's Model) was used as the theoretical framework for including independent variables in the models due to the inclusion of outcomes related to utilization of medications and health services [25]. Based on this model, several factors were controlled for in the analysis [26–29]. Predisposing factors included age, gender, type of health plan, duration of follow-up when studying adverse events and health services utilizations and costs. Enabling factors included metropolitan statistical area, geographic region, and having a rheumatologist visit. Need factors included health services utilization, other medication utilization such as non-biologic DMARDs and/or analgesics, Charlson Comorbidity Index, and

risk adjustment summary score based on Diagnostic Cost Group/Hierarchical Coexisting Condition Model.

Statistical Analysis

Descriptive statistics (i.e., mean, standard deviation) and frequency counts were used to summarize the baseline characteristics of the sample. Kaplan–Meier survival analysis was used to compare the duration of time from RA diagnosis to the initiation of the first biologic DMARD across treatment duration categories, and between individuals who have and have not used corticosteroids. Additionally, the time to biologic initiation across the different corticosteroid dose categories was evaluated. In multivariate analysis, the effects of corticosteroid use patterns on the initiation of biologic DMARDs were examined using Cox proportional hazards models.

To examine corticosteroid-related adverse events before the initiation of biologic DMARDs among patients with RA, the incidence rates per 100 patient years for adverse events were ascertained using diagnosis codes (see Supplementary material; Table S1). The following aspects of adverse events were analyzed: whether a patient experienced any corticosteroid-related adverse events and the number of corticosteroid-related adverse events. Multivariate logistic regression and negative binomial regression models were used to estimate the effects of each measure of corticosteroid utilization on adverse events. Logistic regression was conducted to examine the likelihood of an adverse event occurrence. Negative binomial models were used when examining the number of adverse events.

To investigate the effects of corticosteroid use on healthcare utilization before the initiation of biologic DMARDs among patients with RA, patients were observed from the first time corticosteroids were used to the initiation of the first biologic DMARD. Dependent variables included number of physician visits, hospitalizations, and ED visits, as well as costs of physician visits, hospitalizations, and ED visits, other outpatient costs, medication costs, and total healthcare costs. Multivariate logistic regression and negative binomial regression models were used to determine the effects of corticosteroid use on the utilization measures. Logistic regression was conducted to examine the likelihood of using certain health services. Negative binomial model was used when examining the number of health services. Multivariate generalized linear models with log link and gamma distribution were used to examine the effects of corticosteroid utilization on healthcare costs.

Independent variables in all multivariate regression analyses included patient socio-demographic and health characteristics. Data analysis was conducted using SAS®9.4 (SAS Institute Inc, Cary, NC) and STATA®13.1 (STATA Corporation, College Station, TX, USA). This study was approved by the Institutional Review Board at the University of Tennessee Health Science Center.

RESULTS

A total of 25,542 RA patients were included (see Supplementary materials: Figure S1). Table 1 presents overall baseline patient characteristics and the comparison between corticosteroid users and nonusers. Mean patient age was 53.55 years with a standard deviation (SD) of 14.61 years, and the majority was female (70.17%). Among those who used corticosteroids, 90.22% used the medication for a short duration and 9.77% for a long duration (results now shown). The majority of corticosteroid users, 54.52%, used low-dose corticosteroids, while 40.32% used a medium dose and 4.40% used a high dose (results not shown). Those who used corticosteroids were slightly older, and were more likely to be female, have comprehensive health insurance or preferred provider organization, live outside an MSA, live in the south, and be treated by a rheumatologist. Corticosteroid users had higher healthcare utilization and were slightly more likely to also use non-biologic DMARDS, bone-active medications, analgesics, and NSAIDs. Finally, in general, corticosteroid users had more comorbidities. Further, higher proportions of

Table 1 Summary of patient characteristics by use of corticosteroids

Characteristics	Overall population $N = 25,542$ N (%)	Used corticosteroids $N = 10,433$ N (%)	Did not use corticosteroids $N = 15,109$ N (%)	P value
Age [Mean (SD)]	53.55 (14.61)	54.77 (13.73)	52.70 (15.13)	< 0.01
Gender [N (%)]				
Male	7620 (29.83)	2907 (27.86)	4713 (31.19)	< 0.01
Health plan type [N (%)]				
Comprehensive	2775 (10.86)	1297 (12.43)	1478 (9.78)	< 0.01
Preferred provider organization	14,582 (57.09)	6053 (58.02)	8529 (56.45)	
Health maintenance organization	3089 (12.09)	1047 (10.04)	2042 (13.52)	
Other	5096 (19.95)	2036 (19.52)	3060 (20.25)	
Metropolitan Statistical Area [N (%)]				
Yes	20,732 (81.17)	8190 (78.50)	12,542 (83.01)	< 0.01
Geographic region [N (%)]				
Northeast	4804 (18.81)	1584 (15.18)	3220 (21.31)	< 0.01
Midwest	6198 (24.27)	2581 (24.74)	3617 (23.94)	
South	10,065 (39.41)	4808 (46.08)	5257 (34.79)	
West	3989 (15.62)	1275 (12.22)	2714 (17.96)	
Unknown	486 (1.9)	185 (1.77)	301 (1.99)	
Had rheumatologist visit [N (%)]	14,451 (56.59)	6340 (60.77)	8111 (53.70)	< 0.01
Physician visits [Mean (SD)]	3.72 (3.44)	4.28 (3.66)	3.33 (3.22)	< 0.01
Physician visits Cost [Mean (SD)]	$356.90 ($357.40)	$399.24 ($365.84)	$327.62 ($348.39)	< 0.01
Hospitalizations [Mean (SD)]	0.05 (0.26)	0.05 (0.26)	0.05 (0.26)	0.56
Hospitalization costs [Mean (SD)]	$1079.00 ($9140.00)	$1074.24 ($8699.69)	$1082.04 ($9431.83)	0.95
Emergency department visits [Mean (SD)]	0.42 (1.32)	0.47 (1.34)	0.38 (1.3)	< 0.01
Emergency department cost [Mean (SD)]	$174.70 ($818.70)	$189.27 ($802.84)	$164.72 ($829.37)	0.02
Total medication costs [Mean (SD)]	$8281.00 ($15,122.00)	$9079.83 ($15,437.22)	$7729.41 ($14,875.87)	< 0.01
Used non-biologic DMARDs [Yes: N (%)]	14,078 (55.12)	5910 (56.65)	8168 (54.06)	< 0.01
Used bone-active medications [Yes: N (%)]	3031 (11.87)	1435 (13.75)	1596 (10.56)	< 0.01

Table 1 continued

Characteristics	Overall population $N = 25,542$ N (%)	Used corticosteroids $N = 10,433$ N (%)	Did not use corticosteroids $N = 15,109$ N (%)	P value
Used analgesics [Yes: N (%)]	5822 (22.79)	3235 (31.01)	2587 (17.12)	< 0.01
Used NSAIDs [Yes: N (%)]	13,940 (54.58)	6541 (62.7)	7399 (48.97)	< 0.01
Charlson comorbidity index [Mean (SD)]	1.68 (1.24)	1.73 (1.26)	1.64 (1.23)	< 0.01
Risk adjustment score [Mean (SD)]	0.79 (0.48)	0.82 (0.47)	0.77 (0.49)	< 0.01

P values based on Pearson's Chi-square test for categorical variables, and two-sample t tests for continuous variables
N number; % percentage; *DMARDSs* Disease-modifying antirheumatic drugs; *NSAIDs* Non-steroidal anti-inflammatory medications; *SD* standard deviation

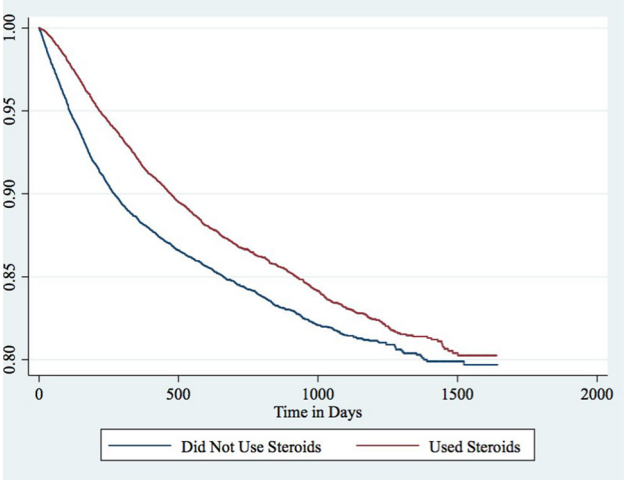

Fig. 1 Time to biologic disease-modifying antirheumatic drug (DMARD) initiation by corticosteroid use

lung diseases, history of infection, and mental illness were found in corticosteroid users (37.99, 11.43, and 20.69%, respectively) than nonusers (30.87, 9.03, 17.62%, respectively; $P < 0.01$; results not shown).

Based on Kaplan–Meier survival analysis, corticosteroid users (Fig. 1), had delayed time to initiation of a biologic DMARD compared to their counterparts (nonusers) ($P < 0.001$, based on log rank tests). Additional Kaplan–Meier survival analysis (not shown) found that those with longer duration of corticosteroid use and those in lower corticosteroid dosage categories had delayed time to initiation of a biologic DMARD compared to their counterparts (those with shorter duration and higher dosages, respectively) ($P < 0.001$, based on log rank tests). According to the Cox proportional hazards analysis (Table 2), lower hazard of biologic DMARD initiation was associated with corticosteroid use [Hazard Ratio (HR) = 0.89, 95% Confidence Interval (CI) = 0.83–0.96, compared to nonusers], long corticosteroid duration (HR = 0.73, 95% CI = 0.60–0.89, compared to short duration) and lower dosages (HR = 1.10, 95% CI = 0.98–1.23 for medium dose and HR = 1.87, 95% CI = 1.53–2.28 for high dose compared to low dose).

Table 2 Cox proportional hazards model concerning the effect of corticosteroid utilization on initiation of a biologic disease-modifying antirheumatic drugs (DMARDs)

Variables	(1) Hazard ratio (95% confidence interval)	(2) Hazard ratio (95% confidence interval)	(3) Hazard ratio (95% confidence interval)
Corticosteroid use	0.89 (0.83–0.96)		
Long-duration corticosteroid use		0.73 (0.60–0.89)	
Medium-dose corticosteroid			1.1 (0.98–1.23)
High-dose corticosteroid			1.87 (1.53–2.28)
Did not use corticosteroid		1.09 (1.02–1.17)	1.30 (1.19–1.43)
Age	0.98 (0.98–0.99)	0.98 (0.98–0.99)	0.98 (0.98–0.99)
Male	1.06 (0.98–1.13)	1.05 (0.98–1.13)	1.04 (0.97–1.12)
Preferred provider organization	1.16 (1.01–1.33)	1.16 (1.01–1.33)	1.16 (1.00–1.33)
Health maintenance organization	1.05 (0.88–1.24)	1.04 (0.88–1.23)	1.04 (0.88–1.23)
Other health plan	1.15 (0.99–1.34)	1.15 (0.98–1.33)	1.15 (0.98–1.33)
Metropolitan statistical area	1.09 (1.00–1.19)	1.09 (0.99–1.19)	1.08 (0.99–1.18)
Geographic region: Midwest	1.13 (1.01–1.26)	1.13 (1.01–1.26)	1.13 (1.01–1.26)
Geographic region: South	1.36 (1.23–1.50)	1.36 (1.23–1.51)	1.38 (1.25–1.52)
Geographic region: West	1.36 (1.21–1.54)	1.36 (1.21–1.53)	1.37 (1.21–1.54)
Geographic region: unknown	1.26 (0.97–1.63)	1.26 (0.97–1.63)	1.27 (0.98–1.64)
Rheumatologist visit	1.49 (1.38–1.61)	1.49 (1.38–1.61)	1.49 (1.38–1.61)
Physician visits	0.99 (0.97–1.01)	0.99 (0.97–1.01)	0.99 (0.97–1.01)
Physician visit costs	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
Hospitalizations	1.24 (1.02–1.50)	1.24 (1.03–1.50)	1.24 (1.02–1.50)
Hospitalization costs	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
Emergency department visits	1.01 (0.98–1.04)	1.01 (0.98–1.04)	1.01 (0.98–1.04)
Emergency department costs	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
Number of medications	0.99 (0.99–1.00)	0.99 (0.99–1.00)	0.99 (0.99–1.00)
Total medication costs	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
Charlson comorbidity score	0.93 (0.89–0.96)	0.93 (0.89–0.96)	0.93 (0.89–0.97)
Risk adjustment score	0.88 (0.79–0.98)	0.88 (0.79–0.98)	0.87 (0.78–0.97)
Monotherapy, non-biologic DMARDs	3.16 (2.89–3.46)	3.16 (2.89–3.45)	3.14 (2.88–3.44)

Table 2 continued

Variables	(1) Hazard ratio (95% confidence interval)	(2) Hazard ratio (95% confidence interval)	(3) Hazard ratio (95% confidence interval)
Dual therapy, non-biologic DMARDs	3.79 (3.43–4.18)	3.78 (3.43–4.18)	3.79 (3.43–4.18)
Bone-active medications	0.75 (0.67–0.83)	0.75 (0.68–0.84)	0.75 (0.68–0.84)
Analgesics	0.83 (0.76–0.90)	0.83 (0.76–0.91)	0.84 (0.77–0.91)
Nonsteroidal anti-inflammatory drugs	0.58 (0.54–0.62)	0.58 (0.54–0.62)	0.58 (0.54–0.62)

Number of observations: 25,463. Comparison groups: did not use corticosteroids, short duration of corticosteroid use, low-dose corticosteroid, female, comprehensive health plan, non-metropolitan statistical area, geographic region Northeast, no rheumatologist visit, no non-biologic DMARDs, no bone-active medications, no analgesics, and no nonsteroidal anti-inflammatory drugs

Corticosteroid users compared to non-users had significantly higher incidence rates of cardiovascular events, gastrointestinal events, infections, skin events, lipodystrophy, metabolic/endocrinologic events, neuropsychiatric events, and ophthalmologic events ($P < 0.05$; Table 3). In the multivariate regression (Table 4), corticosteroid use was associated with higher likelihood of experiencing an adverse event (OR = 1.13, 95% CI = 1.06–1.20). Long-duration of corticosteroid use compared to short duration was associated with increased likelihood of an adverse event (OR = 1.75, 95% CI = 1.47–2.09). Corticosteroid dosage categories were not associated with likelihood of an adverse event. Corticosteroid use was also associated with increased number of adverse events compared to non-use [incidence rate ratio (IRR) = 1.09, 95% CI = 1.05–1.14]. Long duration of corticosteroid use compared to short duration was associated with increased number of adverse events (IRR = 1.31, 95% CI = 1.19–1.44). Among the dosage categories, medium dose compared to low dose was associated with reduced number of adverse events (IRR = 0.94, 95% CI = 0.88–0.99). There was no significant difference in the number of adverse events between high dose and either medium or low dose.

Differences in average annualized healthcare utilizations and costs per patient between corticosteroid users and non-users are summarized in Table 5. In the unadjusted analysis (Table 5, Panel 1), corticosteroid use compared to non-use was associated with increased number of physician visits (SD) [10.06 (6.71) vs. 7.27 (5.97), respectively; $P < 0.001$], hospitalizations [0.15 (0.42) vs. 0.10 (0.10), respectively; $P < 0.001$], and ED visits [0.84 (1.90) vs. 0.57 (2.15), respectively; $P < 0.001$]. After adjustment with multivariate negative binomial regression (Table 5, Panel 2), corticosteroid use compared to non-use was associated with an increase of 2.82 physician visits (from 7.29 to 10.11, $P < 0.001$), an increase of 0.04 hospitalizations (from 0.11 to 0.15, $P < 0.001$), and an increase of 0.32 ED visits (from 0.57 to 0.89, $P < 0.001$).

In the unadjusted analysis (Table 5, Panel 1), corticosteroid users had higher mean costs (SD) compared to non-users for total healthcare costs [$9130.75 (21,083.24) vs. $6659.03 (24,631.57), respectively; $P < 0.001$], physician visits [$729.94 (715.53) vs. $570.89 (856.02), respectively; $P < 0.001$], ED visits [$253.56 (940.1) vs. $179.08 (893.55), respectively; $P < 0.001$], and medications [$1807.48 (3484.32) vs. 1311.39 (3154.19), respectively; $P < 0.001$]. Costs were similar between corticosteroid users and non-users for hospitalizations [$2351.68 (10,760.88) vs. $1957.77 (20,289.88), respectively; $P = 0.07$]. After adjusting for baseline characteristics (Table 5, Panel 2), corticosteroid users

Table 3 Incidence rates of adverse conditions (per 100 patient years) across study cohorts

Study outcomes	All patients			Corticosteroid users			Non-users			*P* value
	No. of events	Observed patient years	Incidence rate	No. of events	Observed patient years	Incidence rate	No. of events	Observed patient years	Incidence rate	
Cardiovascular	19,541	43,626	44.79	7767	15,584	49.84	11,774	28,042	41.99	0.02
Gastrointestinal	6344	43,626	14.54	2634	15,584	16.90	3710	28,042	13.23	< 0.01
Infections	11,978	43,626	27.46	5244	15,584	33.65	6734	28,042	24.01	< 0.01
Skin (excluding infections)	6980	43,626	16.00	3081	15,584	19.77	3899	28,042	13.90	< 0.01
Lipodystrophy	9784	43,626	22.43	4484	15,584	28.77	5300	28,042	18.90	< 0.01
Metabolic/ endocrinologic	8239	43,626	18.89	3330	15,584	21.37	4909	28,042	17.51	< 0.01
Neuropsychiatric	11,298	43,626	25.90	4685	15,584	30.06	6613	28,042	23.58	< 0.01
Ophthalmologic	6823	43,626	15.64	2758	15,584	17.70	4065	28,042	14.50	< 0.01
Osteoporotic fracture	3036	43,626	6.96	1169	15,584	7.50	1867	28,042	6.66	0.08
Miscellaneous conditions										
Dysphonia	227	43,626	0.52	104	15,584	0.67	123	28,042	0.44	0.92
Menstrual disorders	1624	43,626	3.72	572	15,584	3.67	1052	28,042	3.75	0.60
Impotence	691	43,626	1.58	298	15,584	1.91	393	28,042	1.40	0.14

Table 4 Logistic regression model concerning the effect of corticosteroid utilization on the occurrence of any adverse event prior to initiation of a biologic disease-modifying antirheumatic drugs (DMARDs)

Variables	(1) Odds ratio (95% confidence interval)	(2) Odds ratio (95% confidence interval)	(3) Odds ratio (95% confidence interval)
Corticosteroid use	1.13 (1.06–1.20)		
Long duration of corticosteroid use		1.75 (1.47–2.09)	
Medium-dose corticosteroid			0.95 (0.86–1.03)
High-dose corticosteroid			1.00 (0.81–1.23)
Did not use corticosteroid		0.92 (0.87–0.98)	0.85 (0.79–0.91)
Duration of follow-up	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
Age	1.02 (1.01–1.02)	1.02 (1.01–1.02)	1.02 (1.01–1.02)
Male	0.76 (0.72–0.81)	0.76 (0.72–0.81)	0.76 (0.72–0.81)
Preferred provider organization	1.02 (0.92–1.14)	1.02 (0.92–1.14)	1.02 (0.92–1.14)
Health maintenance organization	1.03 (0.91–1.18)	1.04 (0.91–1.18)	1.04 (0.91–1.18)
Other health plan	0.92 (0.81–1.03)	0.92 (0.81–1.03)	0.92 (0.81–1.03)
Metropolitan statistical area	0.98 (0.91–1.06)	0.98 (0.91–1.06)	0.98 (0.91–1.06)
Geographic region: Midwest	0.99 (0.91–1.08)	0.99 (0.90–1.08)	0.99 (0.90–1.07)
Geographic region: South	1.00 (0.93–1.08)	1.00 (0.92–1.08)	1.00 (0.92–1.08)
Geographic region: West	1.05 (0.96–1.16)	1.05 (0.96–1.16)	1.05 (0.95–1.16)
Geographic region: unknown	0.99 (0.80–1.23)	0.99 (0.80–1.23)	0.99 (0.80–1.23)
Rheumatologist visit	0.92 (0.86–0.97)	0.92 (0.86–0.97)	0.91 (0.86–0.97)
Physician visits	1.04 (1.02–1.06)	1.04 (1.02–1.05)	1.04 (1.02–1.06)
Physician visit costs	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
Hospitalizations	0.78 (0.67–0.91)	0.78 (0.67–0.91)	0.78 (0.67–0.91)
Hospitalization costs	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
Emergency department visits	0.97 (0.94–1.00)	0.97 (0.94–1.00)	0.97 (0.94–1.00)
Emergency department costs	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
Total medications	1.01 (1.01–1.02)	1.01 (1.01–1.02)	1.01 (1.01–1.02)
Total medication costs	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
Charlson comorbidity score	1.13 (1.09–1.16)	1.13 (1.09–1.16)	1.13 (1.09–1.16)
Risk adjustment score	1.19 (1.09–1.29)	1.19 (1.09–1.30)	1.19 (1.09–1.30)
Non-biologic DMARDs	0.87 (0.82–0.92)	0.87 (0.82–0.92)	0.87 (0.82–0.92)

Table 4 continued

Variables	(1) Odds ratio (95% confidence interval)	(2) Odds ratio (95% confidence interval)	(3) Odds ratio (95% confidence interval)
Bone-active medications	1.23 (1.13–1.35)	1.23 (1.13–1.34)	1.23 (1.13–1.35)
Analgesics	1.33 (1.24–1.42)	1.32 (1.23–1.41)	1.32 (1.23–1.42)
Nonsteroidal anti-inflammatory drugs	1.17 (1.11–1.24)	1.17 (1.10–1.24)	1.17 (1.10–1.23)

Number of observations: 25,463. Comparison groups: did not use corticosteroids, short duration of corticosteroid use, low-dose corticosteroid, female, comprehensive health plan, non-metropolitan statistical area, geographic region Northeast, no rheumatologist visit, no non-biologic DMARDs, no bone-active medications, no analgesics, and no nonsteroidal anti-inflammatory drugs

compared to non-users had higher mean costs (standard error) for total healthcare costs [$10,344.63 (268.84) vs. $7578.95 (272.88), respectively $P < 0.001$], physician visits [$735.91 (5.97) vs. $573.89 (9.07), respectively; $P < 0.001$], hospitalizations [$1661.88 (95.42) vs. $1072.92 (51.02), respectively; $P < 0.001$], ED visits [$273.63 (13.73) vs. $188.18 (9.67), respectively; $P < 0.001$], and medications [$1970.63 (52.31) vs. $1462.53 (43.11), respectively; $P < 0.001$].

DISCUSSION

The current study examined the associations between corticosteroid treatment patterns and initiation of biologic DMARDs, as well as associations between corticosteroid use and adverse events, healthcare utilization and costs before initiation of biologic DMARDs. The findings indicated that compared to non-corticosteroid users, RA patients who use corticosteroids, as well as those patients who use corticosteroids for a longer duration and at lower dosages, are less likely to initiate biologic DMARDS at any particular point in time. Corticosteroid users also experienced higher incidence rates of various adverse events than non-users. Likewise, corticosteroid users compared to non-users had greater healthcare utilization and costs prior to initiating biologic DMARDS.

In contrast to Kim et al., who found that corticosteroid users were more likely than non-users to initiate biologic DMARDs, this study found that corticosteroid utilization was associated with lower likelihood of initiating a biologic DMARD, as were longer duration of corticosteroid use and lower dosage [10]. We speculate that healthcare providers and RA patients who use corticosteroids, particularly for a longer length of time and/or at recommended lower dosages, may be hesitant to disrupt a stable treatment regimen by initiating biologic DMARDs. However, this may have negative consequences for patients, as Emery et al. noted that early initiation of biologic DMARDs was associated with improved outcomes and decreased hospitalizations [30].

As previously stated, corticosteroid use has historically been associated with serious adverse events such as development or worsening of diabetes. Likewise, the current study found that corticosteroid users had greater incidence rates than non-users of an array of adverse events including cardiovascular and metabolic/endocrinologic events, and were more likely to experience an adverse event occurrence as well as an increased number of adverse events. Use of corticosteroids for a longer duration compared to shorter duration was also associated with occurrence and increased number of adverse events. These findings support the ongoing concerns regarding the safety of corticosteroids in this patient population, as well as the conservative approach to corticosteroid use adopted by the 2015 American College of Rheumatology Guideline for the Treatment of RA [1].

Table 5 Comparison of annualized mean healthcare utilization and cost by corticosteroid use

Variables	All patients $N = 25,542$	Corticosteroid users $N = 10,433$	Non-users $N = 15,109$	*P* value
Unadjusted mean healthcare utilization and cost (Mean [SD])				
Number of visits				
Number of physician visits	8.41 (6.43)	10.06 (6.71)	7.27 (5.97)	< 0.0001
Number of hospitalizations	0.12 (0.41)	0.15 (0.42)	0.10 (0.10)	< 0.0001
Number of emergency department visits	0.68 (2.05)	0.84 (1.90)	0.57 (2.15)	<0.0001
Costs of healthcare utilization ($)				
Costs of physician visits	635.91 (805.36)	729.94 (715.53)	570.89 (856.02)	< 0.0001
Costs of hospitalization	2118.81 (17,051.16)	2351.68 (10760.88)	1957.77 (20,289.88)	0.07
Costs of emergency department visits	209.53 (913.56)	253.56 (940.05)	179.08 (893.55)	< 0.0001
Other outpatient costs	3191.08 (11,509.18)	3988.08 (13,377.72)	2639.90 (9594.66)	< 0.0001
Costs of medications	1514.21 (3302.11)	1807.48 (3484.32)	1311.39 (3154.19)	< 0.0001
Total healthcare costs[a]	7669.54 (23,277.77)	9130.75 (21,083.24)	6659.03 (24,631.57)	< 0.0001
Regression adjusted healthcare utilization and cost (Mean [SD])				
Number of visits				
Number of physician visits		10.11 (0.06)	7.29 (0.04)	< 0.0001
Number of hospitalizations		0.15 (0.00)	0.11 (0.00)	< 0.0001
Number of emergency department visits		0.89 (0.02)	0.57 (0.01)	< 0.0001
Costs of healthcare utilization ($)				
Costs of physician visits		735.91 (5.97)	573.89 (9.07)	< 0.0001
Costs of hospitalization		1661.88 (95.42)	1072.92 (51.02)	< 0.0001
Costs of emergency department visits		273.63 (13.73)	188.18 (9.67)	< 0.0001
Other outpatient costs		4270.70 (118.51)	2758.01 (86.47)	< 0.0001
Costs of medications		1970.63 (52.31)	1462.53 (43.11)	< 0.0001
Total healthcare costs[a]		10,344.63 (268.84)	7578.95 (272.88)	< 0.0001

[a] Total healthcare costs include all cost items listed

The issue of corticosteroid safety in RA treatment is further complicated by this study's dosage findings, in which medium dose (defined in this study as 2.5 to < 7.5 mg/day) was associated with reduced number of adverse events compared to low dose. This seemingly contradicts recent studies of corticosteroids in RA treatment suggesting that low dosage (even in the long-term) may result in non-significant, limited or mild adverse events [5, 6, 31]. However, without full access to the medical record of individual patients, it is difficult to fully explain

this finding. Another critical barrier in interpreting and comparing this finding to prior studies is the lack of a consistent definition of "low dosage." The present study set low dose as < 2.5 mg/day, but other studies have used a higher threshold such as < 7.5 mg/day or < 10 mg/day. For example, Panoulas et al. defined low dose as < 7.5 mg compared to medium dose of ≥ 7.5 mg, and found that long-term use of medium-dose corticosteroid therapy was associated with an increased prevalence of hypertension in RA patients compared to low dose and no use groups [32]. Moreover, the literature is by no means consistent concerning low-dose corticosteroids and their association with adverse events. For example, Haraoui et al. found that, compared to non-corticosteroid users, risk of infection was significantly increased among RA patients who used corticosteroids at either lower doses (≤ 5 mg) or higher doses (> 5 mg) [33]. As such, there are challenges in understanding the nuances of how corticosteroid dosage may impact adverse events. This point is reinforced by Santiago and da Silva who cautioned that the quantity and "especially the quality of evidence are too limited to establish conclusions" concerning the safety of low-dose corticosteroid use in RA [31].

Regarding healthcare utilization, this study found that corticosteroid use compared to non-use was associated with increased number of physician visits, hospitalizations, and ED visits. This is consistent with the findings of Yazdany et al. who also found that RA patients on glucocorticoid monotherapy had increased physician visits and hospitalizations compared to those who had at least one DMARD claim [9]. Likewise, the current study found that corticosteroid users had higher total healthcare costs, as well as higher costs associated with physician visits, hospitalizations, ED visits, and medications. While the literature is more limited concerning the impact of corticosteroid use on healthcare costs in the RA population, similar findings have been noted in studies of corticosteroid use in other chronic autoimmune disease populations. For example, a study by Chen et al. among patients with systemic lupus erythematosus found that glucocorticoid users compared to non-users had significantly greater healthcare utilization and costs [34]. Although our findings suggest that RA patients who use corticosteroids incur greater healthcare utilization and costs than those who do not, the reasons for this pattern are not known. A variety of factors may play a role in this finding. Users of corticosteroids may have higher healthcare utilization and costs than nonusers because of side effects associated with the use of corticosteroids, or they may experience more severe RA than nonusers. Another possibility may be that patients were put on corticosteroids for their RA because they had pre-existing medical conditions, which their physician judged would be worsened less by corticosteroids than by DMARDs. Future prospective studies should further explore and clarify the relationship between corticosteroid use and healthcare utilization/costs among RA patients.

LIMITATIONS

This study has limitations. Due to the observational nature of the study, it was impossible to explore the clinical rationale, disease activity, and duration, and/or patient background factors that may guide the observed treatment patterns. For example, patients may be using corticosteroids because they cannot tolerate some DMARDs, or have medical conditions that could be worsened by DMARDs. Second, there is a possibility that the method of calculating corticosteroid use may underestimate or overestimate the daily dosage or duration of therapy. This is because patients may take medications at doses lower or higher than the prescribed doses in the database. Third, this study is based on administrative databases that do not include clinical parameters related to study outcomes such as body mass index, smoking status, lab tests, etc. Further, all adverse events were determined based on the claims database. Other measures such as radiograph of the spine, body weight, hemogram, and lab variables for liver and kidney functions were not available. Finally, it is challenging to establish a causal relationship based on observational analysis such as this study; prospective studies are needed to establish a causal

relationship between corticosteroid use and outcomes such as adverse events and healthcare utilization and costs. Despite these limitations, the methods proposed in this study represent the state of the art for this type of research, and this study produced important findings in relation to the appropriate use of corticosteroids in RA treatment.

CONCLUSIONS

In summary, the findings indicate that RA patients who use corticosteroids, those with longer duration of use and lower dosages are less likely to initiate biologic DMARDS compared to their counterparts. RA patients who use corticosteroids and those with longer duration have increased likelihood and number of adverse events prior to initiating biologic DMARDS. Additionally, RA patients who use corticosteroids have increased healthcare utilization and costs prior to initiating biologic DMARDS. This study thus provides evidence that corticosteroid utilization may have deleterious effects on RA patient health and may increase the cost burden associated with treatment. Future studies should continue to examine the appropriate and optimal use of corticosteroids and biologic DMARDs in RA treatment.

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Data Availability. We cannot share data because our data sources are proprietary. However, we have included additional details of our methods and findings in a supplementary file.

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