A Retrospective Administrative Claims Database Evaluation of the Utilization of Belimumab in US Managed Care Settings

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ABSTRACT

Purpose: Belimumab is an approved therapy for the treatment of systemic lupus erythematosus (SLE). This study examined the real-world utilization patterns of belimumab and standard SLE therapies in patients after regulatory approval of belimumab in the United States.

Methods: A retrospective, observational study of belimumab users in the HealthCore Integrated Research Database was conducted using administrative claims data (GlaxoSmithKline Clinical Study Register Study ID: 114955). The overall population for analysis was composed of patients who were prescribed belimumab, had ≥6 months pre- and ≥6 months post-index medical and pharmacy eligibility, and at least 1 medical claim for SLE. Patients' clinical and demographic characteristics, treatment history, treatment patterns of belimumab, utilization of other medications, all-cause resource utilization, and costs were assessed. No hypotheses were tested.

Findings: All patients who were prescribed belimumab had an SLE claim. Patients who met all eligibility criteria (n = 155) were primarily female (94.2%; mean [SD] age, 44 [12] years) and 94.2% had used standard SLE therapies during the pre- and post-index periods. The majority had moderate SLE disease severity pre-index, and there was a small shift (approximately 8%) from moderate to mild SLE after initiation of belimumab. Two thirds of patients remained on belimumab therapy at 6 months post-index. The percentage of patients with any claim for oral corticosteroids remained stable; however, the point estimate for mean daily dose decreased slightly in months 3 to 6 post-index. Inpatient hospital admissions decreased slightly in the post-index period. The point estimate for total costs (excluding belimumab) decreased after initiation of belimumab, although overall total health care costs (including belimumab) increased.

Implications: All patients with a belimumab prescription had an SLE diagnosis on at least 1 medical claim, and the vast majority of those meeting all eligibility criteria had previously used a standard SLE therapy. Disease severity improved for a number of patients while on belimumab treatment and modest corticosteroid dose reductions were observed in later months. After initiating belimumab, health care costs (excluding belimumab) decreased. GlaxoSmithKline Clinical Study Register Study ID: 114955. (*Clin Ther.* 2015;37:2852–2863) © 2015 The Authors. Published by Elsevier HS Journals, Inc.

Key words: belimumab, real world, systemic lupus erythematosus, utilization patterns.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can result in organ damage, negatively affects health-related quality of life, and is associated with increased mortality.[1–4] In many patients with SLE, there is overexpression of the cytokine B lymphocyte stimulator, which is a major factor in the selection and survival of B cells.[5] Elevated circulating cytokine B lymphocyte stimulator levels are associated with increased disease activity and autoantibody concentrations.[5–7]

Belimumab is a human immunoglobulin G1λ (IgG1λ) monoclonal antibody that binds to and

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inhibits the activity of cytokine B lymphocyte stimulator.[8] The clinical efficacy of belimumab was reported in the BLISS Phase III clinical trials (BLISS-76 [ClinicalTrials.gov identifier: NCT00410384] and BLISS-52 [ClinicalTrials.gov identifier: NCT00424476]).[9,10] In March 2011, belimumab was approved for the treatment of moderate to severe SLE for patients with active autoantibody-positive SLE receiving standard therapy, and was the first new drug approved for SLE in >50 years.[11,12]

The objectives of the present retrospective observational study were to describe the clinical and demographic characteristics of patients receiving belimumab, including treatment history within the 6 months before initiation of belimumab; medication treatment patterns of belimumab (compliance and discontinuation) and the use of other standard lupus therapies after belimumab initiation; and all-cause resource use and costs pre- and post-belimumab initiation among patients initiating belimumab during the first 17 months after US Food and Drug Administration approval.

METHODS

Study Design and Population

This study (GHO-11-3501/GSK114955) was a retrospective, observational cohort study of newly initiated belimumab users in the United States that examined claims data from the HealthCore Integrated Research Database. IRB approval was not required, as this was an observational, noninterventional, administrative claims data analysis. The study was conducted in accordance with the appropriate research guidelines, such as the Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology. Patients with at least 1 insurance claim for belimumab (medical claims with belimumab-specific Current Procedural Terminology codes Q2044 or J0490, or pharmacy claims with Generic Product Identifiers 99422015002120 or 99422015002140) were identified during an intake period between March 1, 2011 and July 31, 2012. The index date was defined as the date within the intake period of the first insurance claim for belimumab (Figure 1). Medical, pharmacy, and eligibility data from between September 1, 2010 and January 31, 2013 (study period) were collected (Figure 1). Patients who had at least 1 medical or pharmacy claim for belimumab, ≥6 months pre- and ≥6 months post-index continuous medical and pharmacy eligibility (ie, continuous insurance coverage for this period), and at least 1 medical claim for SLE during the 6-month pre-index period or 6-month post-index period were selected for the final analysis (overall population). Patients were followed until loss of insurance eligibility or the end of the study period, whichever occurred first.

Study Assessments

Age and gender of participants were recorded at the index date. As validated clinical measures of SLE disease activity were not available in the database, the severity of SLE during the 6-month pre-index period and 6-month post-index period was determined using a previously published claims-based algorithm that was

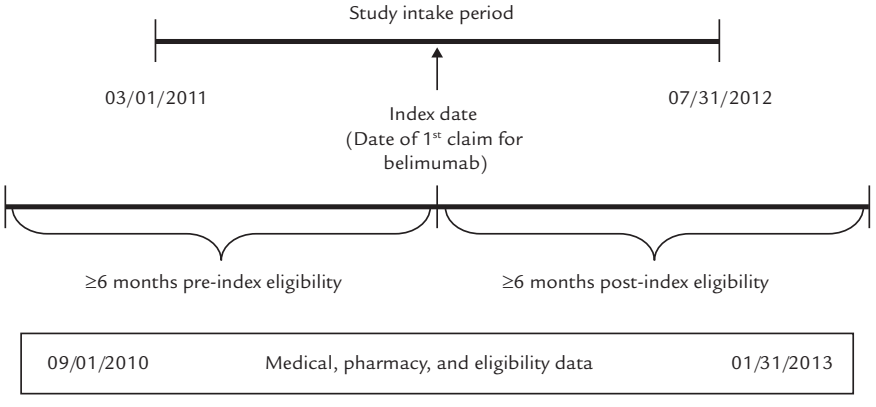

Figure 1. Study design.

developed using information from the literature and clinical consultations.[13] Patients were categorized as having mild, moderate, or severe SLE disease activity. The patient's overall condition was measured by the Deyo-Charlson Comorbidity Index both pre- and post-index.[14,15] In addition, SLE-specific comorbidities[16] and other comorbidities, determined by the *International Classification of Diseases, Ninth Revision* codes in medical claims, were recorded. Prescribed SLE medications included corticosteroids, antimalarials, and immunosuppressants. The number of patients who received prescribed SLE medications and the mean daily doses in the 6-month pre-index and 6-month post-index period were recorded by month for the overall population (patients meeting all inclusion criteria) and the subset of patients who remained on belimumab for at least 6 months. Treatment patterns were assessed by the number of patients who discontinued belimumab therapy (>105 days between 2 administrations) and the number of patients who complied (≤45 days between consecutive administrations [dosing interval multiplied by 1.5]) with treatment. In calculating discontinuations occurring >6 months after initiating belimumab, standard survival analysis techniques were used to account for censored data. All-cause health care resource utilization was based on the prevalence and the number of unique health care encounters during the specified time period. Resource use and health care costs were stratified by medical encounters (physician office visits [office evaluation and management services], emergency department visits, other outpatient services [all encounters not belonging to physician office visits, for example inpatient or emergency department visits, including claims reported as outpatient hospital visits, laboratory, urgent care, outpatient other facility, or office and clinic visits without Current Procedural Terminology codes shown as evaluation and management], inpatient hospitalizations) and pharmacy dispensing. Health care costs were reported as total costs across all resources (medical and pharmacy) and the combined amount paid by both the health plan and the patient; values were adjusted to 2013 US dollars based on the most recent medical care price index information provided by the Bureau of Labor Statistics at the time of analysis.

Data Analyses

The primary analyses were carried out on the overall population (as defined here). The study was descriptive and no formal comparison or hypothesis testing was performed. Descriptive statistics included mean (SD) and median, range, and relative frequency for continuous and categorical data, respectively. Concomitant medications were examined for the overall population and for a subgroup of patients who remained on belimumab treatment for at least 6 months. Mean daily doses of concomitant medications were calculated from strength × quantity dispensed/days of supply; prednisone-equivalent doses were calculated for corticosteroids.

RESULTS

Clinical and Demographic Characteristics of Patients Receiving Belimumab

Among approximately 18.5 million patients in the database who had at least 1 day of medical and pharmacy eligibility during the study period, there were 36,326 patients with at least 1 claim for SLE and 265 patients with a belimumab claim during the study period. All patients with a belimumab claim also had at least 1 medical claim for SLE. A total of 155 patients met all the eligibility requirements (at least 1 insurance claim for belimumab, at least 1 medical claim with a diagnosis code for SLE, and ≥6 months pre- and ≥6 months post-index insurance coverage) and were included in the final analysis (Table). The patient population was primarily female (94.2%) with a mean age of 44 years. The majority of patients had moderate SLE and there was a small shift (approximately 8%) from moderate to mild SLE severity in the 6-month post-index period, while the proportion of patients with severe SLE had no appreciable change. Mean and median follow-up times of continuous post-index eligibility (medical and pharmacy) were 383 and 372 days, respectively (quartile 1: 255 days; quartile 3: 507 days; maximum, 651 days). The mean Deyo-Charlson Comorbidity Index increased from 1.46 (pre-index) to 1.85 (post-index), indicating an increasing comorbidity burden. During both the pre- and post-index 6-month periods, the most common SLE-related comorbidities were cardiac disease, hypertension, rheumatoid arthritis (RA) or other inflammatory polyarthropathies, and myositis. In the pre-index period, 17.4% of patients had at least 2 claims for RA.

Belimumab Treatment Patterns Postinitiation

By 12 months post-index, 54.8% of patients remained on belimumab and at 18 months more than

Table. Demographics, disease severity, and possible comorbidities.
Data are given as percentages unless otherwise noted.

Patient Characteristics	Pre-index	Post-index
n	155	155
Female	94.2	—
Age, y, mean (SD)	44 (12)	—
SLE severity*		
Severe	16.1	16.8
Moderate	66.5	58.1
Mild	17.4	25.2
SLE-related comorbidities in ≥7.5% of patients (pre-index)†		
Anxiety	9.7	7.7
Depression	12.3	18.7
Nephritis	7.7	8.4
Renal disease	9.7	10.3
Cardiac disease	36.1	29.7
Hypertension	29.0	30.3
Rheumatoid arthritis	27.1	27.7
Osteoporosis	11.0	16.8
Myositis	25.2	24.5
Rash	8.4	4.5
Anemia	10.3	12.9
Raynaud syndrome	11.0	7.7
Non–SLE-related comorbidities in ≥7.5% of patients (pre-index)†		
Diabetes mellitus	11.0	9.7
Depression (other than major depressive disorder)	8.4	12.9
Urinary tract infection	14.8	11.6

SLE, systemic lupus erythematosus.
*Severity determined using a claims-based algorithm published previously.[13]
†Percentages for patients with at least 1 claim.

half of patients were still using belimumab (50.8%) (Figure 2). Approximately 7.1% of 155 patients discontinued belimumab after just one infusion. Most treatment withdrawals occurred in the first 6 months post-index and 66.5% of patients remained on therapy at 6 months post-index. During the entire post-index period, 43.2% of patients discontinued. A high percentage (90.3%) of patients had at least 1 episode of compliant administration (≤45 days between consecutive administrations) of belimumab and 47.7% of patients had noncompliant administration (>45 days and ≤105 days between consecutive administrations).

Prior and Concomitant Utilization of Standard Therapies for SLE

In this study, 94.2% of patients used a standard SLE therapy (corticosteroid, immunosuppressant, antimalarial) at some time during the 6-month pre-index and 6-month post-index period (Figure 3). The most common combination was antimalarials plus oral corticosteroids plus immunosuppressants (29.0% and 25.2% of patients pre- and post-index, respectively).

Pre-index, 66.5% of patients had a claim for oral corticosteroids with an estimated mean oral prednisone-equivalent daily dose of 17.6 mg among those on oral corticosteroids. The percentage of patients with a claim for oral corticosteroids remained in a stable range in both the overall population and among patients who received belimumab for at least 6 months, with some increase in the months immediately after the first belimumab infusion (Figure 4). Oral prednisone-equivalent daily dose, for patients prescribed corticosteroids initially, declined in the pre-index period but increased as the index date approached for both the overall population and patients who were on belimumab for at least 6 months (Figure 5). Post-index mean oral prednisone-equivalent daily dose tended to increase in months 1–2 and decrease thereafter. For patients who started oral corticosteroids within the pre-index period and did not discontinue before index (n = 42), 21 discontinued oral corticosteroids in post-index month 1, and 39 discontinued by post-index month 6.

The percentage of the overall population using oral immunosuppressant therapies was within a stable range from pre-index month 6 (35.5%–40.7% across all pre-index time points) to post-index month 6 (36.1%–39.4% across all post-index time points). Among patients who were on belimumab for at least 6 months, use of oral immunosuppressants was generally stable before belimumab initiation (36.9%–44.7% across all pre-index time points), but appeared to decline slightly from month 3 (39.8%) to month 6 (35.0%) post-index. The mean daily

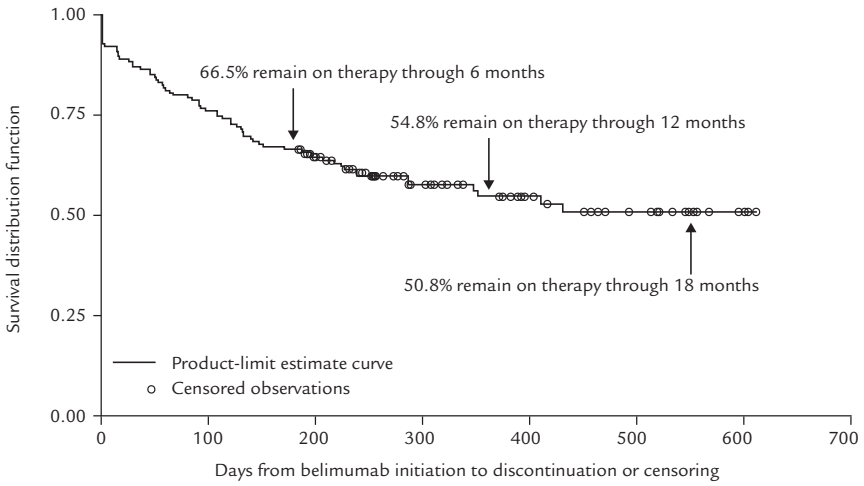

Figure 2. Time from belimumab initiation to discontinuation or censoring for all patients (n = 155).

dose of immunosuppressant among patients prescribed immunosuppressants in the overall population increased as the index date approached (from 556.7 mg at pre-index month 6 to 745.5 mg at pre-index month 1). There was a similar pattern among patients who were on belimumab for at least 6 months (494.0 mg at pre-index month 6 increasing to 690.7 mg at pre-index month 1). Post-index, the mean daily dose tended to decrease slightly (post-index month 2: overall population, 658.4 mg; patients on belimumab for at least 6 months, 659.5 mg) and then increased later in the post-index period (post-index month 6: overall population, 732.1 mg; patients on belimumab for at least 6 months, 777.4 mg).

Among patients prescribed oral antimalarials, use remained stable in the overall population (52.9%–60.0% pre-index; 52.9%–58.1% post-index) and among patients on belimumab for 6 months (52.4%–59.2% pre-index; 51.5%–58.3% post-index). The mean daily dose of oral antimalarials in the overall population (382.6–392.9 mg pre-index; 380.0–385.1 mg post-index) and among patients on belimumab for 6 months (390.2–398.8 mg pre-index; 382.2–386.4 mg post-index) was also stable pre- and post-index.

All-Cause Resource Use and Costs Pre- and Post-belimumab Initiation

Inpatient hospital admissions decreased slightly from 20.0% (31 patients) pre-index to 17.4% (27 patients) post-index (Figure 6A). Both the mean number of physician office visits and other outpatient visits increased post-index versus pre-index (Figure 6B).

Post-index, excluding belimumab, the cost of inpatient admissions, emergency department visits, and outpatient services decreased. Pharmacy costs remained very similar, while the cost of physician office visits increased slightly. Overall total costs, excluding belimumab, decreased pre- to post-index. However, total costs including belimumab increased from pre- to post-index (Figure 6C).

DISCUSSION

This is the first study to describe the real-world treatment patterns of belimumab in patients with SLE and explore its impact on the utilization of standard SLE therapies and all-cause health care resource utilization and costs.

The study population demographics were similar to those of the BLISS-76 trial (conducted in 19 countries in Europe and North and Central America),[9] the BLISS-52 trial (conducted in 13 countries in Latin America, Asia-Pacific, and Eastern Europe),[10] and the OBSErve study (a medical chart review of US patients with SLE that examined the clinical effectiveness of adding belimumab to standard SLE therapies for at least 6 months).[17] In the present study, a majority of the population were estimated to have moderate SLE. After belimumab treatment, a small proportion of

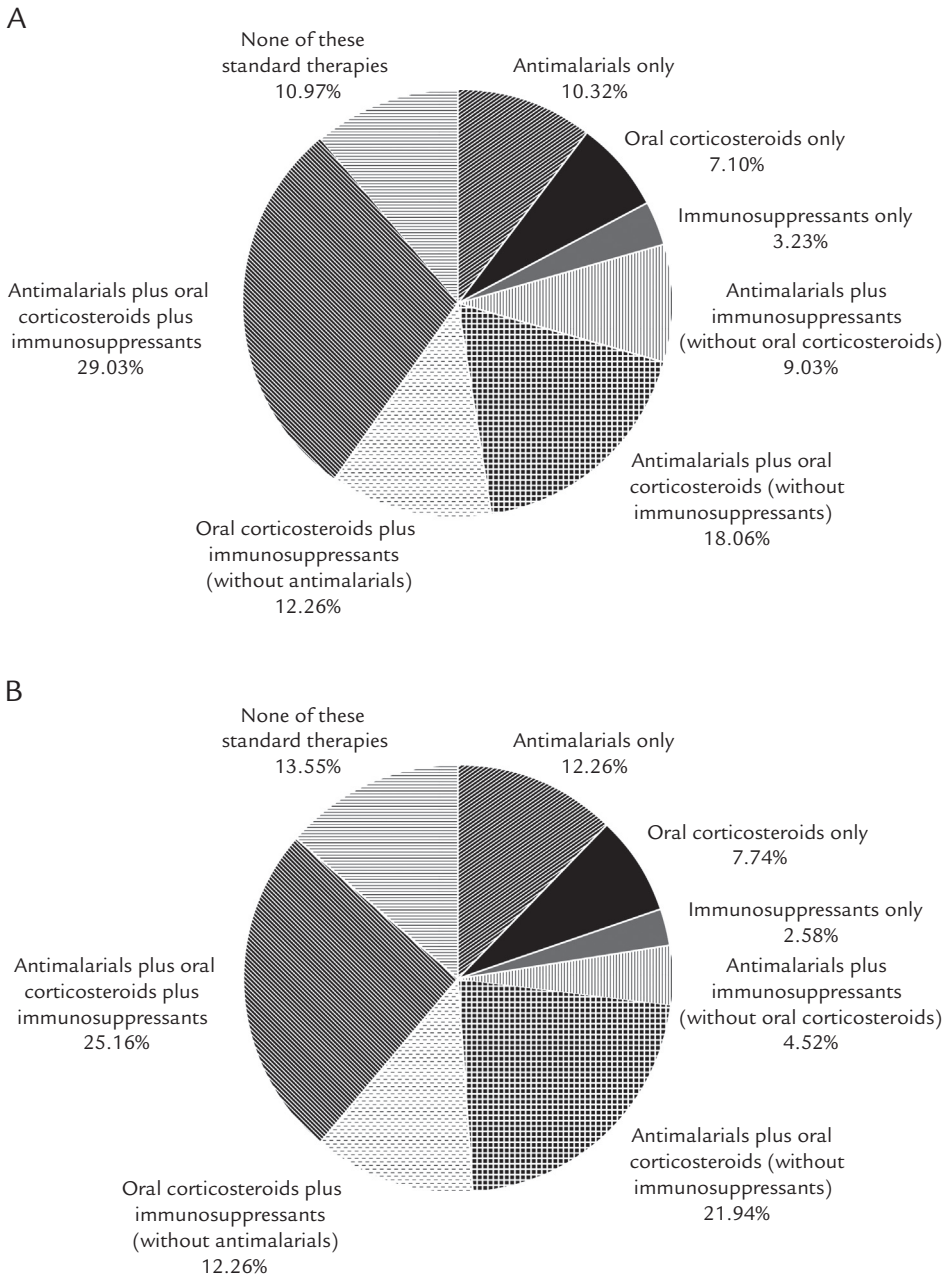

Figure 3. Percentage of patients using standard therapies for systemic lupus erythematosus in the pre-index (A) and post-index (B) periods.

Corticosteroids (betamethasone, budesonide, cortisone, desoxycorticosterone, dexamethasone, fludrocortisone, hydrocortisone, methylprednisolone, paramethasone, prednisolone, prednisone, triamcinolone), antimalarials (artemether-lumefantrine, atovaquone-proguanil, chloroquine, halofantrine, hydroxychloroquine, mefloquine, primaquine, pyrimethamine, quinacrine, quinine, sulfadoxine and pyrimethamine, chloroquine, and primaquine), and immunosuppressants (azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil, and chlorambucil).

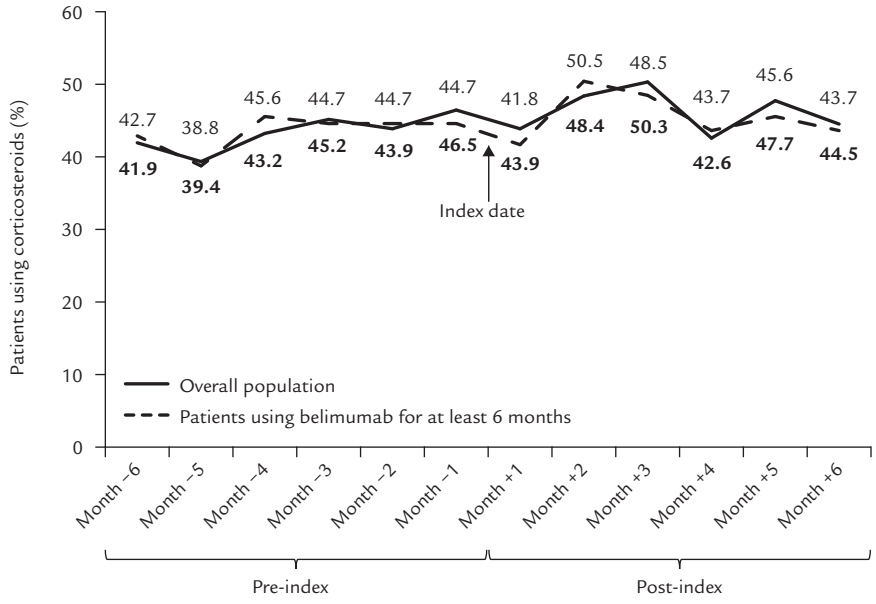

Figure 4. Percentage of patients using oral corticosteroids in the overall population and among patients using belimumab for at least 6 months.

Lower data labels in bold represent the overall population. Labels above represent patients using belimumab for 6 months.

patients (approximately 8%) reported improved disease severity from moderate to mild.

A high number of RA claims were recorded in this study, pre- and post-index; 27.7% of patients had at least 1 post-index RA claim, despite being treated with belimumab, which possibly indicates a coding issue. Overlap between RA and SLE can occur, although it is not thought to be common; 1 study of medical records found SLE features in 15.5% of patients with RA over 25 years.[18] This is somewhat lower than the overlap in the present analysis, further suggesting the possibility of a coding issue. The reasons for this coding issue are unknown, but the high number of RA claims may be due to payers' expectation of an RA code for certain tests and physicians' consequent use of this particular code to ensure reimbursement.

The recommended dosing regimen for belimumab is 10 mg/kg on days 0, 14, and 28, and at 4-weekly intervals thereafter.[12] In the real world, patients might not be able to adhere to the monthly dosing schedule due to time constraints through work, family, or other commitments. Based on the criterion of $\leq$45 days for compliant administration, a high percentage of patients (approximately 90%) had at least 1 compliant administration of belimumab. However, >40% of patients had at least 1 instance of noncompliance, which might have had an impact on efficacy. The pattern of belimumab use found that most treatment withdrawals occurred in the first 6 months of treatment, which might not be sufficient time to adequately assess the efficacy of belimumab.

The majority of patients (94.2%) used a standard therapy at some point during the 6-month pre-index and 6-month post-index period. The monthly use of oral corticosteroids in the 6-month pre-index period ranged from 39.4% to 46.5% of patients and is comparable with the percentages of patients taking oral corticosteroids (>7.5 mg/d at baseline; 44.0%–48.0%) in the BLISS-76 trial.[10] However, in the OBSErve study and BLISS-52 trial, 78.7% and 69.4% of patients, respectively, were taking oral corticosteroids (>7.5 mg/d in the case of the BLISS-52 trial) at baseline.[10,17] During the first 6 months on belimumab, the percentage of patients using oral corticosteroids in the present study remained stable. However, the mean daily dose increased slightly in months 1 to 2 post-index, and then subsequently dropped in the later post-index period (3 to 6 months),

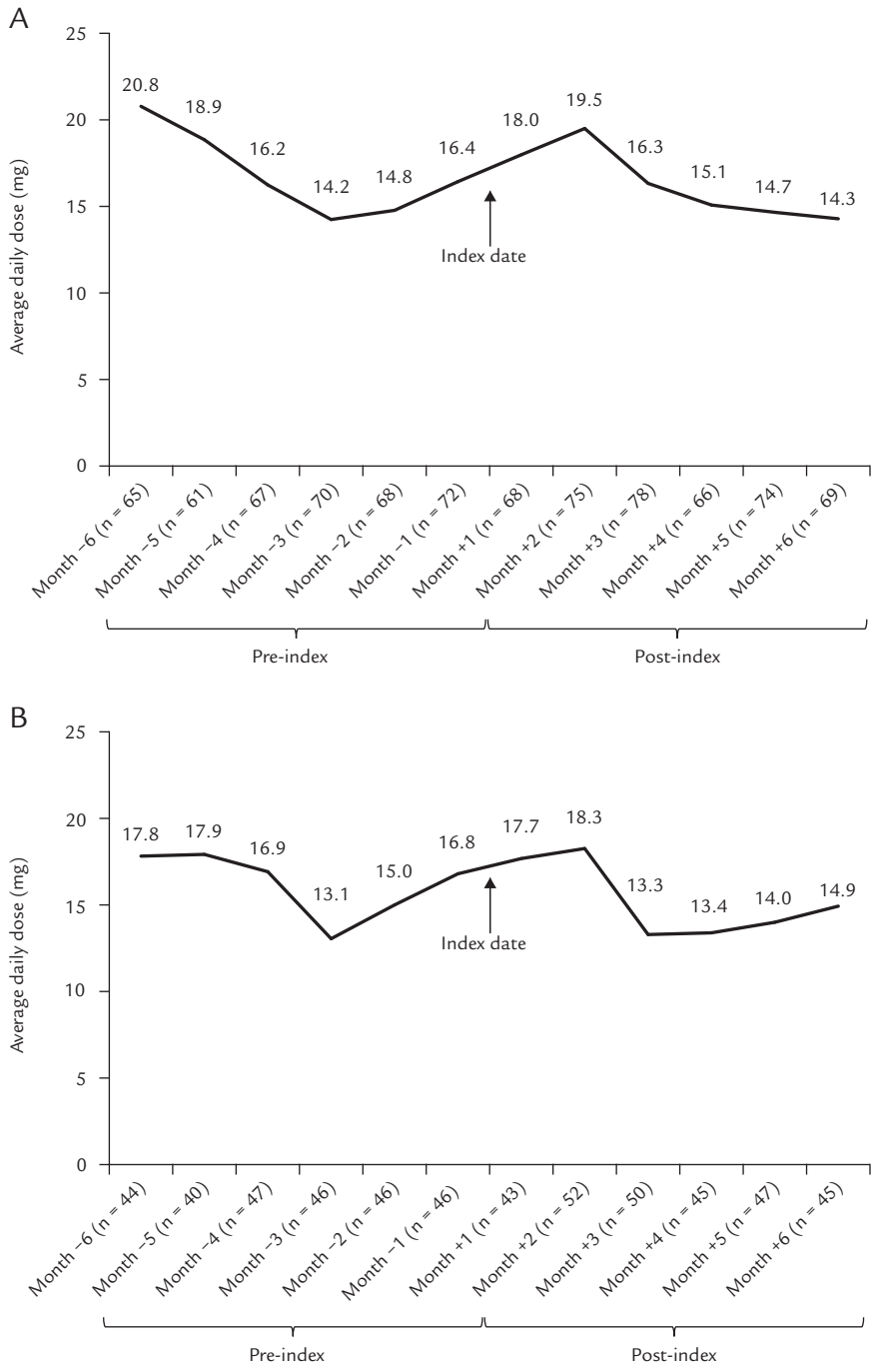

Figure 5. Mean prednisone equivalent daily dose of oral corticosteroids in the overall population (A) and among patients using belimumab for at least 6 months (B).
n, number of patients receiving oral corticosteroids at each time point.

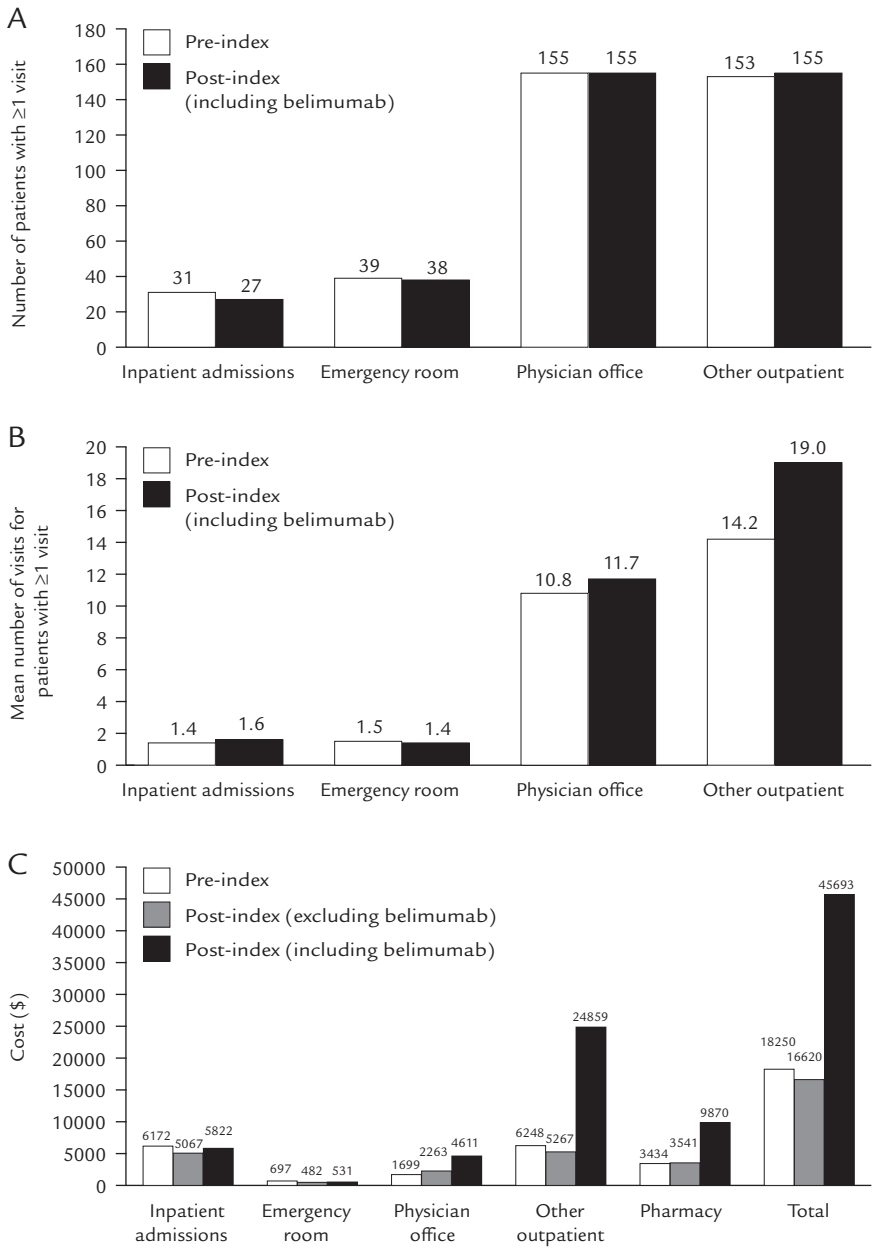

Figure 6. Number of patients with a recorded visit (A), mean number of visits for patients with recorded visits (B), and health care costs in the pre- and post-index periods (C).

which could indicate a potential decrease in corticosteroid dose with the use of belimumab, as was observed in the BLISS-52 trial.[10] However, speculation is limited by the fact that an insurance claim might not necessarily indicate corticosteroid use in this study, whereas in the BLISS trials and OBSErve study, the dose of corticosteroids taken by patients was recorded by the physician.[9,10,17] In the BLISS trials and OBSErve study, the mean daily oral corticosteroid dose decreased steadily over time, although a significant change was only found in BLISS-52, which might reflect treatment patterns in non-US

countries.[9,10,17] In the BLISS trials, changes in corticosteroid dose were controlled in part by the study protocol[9,10]; observational studies such as this, which measure real-world outcomes, are important for the understanding of treatment patterns.

In this study, the relatively constant proportion of patients on corticosteroids, and the small increase in dose in the early post-index period, might be due to some initial caution among physicians prescribing belimumab for the first time. Anecdotal evidence suggests that some physicians might want their patients to have corticosteroids available to treat acute SLE symptoms during times of flare, and might have verbally advised them to increase or decrease their dose as needed. Alternatively, belimumab could have been initiated during an SLE flare and treating physicians might have felt the need to treat the flare with corticosteroids, given that the effectiveness of belimumab is thought to increase slowly during the first few months after therapy initiation.[9,10] The percentages of patients using oral immunosuppressants and antimalarials were generally comparable with those in the BLISS trials.[9,10]

This study suggested there was a small drop in the number of hospitalizations with a small reduction in associated costs. There was a slight increase in physician office visits, which was likely due to patients receiving belimumab infusions in the physician's office. Costs for patients receiving belimumab were relatively large and included in-pharmacy claims and other outpatient claims, probably due to infusion visits. After the initiation of belimumab, as expected, overall total costs increased, mainly due to the costs associated with belimumab. However, total costs excluding belimumab decreased slightly, primarily driven by the decrease in inpatient admissions cost and other outpatient services.

There are several limitations of the study. First, claims data may not give a complete picture of the actual treatments and doses taken by the patient, providing only data on those who filled a prescription that resulted in a processed insurance claim and providing no information on the safety of belimumab. Second, the presence of a diagnosis code on a medical claim does not guarantee positive presence of a disease, as the diagnosis code may be incorrectly coded or included as physicians order tests that would rule out the hypothesized diagnosis. However, 94% of patients in this study had evidence of receiving standard lupus therapies, which suggests that in the majority of cases the SLE diagnosis was accurate. Third, as with all claims-based analyses, the study results may not be generalizable to the overall belimumab user population because patients who have commercial health insurance may have different characteristics from those without health insurance. Fourth, another limitation of database studies is the lack of information on clinical measures, including severity, level of organ involvement and laboratory findings; thus, it was not possible to control for such factors. A previously published algorithm was used to measure disease severity,[13] but this algorithm is not yet validated and misclassification of patients could have occurred. Finally, the data presented in this study are purely descriptive, with no formal comparisons made between pre-index and post-index periods for statistical significance. It would be beneficial to compare the belimumab group against a control group, but selecting an appropriate control group without randomization would be challenging. Similarly, using patients as their own controls could be problematic, if in fact many belimumab patients initiate therapy during an SLE flare.

CONCLUSIONS

The results of this claims database study reported on the real-world use of belimumab; patients are adults with an SLE diagnosis code on at least 1 medical claim, and the majority had used a standard SLE therapy in the 6-month pre-index and 6-month post-index period. Most belimumab discontinuations occurred in the first 6 months of treatment, and there was a decline in corticosteroid dose in the later post-index period, which suggested a conservative approach to corticosteroid use with some potential for corticosteroid dose reduction in subsequent months. Excluding the cost of belimumab, total health care costs for belimumab users decreased relative to the pre-treatment period, due to a reduction in inpatient and other outpatient costs. However, total costs that include belimumab increased after starting treatment with belimumab. This study is a valuable first step in understanding the profile of patients prescribed belimumab in clinical practice during the first 18 months it was available, and offers an opportunity to inform hypothesis generation for future studies.

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All named authors meet the International Committee of Medical Journal Editors criteria for authorship of this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published. The authors would like to thank David Chang, MD and Michael Cinoman, MD, of GlaxoSmithKline, for their critical review of the manuscript.

AUTHOR CONTRIBUTIONS

X. Ke and D. Eisenberg Lawrence contributed to the conception and design of the study, and acquisition, analysis and interpretation of the data. R. Boggs and H. Kan contributed to data analysis and interpretation. A. Oglesby and J. Patel contributed to the conception and design of the study, and data analysis and interpretation. All authors contributed to the drafting and revision of the manuscript and gave final approval of the version to be published. The authors agree to be accountable for all aspects of the work.

CONFLICTS OF INTEREST

HealthCore Inc. and GlaxoSmithKline plc (GSK) designed and conducted this study, which was funded by GSK. The study sponsor (GSK) contributed to interpretation of the data, and supported the authors in development of the manuscript. GSK is committed to publicly disclosing the results of GSK-sponsored clinical research that evaluates GSK medicines, and as such was involved in the decision to submit. Medical writing and editorial assistance were provided by Clare Slater, PhD, and Louisa Pettinger, PhD, of Fishawack Indicia Ltd, which was funded by GSK. A. Oglesby, H. Kan, R. Boggs and J. Patel were employees of GlaxoSmithKline at the time of the study and own GlaxoSmithKline stock. X. Ke is an employee of HealthCore Inc., which received funding from GlaxoSmithKline to conduct the study. D.F. Eisenberg Lawrence was an employee of HealthCore Inc. at the time of the study. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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