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ORIGINAL RESEARCH

Real-World Effectiveness of Intravenous Belimumab on Clinical Outcomes in Patients With Systemic Lupus Erythematosus in Saudi Arabia: The OBSErve Observational Study

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Purpose: To describe intravenous (IV) belimumab's clinical effectiveness in patients with systemic lupus erythematosus (SLE) in real-world practice in Saudi Arabia.

Patients and methods: This retrospective, observational OBSErve study (GSK Study 215349) analyzed medical record data for adults with SLE receiving IV belimumab. Index date was the date of belimumab initiation. The primary endpoint was overall clinical response per physician judgement (categorized as worse, no improvement, improvement of <20%, 20–49%, 50–79%, ≥80%) at 6 months post-index. The secondary endpoints included changes from index in Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index (SELENA-SLEDAI) score and corticosteroid dose at 6 months post-index; and healthcare resource utilization (HCRU) 6 months pre- and post-index.

Results: Of 47 patients enrolled, 44 patients completed ≥6 months of IV belimumab treatment and were included in the analysis. Most patients were female (91.5%) and the mean (standard deviation [SD]) age was 33.1 (8.1) years. At 6 months post-index, overall physician-assessed clinical improvements of ≥20% and ≥50% were reported for 97.7% (n=43) and 79.5% (n=35) of patients, respectively; 2.3% (n=1) of patients had no improvement, and no patient worsened. Mean SELENA-SLEDAI score decreased by 7.8 points during the 6 months post-index. Mean (SD) corticosteroid dose decreased from 10.2 (7.5) mg/day at index to 6.2 (3.4) mg/day at 6 months post-index. Reductions in unscheduled physician office and emergency room visits were observed during the post-index versus pre-index periods.

Conclusion: Real-world data from patients with SLE treated with IV belimumab in Saudi Arabia demonstrated clinical improvements and reductions in corticosteroid dose and HCRU. Although the low number of patients and lack of a control group limit interpretation, the similar findings to the other OBSErve studies support the effectiveness of belimumab for patients with SLE in Saudi Arabia.

Keywords: disease activity, disease modification, glucocorticoids, monoclonal antibody, systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with diverse clinical and laboratory manifestations.[1] Despite the emergence of biological therapies, SLE remains difficult to manage,[2] and its highly

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heterogeneous and relapsing–remitting nature contributes to increased use of healthcare services and costs in this patient population.[3,4]

SLE prevalence in the Al-Qaseem region of Saudi Arabia is estimated at 19.28 per 100,000 population, which aligns with 4.3–85 per 100,000 population globally;[5–8] however, epidemiological data in Saudi Arabia are limited.

SLE manifestations in patients in Saudi Arabia appear to be similar to those of patients from other Arab and non-Arab countries,[9] with treatment strategies also broadly aligning with those of the rest of the world.[10,11] Antimalarials, corticosteroids and immunosuppressive agents form the standard of care for SLE. However, long-term, cumulative corticosteroid use is associated with an increased risk of adverse events and organ damage, increasing mortality risk.[12,13] Therefore, reducing corticosteroid dose to ≤5 mg/day or completely withdrawing corticosteroids where possible is an important goal for SLE management.[10]

Belimumab, a human immunoglobulin monoclonal antibody, is approved as an add-on therapy in patients with SLE and active lupus nephritis (LN) in several countries.[14,15]

The efficacy and safety of intravenous (IV) belimumab have previously been demonstrated in randomized clinical trials,[16–19] although their eligibility criteria may limit their generalizability to real-world settings.[20] Belimumab's effectiveness has been evaluated across North America, South America, and Europe through the global OBSErve program, a multi-country, real-world evaluation of belimumab in SLE, using a broadly similar protocol to conduct independent studies in different countries. OBSErve has consistently demonstrated clinical improvements across SLE manifestations among patients treated with belimumab, according to the local indication in routine clinical practice.[21–27]

This OBSErve Saudi Arabia observational study investigated the effectiveness of belimumab (licensed for SLE in Saudi Arabia in June 2013)[28] in real-world clinical practice in patients with SLE in Saudi Arabia after 6 months of IV treatment and by describing socio-demographic and clinical characteristics, including the characteristics of belimumab treatment, change in Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index (SELENA-SLEDAI) score, use of concomitant medications, and healthcare resource utilization (HCRU).

Methods

Study Design

OBSErve Saudi Arabia was an observational study (GSK Study 215349), designed to retrospectively collect real-world information from patient medical records on the short-term outcomes of IV belimumab use in patients with SLE. De-identified data were collected via standardized electronic case report form (eCFR) between September 2021 and March 2022. The study time points/periods were 6 months before belimumab initiation, at belimumab initiation (index date) and 6 months after (follow-up period; Supplementary Figure 1). Data collected included patient characteristics, characteristics of IV belimumab treatment (reasons for initiation/discontinuation), comorbidities, treatment outcomes, medication use and healthcare resource utilization (HCRU).

This study was reviewed and approved by the relevant Institutional Review Board or Ethics Committee for Saudi Arabia for each participating site and complied with the Declaration of Helsinki. The requirement for patient informed consent was waived as all data were anonymized and de-identified (retrospectively) from patient records.

Physicians

Rheumatologists from sites prescribing IV belimumab as part of standard care were invited and selected to participate in the study if deemed eligible based on a feasibility questionnaire. Eligible rheumatologists were those currently managing ≥10 patients with SLE, had ≥5 years of experience treating SLE, had treated ≥2 patients who were receiving IV belimumab, and had ≥1 patient receiving IV belimumab at the time of recruitment.

Patient Eligibility Criteria

The site physician selected eligible patients according to the following criteria: ≥18 years of age; confirmed SLE diagnosis; received first IV administration as part of standard care ≥6 months before inclusion; and had documented

medical records for the duration of the study follow-up period. Patients who discontinued before completing 6 months of IV belimumab treatment were also included if they had received ≥1 dose of IV belimumab.

Patients who received SC belimumab during the follow-up period, who enrolled in an SLE-related clinical trial during the 12-month patient observational period or who started IV belimumab as part of a clinical trial, were excluded from this study; of note, patients who received any other therapies, including biologics, pre- or post-index were eligible for inclusion. Patients were also excluded if they had severe active LN (defined as: proteinuria >6 g/24 h or equivalent using spot urine protein-creatinine ratio or serum creatinine >2.5 mg/dL; or active nephritis; or requirement for hemodialysis or extreme high-dose prednisone >100 mg/day) or kidney disease within 90 days pre-index, or documented record of severe active central nervous system lupus (eg, seizures, psychosis, organic brain syndrome, cerebrovascular event) within 60 days pre-index, in line with belimumab prescribing information at the time of the study.

To minimize selection bias, all patients meeting the inclusion criteria were considered for inclusion. However, sites consecutively enrolled patients starting with the most recent patient to have completed 6 months of IV belimumab treatment and worked backwards until the site's target was reached.

Outcomes

The primary outcome was the proportion of patients with a clinical improvement from index to 6 months post-index, as assessed using a physician-deemed clinical improvement scale and categorized as worse, no improvement, or improvement of <20%, 20–49%, 50–79%, or ≥80%.

Secondary outcomes included change in Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index (SELENA-SLEDAI) score from index to 6 months post-index; treatment patterns of concomitant SLE medications, particularly corticosteroids, at and/or before index and during 6 months post-index; change in laboratory results (anti-dsDNA antibody and complement C3/C4 levels) from index to 6 months post-index; SLE flares (defined in Supplementary materials) 6 months pre-and post-index; and HCRU (number of scheduled/unscheduled physician office visits, and emergency room [ER] visits) 6 months pre-/post-index.

Statistical Analysis

Given the study's descriptive nature, no formal sample size calculations were conducted. The enrolled set, comprising all patients who met the eligibility criteria and received ≥1 dose of IV belimumab, was used to analyze patient baseline characteristics, concomitant medications, belimumab use and disease activity measured by SELENA-SLEDAI. The full analysis set (FAS), comprising all patients from the enrolled set who completed ≥6 months of IV belimumab, was used to analyze clinical outcomes, shifts in concomitant SLE-related corticosteroid dose, and HCRU.

Descriptive statistics (counts and percentages) were used to analyze categorical data, and mean, median, standard deviation (SD), minimum and maximum were used to analyze continuous data. No imputation of missing data was used.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting or dissemination plans of our research.

Results

Patient Baseline Characteristics

Overall, four physicians from four sites enrolled 47 eligible patients with SLE (enrolled set); 44 completed ≥6 months of IV belimumab treatment and were included in the FAS. In total, 51.1% (n=24) completed >24 months of IV belimumab treatment and were still receiving the treatment at the time of study conclusion.

Most patients were female (91.5%, n=43); mean (SD) age was 33.1 (8.1) years (Table 1). At index, most patients had moderate or severe SLE (74.5%, n=35) and 19.1% (n=9) were previously diagnosed with LN. Most patients were diagnosed with SLE within 10 years of the index date (1–5 years: 31.9%, n=15; 6–10 years: 42.6%, n=20). Overall, 44.7% (n=21) of patients had ≥1 comorbid condition; depression (19.0%, n=4/21), anxiety, antiphospholipid syndrome, fibromyalgia, and rheumatoid arthritis (each 14.3%; n=3/21) were reported most frequently (Table 1).

Table 1 Patient Socio-Demographic and Clinical Characteristics (Enrolled Set, N=47)

	N=47
Female, n (%)	43 (91.5)
Age, years, mean (SD)	33.1 (8.1)
Race/ethnicity, n (%)	
Arab	47 (100.0)
Comorbid condition(s) present pre-index[a]	
n (%)	21 (44.7)
Mean (SD)	1.8 (0.9)
Comorbid condition(s) present pre-index by type, n (%)[b]	
Depression	4 (19.0)
Anxiety	3 (14.3)
Antiphospholipid syndrome	3 (14.3)
Fibromyalgia	3 (14.3)
Rheumatoid arthritis	3 (14.3)
Previously diagnosed with LN, n (%)	9 (19.1)
Time since SLE diagnosis (years), n (%)[c]	
<1	0
1–5	15 (31.9)
6–10	20 (42.6)
11–15	7 (14.9)
>15	4 (8.5)
Unknown	1 (2.1)
SLE severity at initial diagnosis, n (%)	
Mild	5 (10.6)
Moderate	22 (46.8)
Severe	14 (29.8)
Unknown	6 (12.8)
SLE severity at index, n (%)	
Mild	4 (8.5)
Moderate	26 (55.3)
Severe	9 (19.1)
Unknown	8 (17.0)

(*Continued*)

Table 1 (Continued).

	N=47
Disease activity at index, n (%)[d]	
Persistent activity	27 (57.4)
Flare	17 (36.2)
Remission	1 (2.1)
Unknown	2 (4.3)
Disease characteristics at index, n (%)[e,f]	
Any of below	37 (78.7)
Low C3 (<LLN)[g]	21 (44.7)
Low C4 (<LLN)[g]	14 (29.8)
High anti-dsDNA	22 (46.8)
Proteinuria (>ULN)	4 (8.5)
Leukopenia	25 (53.2)
Thrombocytopenia	1 (2.1)
Hemolytic anemia	6 (12.8)

Notes: [a]All comorbid conditions of interest documented at any time pre-index; number of conditions are summarized only for patients with >0 documented condition; [b]among patients with comorbid conditions at index (n=21). More comorbidities were collected during the study, but only the most relevant are reported here; [c]data collected prior to or at index date; [d]SLE severity was assessed based on physician judgement; [e]denominator for "Any of below" percentages equals patient count within the enrolled set; denominator for individual laboratory characteristics equals patient count within "Any of below"; [f]multiple reasons possible; [g]LLN was according to the local laboratory.

Abbreviations: LLN, lower limit of normal; LN, lupus nephritis; SD, standard deviation; SLE, systemic lupus erythematosus; ULN, upper limit of normal.

At index or 30 days before, the most commonly reported clinical and immunological manifestations were arthritis (74.5%, n=35), fatigue (38.3%, n=18), alopecia and rash (36.2% each, n=17), leukopenia (27.7%, n=13), low complement levels (C3, C4 or CH50; 25.5%, n=12) and increased anti-dsDNA antibody levels (21.3%, n=13). Physicians rated these manifestations as moderate or severe in most of the documented cases.

Overall, 93.2% (n=41) of patients received corticosteroids during 6 months pre-index and 90.9% (n=40) at index (Table 2). Mean (SD) corticosteroid dose at index was 10.2 (7.5) mg/day. The most frequently received SLE medications (excluding steroids) up to index were antimalarials (89.1%, n=41), methotrexate (30.4%, n=14), mycophenolate mofetil (21.7%, n=10), azathioprine and rituximab (15.2% each, n=7; Table 2).

Most patients initiated belimumab in 2019 (44.7%, n=21) or 2020 (25.5%, n=12), and 68.1% (n=32) of patients were initiated on belimumab by the current treating physician (Supplementary Table 1). The mean (SD) starting dose was 10.9 (5.8) mg/kg; 38.3% (n=18) of patients received 6 doses of IV belimumab during the first 6 months and 29.8% (n=14) received the expected 8 doses (Supplementary Table 1). Most patients (87.2%, n=41) did not have any changes to their belimumab therapy during the first 6 months. Of the 6 patients who had changes in the first 6 months, 3 patients missed/skipped a mean (SD) of 5.7 (5.5) infusions due to the COVID-19 pandemic restricting access (Supplementary Table 1).

The most common reasons reported for belimumab initiation (multiple reasons allowed) were previous treatment regimen not effective (68.1%, n=32), patient's condition worsening (51.1%, n=24) and intent to reduce corticosteroid use (27.7%, n=13; Supplementary Table 1). Overall, 6.4% (n=3) of patients discontinued treatment within the first 6 months of initiation, owing to loss to follow-up (n=1), emergent adverse event (n=1; pulmonary embolism) and the COVID-19 pandemic (n=1).

Table 2 SLE Medications Received up to Index and Post-Index (Enrolled Set, N=47)

	Up to Index	During 6 Months Post-Index
Received any SLE medications (excluding corticosteroids), n (%)[a]	46 (97.9)	41 (87.2)
Azathioprine	7 (15.2)	6 (14.6)
Cyclophosphamide	1 (2.2)	-[b]
Methotrexate	14 (30.4)	11 (26.8)
Antimalarials	41 (89.1)	40 (97.6)
Mycophenolate mofetil	10 (21.7)	8 (19.5)
Mycophenolic acid	1 (2.2)	-[b]
NSAIDs	3 (6.5)	1 (2.4)
Rituximab	7 (15.2)	2 (4.9)[c]
Received SLE-related corticosteroids, n (%)	41 (93.2)[d,e]	40 (90.9)[e]
Corticosteroid dose (mg/day), mean (SD)	10.2 (7.5)[f]	6.2 (3.4)
Change in corticosteroid dose (mg/day), mean (SD)	−4.0 (7.1)	

Notes: [a]Patients could have more than one medication documented; [b]data not available at 6 months post-index; [c]no information is available on when rituximab was administered relative to belimumab; [d]during 6 months pre-index; [e]among patients with available data (n=44); [f]the dose at index.
Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; SD, standard deviation; SLE, systemic lupus erythematosus.

Overall Clinical Response

Of the 44 patients included in the FAS, 97.7% (n=43) had an overall physician-assessed clinical improvement of ≥20% and 79.5% (n=35) had an improvement ≥50% (Figure 1). One patient had no improvement and no patients worsened.

Change in SELENA-SLEDAI Score

Overall, 31 patients had data on the disease activity assessment by SELENA-SLEDAI at both index and 6 months post-index. Among these patients, an improvement in disease activity was observed as indicated by a decrease in the total mean (SD) SELENA-SLEDAI score from 12.7 (5.7) at index to 4.5 (4.1) at 6 months post-index (Supplementary Table 2).

SLE Medications

Overall, 90.9% (n=40) of patients received corticosteroids at index and at 6 months post-index (Table 2). At index, 52.5% (n=21/40) of patients were receiving a corticosteroid dose ≥7.5 mg/day; 22.5% (n=9/40) had a dose decrease to <7.5 mg/day, 10.0% (n=4/40) discontinued steroids and 20.0% (n=8/40) remained at ≥7.5 mg/day dose at 6 months post-index

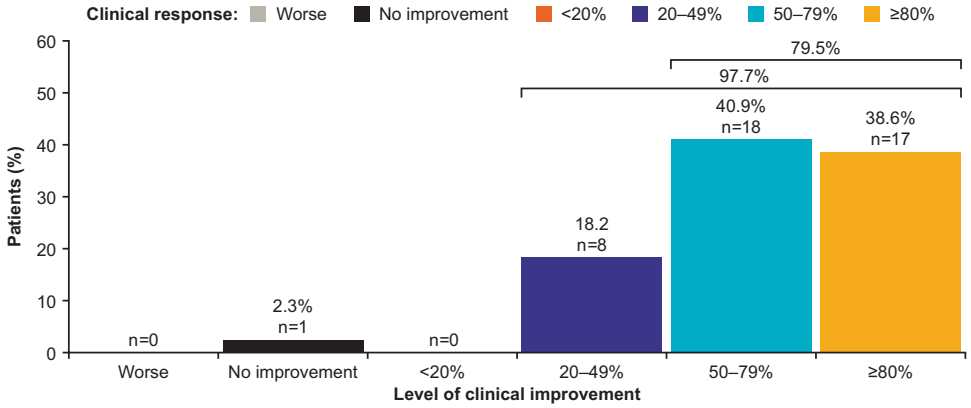

Figure 1 Clinical response at 6 months post-index versus index using the physicians' judgement scale for overall disease activity (FAS, N=44).
Abbreviation: FAS, full analysis set.

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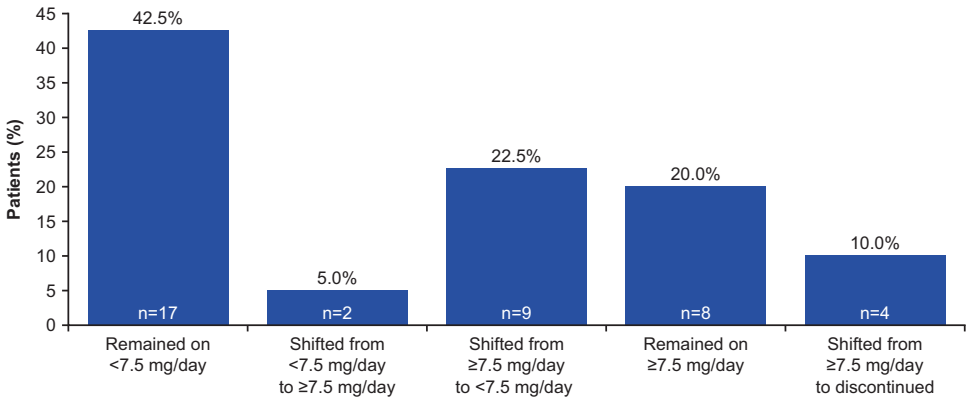

Figure 2 Shifts in concomitant SLE-related corticosteroid dose from index to 6 months post-index (FAS, N=44[a]).
Notes: [a]40 out of 44 patients had data on corticosteroid use at both index and 6 months post-index time points and were included in this analysis.
Abbreviations: FAS, full analysis set; SLE, systemic lupus erythematosus.

(Figure 2). At index, 47.5% (n=19/40) of patients were receiving a corticosteroid dose <7.5 mg/day; 42.5% (n=17/40) remained at <7.5 mg/day dose and 5.0% (n=2/40) had a dose increase to ≥7.5 mg/day at 6 months post-index (Figure 2). The mean corticosteroid dose decreased from 10.2 (7.5) mg/day from index to 6.2 (3.4) mg/day 6 months post-index.

The proportion of patients receiving SLE medications other than steroids and belimumab decreased from 97.9% (n=46) during the 6-month pre-index period to 87.2% (n=41) during the 6 months post-index (Table 2).

Laboratory Assessments

The mean (SD) anti-dsDNA antibody level decreased from 261.1 (497.9) IU/mL (n=31) pre-index to 171.2 (302.6) IU/mL at 6 months post-index (n=21). Mean (SD) complement levels remained consistent throughout the study (C3, 0.8 [0.4] g/L at index [n=39] and 6 months post-index [n=32]; C4, 0.2 [0.2] g/L at index [n=39] and 0.2 [0.1] g/L at 6 months post-index [n=32]).

SLE Flares

Data on SLE flares were documented for 19/47 enrolled patients in the pre-index period; 57.9% (n=11/19) had ≥1 mild/moderate flare and 47.4% (n=9/19) had ≥1 severe flare. Post-index, 21 patients had data on SLE flares documented; 61.9% (n=13/21) had 0 mild/moderate flares, 38.1% (n=8/21) had 1 mild/moderate flare, 90.5% (n=19/21) had 0 severe flares and 9.5% (n=2/21) had 1 severe flare. No patient had ≥1 SLE flare (mild/moderate and severe) during the post-index period. The mean (SD) number of total SLE flares reduced from 1.5 (1.6) pre-index to 0.5 (0.5) in the post-index period.

HCRU

All 44 patients in the FAS had data recorded on SLE-related scheduled physician's office visits during both pre- and post-index periods. During the pre- and post-index periods, the mean (SD) number of scheduled visits was 2.9 (1.6) and 3.2 (1.9), respectively, with 97.7% (n=43) and 88.6% (n=39) of patients, respectively having ≥2 visits (Table 3).

Overall, 43 and 41 patients had data recorded on SLE-related unscheduled visits during pre-index and post-index periods, respectively. Pre-index, the mean (SD) number of unscheduled visits was 0.4 (0.7), with 32.6% (n=14) of patients having ≥1 unscheduled visit and 67.4% (n=29) of patients having no unscheduled visits (Table 3). Post-index, the mean (SD) number of unscheduled visits per patient was 0.2 (0.5); most patients (82.9%, n=34) had no unscheduled visits during this period, and only 17.1% (n=7) had ≥1 unscheduled visit (Table 3).

During the observation period, 20.5% (n=9/44) of patients had any SLE-related emergency room visit, but the number of visits was only recorded for 6 patients. Of these 6 patients, one had ≥2 visits pre-index and none had ≥2 visits post-index (Table 3). Pre-index, the mean (SD) number of emergency room visits was 1.3 (1.4), falling to 0.5 (0.5) post-index.

Table 3 Summary of HCRU 6 months Before Index and After 6 months of IV Belimumab Treatment (FAS, N=44)

	Pre-Index N=44	Post-Index N=44
Number of SLE-related scheduled visits to physician office		
n	44	44
Mean (SD)	2.9 (1.6)	3.2 (1.9)
0 visits, n (%)	0	0
1 visit, n (%)	1 (2.3)	5 (11.4)
≥2 visits, n (%)	43 (97.7)	39 (88.6)
Unknown, n (%)	0	0
Number of SLE-related unscheduled visits to physician office		
n	43	41
Mean (SD)	0.4 (0.7)	0.2 (0.5)
0 visits, n (%)	29 (67.4)	34 (82.9)
1 visit, n (%)	10 (23.3)	6 (14.6)
≥2 visits, n (%)	4 (9.3)	1 (2.4)
Unknown, n (%)	1 (2.3)	3 (6.8)
Number of SLE-related emergency room visits, n=6[a]		
Mean (SD)	1.3 (1.4)	0.5 (0.5)
0 visits, n (%)	1 (16.7)	3 (50.0)
1 visit, n (%)	4 (66.7)	3 (50.0)
≥2 visits, n (%)	1 (16.7)	0
Unknown, n (%)[b]	3 (6.8)	3 (6.8)
Number of SLE-related hospitalizations, n=7[c]		
Mean (SD)	0.4 (0.5)	0.8 (0.8)
0 visits, n (%)	3 (42.9)	2 (28.6)
1 visit, n (%)	2 (28.6)	2 (28.6)
≥2 visits, n (%)	0	1 (14.3)
Unknown, n (%)[b]	2 (4.5)	2 (4.5)

(*Continued*)

Table 3 (Continued).

	Pre-Index N=44	Post-Index N=44
Duration of SLE-related hospitalizations (nights), n=7[c]		
Mean (SD)	1.0 (1.7)	4.3 (5.1)
0 nights, n (%)	3 (42.9)	2 (28.6)
1 night, n (%)	1 (14.3)	0
≥2 nights, n (%)	1 (14.3)	2 (28.6)
Unknown, n (%)[b]	2 (4.5)	2 (4.5)

Notes: [a]Among patients with ≥1 emergency room visit; [b]among patients of full analysis set population (n=44); [c]among patients with ≥1 SLE-related hospitalization before or after index. Note, due to the type of information collected, it was not possible to differentiate between hospitalizations related to IV infusions and those that were SLE-related.

Abbreviations: FAS, full analysis set; HCRU, healthcare resource utilization; IV, intravenous; SD, standard deviation; SLE, systemic lupus erythematosus.

Data on SLE-related hospitalizations were available for 15.9% (n=7) of patients. For the 5 patients with a known number and duration of hospitalizations before index, the mean (SD) number of hospitalizations was 0.4 (0.5) and the mean (SD) duration of hospitalizations was 1.0 (1.7) nights (Table 3). The mean (SD) number and duration of hospitalizations increased to 0.8 (0.8) and 4.3 (5.1), respectively, during the post-index period. To note, 1 patient had a record of 10 nights hospitalized and, thus, the data on the increased number and duration of hospitalizations post-index should be interpreted with caution.

Discussion

This non-interventional study investigated physician-reported clinical response to 6-month IV belimumab therapy as well as treatment patterns for SLE in real-world practice in Saudi Arabia. After 6 months of IV belimumab treatment, patients who did not discontinue treatment experienced overall clinical improvements consistent with the OBSErve studies conducted in other countries, including a pooled analysis of multi-country data (Supplementary Table 3).[21–27] All but one patient saw an improvement of at least 20% in their overall clinical condition and no patient worsened. Almost 80% of patients had an improvement of more than 50% in overall clinical response. Notable improvement was also observed in overall SELENA-SLEDAI score, with a 7.8-point reduction from index to 6 months post-index.

Corticosteroids generally provide rapid symptom relief in patients with SLE; however, long-term use increases the risk of irreversible organ damage accrual.[12,13] Therefore, minimizing corticosteroid use is a crucial goal in the management of SLE.[29] In this study, 75% of patients were able to discontinue, reduce to, or maintain their corticosteroid dose at <7.5 mg/day, versus 25% who either shifted to, or remained on ≥7.5 mg/day. These corticosteroid-sparing results support findings of a previous IV belimumab clinical trial, in which a greater proportion of belimumab-treated patients had a dose reduction of ≥25% to ≤7.5 mg/day compared with placebo-treated patients,[19] as well as some previous OBSErve studies.[21,23,25–27,30] In a previous OBSErve study with a longer follow-up period, greater proportions of patients experienced corticosteroid dose reductions with longer belimumab treatment (up to 24 months; 76.9%)[23] compared with shorter treatment duration (up to 6 months; 46–67%).[25–27,30]

A reduction in the overall use of SLE-related medications was observed. While 9 patients were reported to have received rituximab during the study period (n=7 before or at belimumab initiation; n=2 after belimumab initiation), information on medications prescribed before and at index was merged, and no information on the concomitant treatment timing was collected. Thus, it is unknown if these patients were receiving rituximab at the time of belimumab initiation or if they used rituximab earlier in their treatment history. Over the past several years, the off-label use of rituximab, a B-cell–depleting, anti-CD20 monoclonal antibody, has emerged as one of the biological therapies used in clinically

challenging cases,[31] despite failed clinical trials in SLE and LN.[32,33] Previous attempts to identify patient features predictive of treatment failure on rituximab had modest results other than the suggestion that rituximab's effectiveness appears decreased in less active disease, and in patients with renal involvement.[34] The BLISS-BELIEVE study, which evaluated treatment with belimumab combined with a single cycle of rituximab, showed that this sequential treatment did not improve control rates among patients with SLE, and more serious infections were observed compared with belimumab combined with placebo or standard therapy.[35] However, the administration of rituximab before belimumab has been shown to significantly reduce the risk of flare in patients with SLE refractory to conventional therapy.[36] Despite the mixed results, rituximab may be considered as a therapeutic option in organ-threatening disease refractory or with intolerance/contraindications to standard immunosuppressants.[29]

Most patients in this study (44.7%) initiated IV belimumab in 2019 and 25.5% initiated in 2020. The date of initiation of IV belimumab should not be seen as evidence or proxy for medication access, as factors such as healthcare center procurement may play a role in limiting the number of patients who initiated belimumab each year. The mean starting IV belimumab dose was 10.9 mg/kg, which is slightly higher than the recommended 10.0 mg/kg dose; however, this was most likely due to a potential data entry error for one patient (receiving a 50.0 mg/kg starting dose) which was included in the analysis for completeness. One-fifth (19%) of belimumab initiators had a documented history of depression pre-index; however, it is unknown how many patients may have suffered from depression at the time of belimumab initiation. In this study, neither information on the timing or severity of depression pre-index were recorded. Three patients discontinued belimumab therapy during the first 6 months of treatment and there were no deaths recorded during the duration of belimumab treatment. Notably, only one patient discontinued belimumab therapy due to an emergent adverse event (pulmonary embolism), suggesting that belimumab was well tolerated by most patients. The other two discontinuations were due to the COVID-19 pandemic and loss to follow-up.

There was a slight reduction in the number of unscheduled physician and ER visits during the 6 months of belimumab therapy. In contrast, the mean number of scheduled physician visits increased slightly in the 6 months after belimumab therapy start compared with the previous 6 months; this is likely due to the requirement to attend for monthly infusions for the IV formulation. SC belimumab administration may reduce the number of scheduled physician visits. It would be of interest to investigate the difference in physician visits among patients on IV belimumab compared with those on SC belimumab. The mean number and duration of hospitalizations increased during the 6-month period of belimumab therapy. However, these results should be interpreted with caution as one patient had a record of 10 hospitalization nights during this time. As physicians were required to capture only SLE-related hospitalizations, based on the unexpected results found, we hypothesize that IV belimumab infusions (which should have been recorded as scheduled visits), or another unrelated event, were incorrectly recorded and contributed to this outlier result. Furthermore, as fewer patients experienced fewer flares requiring hospitalization in the post-index period, it is reasonable to hypothesize that the increase in hospitalizations was not SLE-related.

One of the possible limitations of this study is the relatively short duration of 6 months of belimumab treatment; however, the chosen study duration was considered adequate based on the results of the BLISS-52 and BLISS-76 studies, which showed the SLE responder index efficacy measure was found to plateau after 6 months.[16,17] In addition, patient population and investigation procedures may have varied across different sites. The primary endpoint of clinical response was evaluated based on the individual, subjective clinical judgement of the treating physician; however, the physicians enrolled in this study had considerable experience in managing SLE. Furthermore, this clinical judgement reflects the real-world practice where patients are often assessed without the use of any standard tools. In addition, the results may be biased by identification of eligible patients who had a beneficial response to IV belimumab and exhibited favorable tolerance to IV belimumab with limited safety events. A number of patients also received rituximab therapy prior to or following belimumab administration, limiting the ability to evaluate the effect of belimumab in these patients. Furthermore, patient identification by physicians may have differed between sites, consisting of a mix of both paper and electronic medical records, which could introduce a sampling bias and impact the generalizability of the results. There may have been a potential for diagnostic misclassification in the absence of an objective differential diagnosis recorded or conducted by the treating physician. Due to the retrospective nature of the study, the number of patients without flares could have been underestimated, as it is possible that physicians may have recorded no flares as "not

documented/unknown". Other limitations include the low number of patients included in some analyses, the lack of a control group, no imputation of missing data and the descriptive nature of this study, meaning that caution should be used when interpreting the results. However, when compared with other OBSErve studies, many of which had larger patient samples and similar designs, as well as the pooled analysis of some OBSErve studies, our findings were similar. Despite the mentioned limitations inherent to the nature of a retrospective observational study, the results of this and other OBSErve studies help improve our understanding of the effectiveness of new therapies and how they are used in a real-world setting.

Conclusions

In this retrospective, observational OBSErve Saudi Arabia study, patients receiving IV belimumab for a minimum of 6 months achieved clinically meaningful improvements in their overall condition and a reduction of steroid use, thus providing real-world evidence for belimumab's effectiveness for the treatment of SLE in patients in Saudi Arabia.

Patient and Public Involvement

Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Data Sharing Statement

Please refer to GSK weblink to access GSK's data sharing policies and as applicable seek anonymized subject level data via the link https://www.gsk-studyregister.com/en/.

Ethics Approval

This study was reviewed and approved by the Research King Saud University College of Medicine Institutional Review Board (IRB; E-21-6207) for the King Khaled University Hospital site, King Fahad Medical City IRB (21-300) for the King Fahad Medical City site, Tabuk IRB (TU-077/021/107) for the New King Fahd Multi Speciality Hospital site, and Ministry of Health Regional Committee for Research Ethics (17-07-2021) for the Asir Central Hospital site.

Patient Consent for Publication

The requirement for patient informed consent was waived by the Institutional Review Board (IRB) Sub-Committee for Health Sciences Colleges Research on Human Subjects King Saud University College of Medicine (E-21-6207) for the King Khaled University Hospital site, King Fahad Medical City IRB (21-300) for the King Fahad Medical City site, Tabuk IRB (TU-077/021/107) for the New King Fahd Multi Speciality Hospital site, and Ministry of Health Directorate Health Affairs – Aseer Region (REC-17-07-2021) for the Asir Central Hospital site, as all data were anonymized and de-identified (retrospectively) from patient records.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

IAl-H is an employee of King Fahad Medical City, has received grant/research support from GSK and Pfizer and speaker honoraria from Pfizer, AbbVie, GSK, Novartis, and Eli Lilly. IA has received grant/research support from College of Medicine, King Saud University and is an employee of King Saud University. HH has received grant/research support from GSK and speaker honoraria from Pfizer, AbbVie, Jansen, and Novartis. MK, LT, JQ, AM, and SN are employees of GSK. AliA, TE, MO, and DdS, were employees of GSK at the time of the data collection and analysis. MK, TE, and SN hold financial equities in GSK. The authors report no other conflicts of interest in this work.

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