Real-World Effectiveness of Belimumab in Systemic Lupus Erythematosus: A Systematic Literature Review

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ABSTRACT

Introduction: Belimumab is a recombinant human monoclonal antibody that binds to soluble B-lymphocyte stimulator and inhibits its biological activity. Since receiving approvals for the treatment of systemic lupus erythematosus (SLE), several observational studies have investigated the effectiveness of belimumab in the real-world setting. This study reports a systematic review and meta-analysis of the literature to evaluate the real-world effectiveness of belimumab for the treatment of SLE.
Methods: A literature search following PRISMA Guidelines and limited to studies in English was performed (2014−2020) to identify relevant studies reporting effectiveness outcomes of belimumab in patients with SLE. A modified version of the Newcastle–Ottawa Scale was used to assess study quality. Outcomes, including SLE Disease Activity Index (SLEDAI) score, prednisone-equivalent use, and SLE flare were pooled and analyzed using statistical aggregation methods.
Results: The literature search identified 514 articles for initial review. Of these, 17 articles were suitable for data extraction and summary. Baseline characteristics of patients in real-world studies were generally similar to those of relevant clinical trials, including age, sex, disease duration, SLEDAI score, and prednisone-equivalent use. Real-world use of belimumab was associated with reductions in SLEDAI score (mean baseline score to month 6: 10.1–4.4; 57% reduction), prednisone-equivalent dosing (mean baseline dose to month 6: 12.1 mg/day to 6.9 mg/day; 43% reduction), and flare frequency (12 months prior to belimumab to 12 months after belimumab: 1.15–0.39 mean flares per patient per year; 66% reduction). Long-term data (up to 2 years post-treatment initiation) for SLEDAI score and prednisone-equivalent dose indicated that improvements in both outcomes continue over time among patients remaining on therapy.
Conclusions: In the real-world setting, observed outcomes with belimumab for the treatment of SLE are consistent with those reported from randomized clinical trials. Improvements persist long-term for SLEDAI

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activity and prednisone-equivalent use with belimumab.

Keywords: Belimumab; Real-world; Systematic literature review; Systemic lupus erythematosus

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Key Summary Points

What is already known about this subject?

Belimumab is a targeted human monoclonal antibody that is approved for use in patients with active systemic lupus erythematosus (SLE) and adult patients with active lupus nephritis.

Although the efficacy and positive benefit–risk profile of belimumab has been demonstrated in several phase 3 trials, a number of real-world, observational studies have also investigated the effectiveness and safety of belimumab outside of a research setting.

What does this study add?

This systematic review and meta-analysis evaluated the real-world effectiveness of belimumab in SLE by using data from 17 relevant observational studies published between 2014 and 2020.

Use of belimumab in real-world clinical practice was associated with reduced disease activity, corticosteroid use, and frequency of SLE flares; furthermore, long-term data indicated that improvements continue over time among patients remaining on therapy.

How might this impact clinical practice or future developments?

These data demonstrate that real-world belimumab use provides favorable outcomes consistent with those observed in randomized controlled trials, with improvements persisting over a 24-month period.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a complex autoimmune disease that can affect many different organ systems and has various clinical presentations that may mimic the signs and symptoms of other conditions [1, 2]. Symptoms can include fatigue, joint pain, fever, shortness of breath, chest pain, and a distinct facial butterfly rash, all of which can periodically worsen in flare episodes [1, 2]. Given the heterogeneous presentation of symptoms, the diagnosis of SLE is difficult, and is typically based on characteristic clinical findings of the joints, skin, kidneys, the central nervous system, and blood [1]. There is no cure for SLE, and treatment goals focus on decreasing disease activity, preventing new flares, and slowing organ damage progression [3].

A variety of medications can be used for SLE treatment, including non-steroidal anti-inflammatories, corticosteroids, anti-malarials, immunosuppressants, and biologic agents [3]. A serological characteristic of SLE is the presence of autoreactive B cells [4]; belimumab is a targeted recombinant human monoclonal antibody that inhibits the action of circulating B-lymphocyte stimulator. Belimumab is approved for use in patients aged ≥ 18 years with active, autoantibody-positive SLE in both intravenous (IV) and subcutaneous (SC) formulations [5]. Approval has also been granted in the USA, EU, Brazil, China, Japan, and Russia for IV use of belimumab in pediatric patients aged ≥ 5 years [5–10]. Further approval has been granted in the USA for the treatment of adult active lupus nephritis [11].

In the randomized clinical trial setting, several phase 3 trials (including BLISS-52 [NCT00424476], BLISS-76 [NCT00410384], BLISS-SC [NCT01484496], and the North East Asian study [NCT01345253]) have been conducted, demonstrating a positive benefit–risk profile with belimumab, including improved SLE Responder Index (SRI) rates and a reduced risk of flares [12–15]. Although such studies provide evidence of efficacy, the strict eligibility criteria of randomized trials can limit their generalizability to everyday clinical practice, as trial populations may differ from patients in a

real-world setting [16]. Since receiving approval for use, a number of observational studies have investigated the real-world effectiveness of belimumab to assess the impact of belimumab outside of the research setting, providing further information on safety, effectiveness, and economic performance [16]. The objective of this systematic review and meta-analysis was to identify effectiveness (e.g., disease activity, standard of care treatment, and quality of life) data reported in published real-world (non-clinical trial) studies of belimumab in SLE, and estimate the overall effectiveness of belimumab in the real-world context.

METHODS

Study Design

To identify articles published between 2014 and 2020 that report effectiveness outcomes of belimumab for the treatment of patients with SLE, a systematic literature review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [17]. Published observational (prospective or retrospective) cohort studies on this topic were identified via simultaneous searches of the MEDLINE and EMBASE databases through ProQuest, using the following database-specific terms: *emb("systemic lupus erythematosus – drug therapy – belimumab") (LIMITS: Document type: Article + Review, English language) NOT (emb("phase 2 clinical trial") OR emb("phase 3 clinical trial") OR emb("phase 1 clinical trial")).* This study is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

The searches were limited to include only those articles and reviews written in English, and to exclude conference abstracts, or articles that had no abstract. Two reviewers independently assessed the identified publications, and specific data of interest were abstracted from the studies that met the inclusion criteria; these are detailed in Table 1. Manual searches of the references cited in published systematic reviews were also conducted, and meta-analyses used to identify relevant studies that were not captured in the database search. Data extraction was performed by one researcher and then reviewed by a second for accuracy. Data for each outcome were collected at baseline and then at any available follow-up points from the respective study publications. The variables extracted from each study comprised study characteristics, patient characteristics, and study outcomes (Supplementary Material, Table S1). This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

The SLE Disease Activity Index (SLEDAI) measures disease activity across the 10 days prior and uses a weighted (by type of manifestation) checklist of 24 variables, comprising clinical and laboratory items [18]. A total SLEDAI score is then calculated, ranging from 0 to 105. The modified SLE Disease Activity Index—Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA-SLEDAI) and SLEDAI-2K were introduced to expand the scope of the SLEDAI [19, 20]. The SELENA-SLEDAI flare index comprises SELENA-SLEDAI score, changes in disease activity, medication changes, hospitalizations, and physician's global assessment of disease [19].

A modified version of the Newcastle–Ottawa Scale was used to assess the quality of the observational studies included in the review. The scale was modified to remove the 'comparability' domain and 'selection of the non-exposed cohort' item, as this literature review was non-comparative; thus, the maximum score of the unaltered scale was reduced from 9 to 6. The Agency of Healthcare Research and Quality conversion of these scores was modified to the following: 'Good' (2 or 3 in selection domain AND 2 or 3 in outcome domain), 'Fair' (1 in selection domain AND 2 or 3 in outcome domain), and 'Poor' (0 in selection domain OR 0 or 1 in outcome domain).

Statistical Analyses

SLE disease activity (as assessed by SELENA-SLEDAI or SLEDAI-2 K [considered equivalent for the purpose of the analysis]), prednisone-equivalent oral corticosteroid use, and

Table 1 Key inclusion and exclusion criteria for systematic literature review (PICOS table)

	Inclusion criteria	Exclusion criteria
Population	Adults/children aged 5 years or older with active, autoantibody-positive SLE; studies including patients with lupus nephritis will also be included	Patients with acute, severe central nervous system manifestations due to lupus
Interventions	Belimumab added to standard therapy	N/A
Comparators	Any or none	N/A
Outcomes	Reporting any effectiveness or quality-of-life outcome	Pharmacokinetic or metabolic studies
Study design	Observational studies (prospective/retrospective)	Case reports or case series
	Systematic reviews	Editorials and letters
		Commentaries
		Open-label clinical trial extensions

N/A not applicable, *PICOS* population, intervention, comparators, outcomes, study design; *SLE* systemic lupus erythematosus

incidence of flares were the only outcomes of interest that provided sufficient data for quantitative pooling. All outcomes were reported for belimumab only (i.e., they were not comparative effectiveness measures) as a single numeric value plus standard error (SE).

Statistical aggregation methods used in the present study included inverse variance weighting and the DerSimonian and Laird method for fixed and random effects pooling, respectively, at 6 months or the closest available timepoint. In studies where standard deviation (SD) was not reported, it was imputed using the sample-size weighted average of the available SDs. Median data were used as a proxy for the mean where reported. Heterogeneity among outcomes was calculated using the Q statistic and associated I^2 values, with values $> 50\%$ indicative of heterogeneity among studies. Sensitivity analyses were not conducted based on heterogeneity results, as the identified observational studies provided insufficient information to adequately assess the potential sources of heterogeneity. In studies reporting prednisone-equivalent dosage and SLEDAI outcomes at multiple time points up to 24 months, the time-varying effects in these outcomes between 6 and 24 months were assessed via linear regression using the OpenBUGS software

program, using a Bayesian analysis framework with vague prior information.

RESULTS

Characteristics of the Included Studies

Systematic review of the literature from MEDLINE/EMBASE records identified 514 articles, of which 39 full-text articles were suitable for review. Publications ($n = 23$) were excluded from the analyses for a variety of reasons, with the most common being a lack of belimumab specificity ($n = 7$) (Fig. 1). Two publications reported US database studies that did not evaluate SLE outcomes of interest, and another article was excluded because it described prevalent belimumab use (i.e., treatment was not newly initiated). Two studies were identified via the manual search. A total of 17 articles were selected as suitable for data extraction and summary (Fig. 1), comprising a mixture of prospective and retrospective studies.

The included studies were conducted in Brazil, Canada, Europe, and the USA, and the majority were restricted to adult patients with SLE (mean age, 37–47 years; Table 2). Where reported, disease duration and baseline SLE
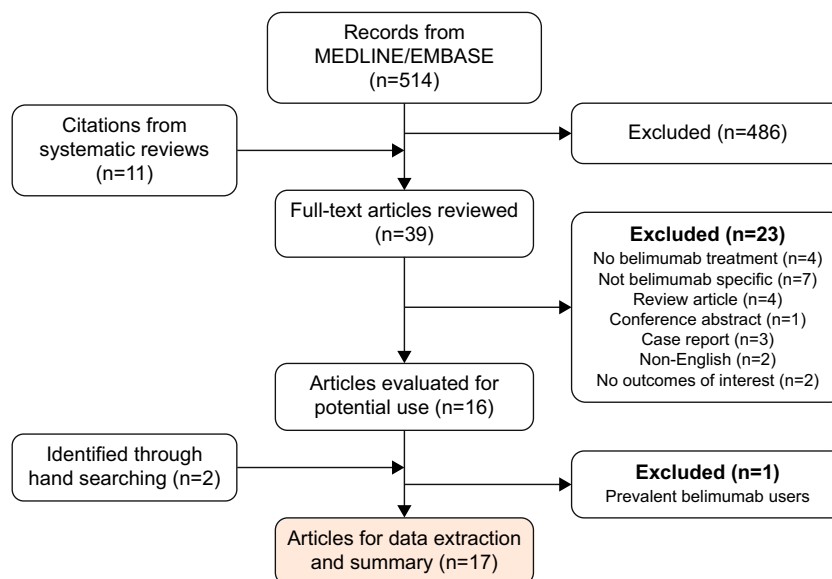
Fig. 1 Systematic review study identification flow diagram (PRISMA flowchart). *PRISMA*, preferred reporting items for systematic reviews and meta-analyses

severity were similar between studies. Most of the studies included patients who were using oral corticosteroids at baseline, with a mean daily dose range (where reported) of prednisone-equivalent 9–30 mg/day. All studies evaluated belimumab 10 mg/kg IV, consistent with recommended dosage levels [5]. New-castle–Ottawa Scale assessments determined that all studies identified for inclusion were of 'good' quality.

Outcomes

SLEDAI
Of the 13 studies reporting SLEDAI score data up to 6 months, the majority saw improvement in SLEDAI between 3 and 6 months (Fig. 2a). Mean baseline SLEDAI score was 10.1 (range, 8.0–12.7). Mean SLEDAI at 6 months was approximately 4.4, a reduction from baseline of 57%. Significant heterogeneity was observed among the 6-month SLEDAI data, with mean SLEDAI scores ranging from 1.1 to 6.0, with relatively large SDs (range, 1.2–4.1).

Those studies (*n* = 6, comprising a total of 888 patients) reporting longer-term mean SLE-DAI score showed an apparent, but small, decline in disease activity after 6 months

[21–26]. A linear regression model estimated that the monthly reduction in mean (standard error [SE]) SLEDAI was 0.08 (0.01; fixed-effect model) and 0.09 (0.05; random-effect model), which corresponds to a SLEDAI decrease of 1.44 over months 6–24.

Prednisone-equivalent use
Mean baseline prednisone-equivalent dose was 12.1 mg/day (range, 8.8–30.0 mg/day). Among the 15 publications reporting such data, observed reductions in prednisone-equivalent use occurred within the first 6 months and converged towards a mean dosage of 6.9 mg/day (mean dose range 5.3 to 9.3 mg/day) at 6 months (Fig. 2b). This represents a 43% reduction in mean prednisone-equivalent dose over the first 6 months. However, there was variation among studies with relatively large SEs being reported for prednisone-equivalent use at 6 months (range, 2.5–7.4 mg/day). There was a reduction in the proportion of prednisone-equivalent users between baseline and 6 months among the three studies that reported this measure (range of 2.1–72.3% reduction) [23, 27, 28].

Among studies reporting longer-term out-comes (*n* = 6, comprising a total of 888 patients

Table 2 Study and patient characteristics of identified studies

| Citation trial name | Study characteristics | | Inclusion/exclusion criteria | Patient characteristics[a] | | | | | |
	Country	Collection type		N	Age, years	Female, %	Disease duration, years	Baseline severity	Other
Andreoli (2014) [21]	Italy	NR	ACR classification for SLE	18	39.6 (22–55)	100	12.3 (1–26)	NR	11 patients had flare in prior year
Anjo (2019) [22]	Spain	Retrospective	SLE by ACR/EULAR criteria	23	41.5 (10.5)	100	171.8 (131.1) months	NR	
Collins (2016) [23] OBSErve	USA	Pre-belimumab: retrospective; Post-belimumab: prospective	SLE, age ≥ 18 years, ≥ 6 months documented medical history prior to belimumab; received ≥ 8 IV infusions of belimumab 10 mg/kg; *Enrolled in a clinical trial*	501	41.3 (12.10)	89.0	< 1 year (3.4%); 1–5 years (42.3%); 6–10 years (24.4%); > 10 years (20.0%)	Mild (2.2%); Moderate (77.6%); Severe (24.2%)	
Fanouriakis (2018) [24]	Greece	Prospective	1982 ACR criteria for SLE or SLICC criteria; active SLE despite ≥ 1 conventional immunosuppressive therapy; treatment with belimumab for ≥ 3 months	91	45.9 (12.5)	94.5	9.7 (median, range, 0.2–36.2)	NR	9 patients with history of LN 9 patients with history of CNS-SLE
Gatto (2020) [30]	Italy	Retrospective	ACR classification for SLR; Active disease classified as SLEDAI > 0 or refractory to standard of care; using IV belimumab; have monthly follow-up	466	41.4 (11.2)	91.6	11.6 (8.8)	NR	DAS-28: 3.8 (1.3) CLASI activity 1 (0–4)

Table 2 continued

Citation trial name	Study characteristics			Patient characteristics[a]					
	Country	Collection type	Inclusion/*exclusion* criteria	N	Age, years	Female, %	Disease duration, years	Baseline severity	Other
Hui-Yuen (2015) [31]	USA, Sweden	Prospective	Diagnosis of SLE, met at least 4 of 11 ACR or SLICC classification criteria, started treatment with belimumab after approval by regulatory agencies *Previously participated in belimumab clinical trials: met fewer than 4 ACR classification criteria* *Severe renal or neuropsychiatric involvement*	195	41.8 (12.7)	82	11.9 (8.1)	NR	Some patients aged 15–17 years included
Iaccarino (2018) [25]	Italy	Prospective	1982 ACR criteria for SLE; active SLE with SLEDAI-2 K > 6; refractory SLE manifestations; positive anti-dsDNA antibodies; low C3 or C3 serum levels *Severe and active LN; severe and active neuropsychiatric lupus*	188	40.7 (10.1)	92.5	12.7 (8.5)	NR	Mean CLASI: 4 (2–8)
Iaccarino (2017) [26]	Italy	Prospective	1982 ACR criteria for SLE; active SLE: SLEDAI-2 K > 6; refractory SLE manifestations; positive anti-dsDNA antibodies; low C3 or C3 serum levels *Severe and active LN; severe and active neuropsychiatric lupus*	67	39.3 (10.2)	91.0	12.8 (8.3)	NR	Mean CLASI: 5 [1–14]

Table 2 continued

Citation trial name	Study characteristics			Patient characteristics[a]					
	Country	Collection type	Inclusion/*exclusion* criteria	N	Age, years	Female, %	Disease duration, years	Baseline severity	Other
Parodis (2019) [34]	Sweden	Prospective	1982 ACR criteria for SLE and SLICC criteria with minimum ≥ 1 year of follow-up	34	40.6 (12.3)	88.2	9.4 (7.5)	NR	
Prete (2018) [44]	Italy	Not reported	SLE according to ACR classification	20	44.15 (2.14)	75	10.37 (6.81)	NR	
Scheinberg (2014) [8]	NR	Not reported	1997 ACR criteria for SLE	20	36 (9.2)	100	≤ 1 year: (30%); 1–5 years (55%); 6–10 years (15%)	NR	Mean (SD) FACIT: 37.6 (3.8)
Scheinberg (2016) [29]	Brazil	Not reported	Active SLE not responsive to standard approaches; 2012 Petri classification of SLE	48	32.6 (19–61)	93.8	11.6 (1.5–18)	NR	
Schwarting (2016) [28] OBSErve	Germany	Retrospective	Age ≥ 18 years, belimumab naïve with confirmed diagnosis of SLE, treatment with belimumab initiated ≥ 6 months before the study. *Current enrollment in an SLE-related trial or initiation of belimumab therapy as part of a clinical trial interventional arm*	102	42.5 (13.83)	91	< 1 year (1%); 1–5 years (23%); 6–10 years (19%); > 10 years (58%)	Mild (8%); Moderate (60%); Severe (25%); unknown (7%)	26 patients with LN
Sthoeger (2017) [27]	Israel	Retrospective	SLE according to ACR classification; patients with active lupus without severe active CNS/renal disease	36	41.6 (12.2)	78	15.7 (9.6)	NR	

Table 2 continued

| Citation trial name | Study characteristics | | | Patient characteristics[a] | | | | | |
	Country	Collection type	Inclusion/*exclusion* criteria	N	Age, years	Female, %	Disease duration, years	Baseline severity	Other
Touma (2017) [32] OBSErve	Canada	Retrospective	Age $\geq$ 18 years with a diagnosis of SLE, received $\geq$ 8 belimumab infusions (6 months of continuous treatment); $\geq$ 6 months of documented medical history prior to belimumab initiation *Enrolled in any other SLE-related clinical trial*	52	46.5 (10.8)	94.2	0–5 years (23.1%); 6–10 years (23.1%); > 10 years (53.8%)	Mild (5.8%); Moderate (76.9%); Severe (17.3%)	
Von Kempis (2019) [45] OBSErve	Switzer-land	Retrospective	Adults aged $\geq$ 18 years, confirmed SLE diagnosis, initiated belimumab plus ST $\geq$ 6 months before inclusion, medical history available up to 6 months pre-index, and whose treatment outcomes were available at 6 months post-index or at discontinuation *Enrolled in an SLE-related clinical trial, or who started belimumab as part of a clinical trial in an intervention arm*	53	46.7 (13.6)	81%	< 1 year (1.9%); 1–5 years (43.4%); 6–10 years (34.0%); > 10 years (18.9%); unknown (1.9%)	Mild (43.4%); Moderate (43.4%); Severe (13.2%)	

Table 2 continued

Citation trial name	Study characteristics			Patient characteristics[a]					
	Country	Collection type	Inclusion/*exclusion* criteria	N	Age, years	Female, %	Disease duration, years	Baseline severity	Other
Yoneva (2014) [33]	Bulgaria	NR	Age > 18 years, diagnosis with at least 4/11 ACR, lack of efficacy of standard treatment for ≥ 6 months, SLEDAI > 6, Positive ANA (above (1;80) and/ or high levels of anti-dsDNA antibodies	10	37.4	90%	7.2 (3–17)	NR	
			Active LN, cerebrovasculitis, or very high disease activity who are to be treated with high dose corticosteroids and cyclophosphamide						

ACR American College of Rheumatology, *ANA* anti-nuclear antibodies, *CLASI* Cutaneous Lupus Erythematosus Disease Area and Severity Index, *CNS* central nervous system, *DAS-28* Disease Activity Score 28, *dsDNA* double-stranded deoxyribonucleic acid, *FACIT* Functional Assessment of Chronic Illness Therapy, *EULAR* European League Against Rheumatism, *IV* intravenous, *LN* lupus nephritis, *NR* not reported, *SD* standard deviation, *SLE* systemic lupus erythematosus, *SLEDAI* SLE Disease Activity Index, *SLEDAI-2 K* SLE Disease Activity Index 2000; *SLICC* Systemic Lupus International Collaborating Clinics, *ST* standard therapy

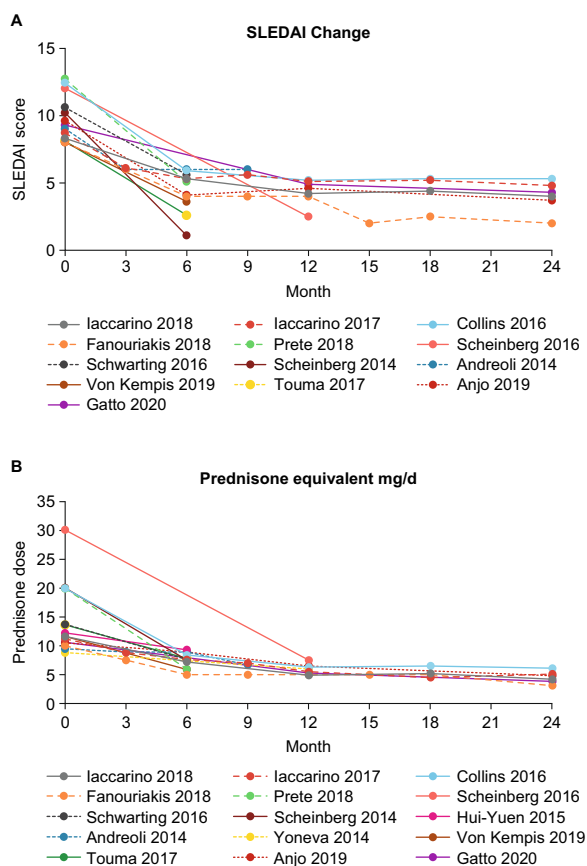[a]Values are mean (SD) or mean (range), unless otherwise specified

Fig. 2 Reported SLEDAI score (**A**) and prednisone-equivalent dosing (**B**) over time in real-world studies evaluating these outcomes (*n* = 13 and 15, respectively). *SLEDAI* SLE Disease Activity Index

[21–26]), there was a demonstrable but small monthly decline in mean prednisone-equivalent dosing after 6 months. A linear regression model estimated the monthly reduction in mean (SE) prednisone-equivalent dose to be 0.14 (0.02) mg/day with the fixed-effect model, and 0.15 (0.05) mg/day with the random-effect model. While these findings are not necessarily a clinically significant change per day, this represents a 2.6 mg/day reduction across the 18-month period between months 6 and 24 (an additional 38% reduction in mean dose from the estimated 6-month value of 6.9 mg/day).

Flare incidence

The proportion of patients with a flare incidence within 12 months of treatment initiation ranged from 10% [29] to 61% [21] across the ten

studies reporting such data; however, the definition of flare was not consistent between studies. Three studies reported flare incidence in the 12- and 24-month periods before and after belimumab initiation using the SELENA-SLEDAI flare index (Table 3) [25, 26, 30]. The mean flare incidence per patient, per year in the 12 months prior to belimumab treatment was 1.15, while after 12 months of treatment the mean incidence decreased to 0.39, a reduction of 66%. Over the first 24 months after belimumab initiation, the overall mean number of flares per patient, per year was 0.30 for the fixed-effect model, and 0.31 for the random-effect model.

Additional outcomes

Clinical Response
Six studies provided clinical response data [23, 24, 28, 31–33]. Of the studies reporting physician assessment of clinical improvement, 78–88% reported at least a 20% improvement at 6 months [23, 28]. The proportion of patients achieving ≥ 50% improvement in clinical response ranged from 42% [28] to 51% [31].

Global Assessment Score
Of the five studies that reported global assessment score, only two used the same measure, Schwarting [28] and Touma [32], both using a scale from 0 to 100. Patients in the Schwarting study (*n* = 8) reported a mean reduction in global assessment of disease at 6 months of 50, whereas patients in the Touma study (*n* = 22) reported a mean change of only 0.5 [28, 32]. Physicians participating in the Schwarting study reported a mean reduction in global assessment at 6 months of 24.8 [28], whereas physicians in the Touma study reported a mean reduction of 18.4 [32].

Quality of Life
Quality-of-life measures were provided by only two studies. Of these, Parodis [34] reported increases over 24 months in the 36-item Short Form Health Survey (SF-36) physical component score and Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue instruments, but little change in the SF-36

Table 3 Study data for flare incidence (per patient per year) over the 12 and 24 months before and after belimumab treatment

Study	After treatment			Before treatment		
	N	Mean	SE	N	Mean	SE
Over 12 months						
Gatto 2020	262	0.42	0.04	262	1.39	0.07
Iaccarino 2017	38	0.26	0.08[a]	38	0.78	0.14
Iaccarino 2018	111	0.39	0.05	111	1	0.08
Fixed-effect average		0.39	0.03		1.15	0.05
Random-effect average		0.38	0.04		1.07	0.17
I^2	34%			91%		
Over 24 months						
Gatto 2020	234	0.31	0.03	234	1.02	0.05
Iaccarino 2017	18	0.22	0.08[a]	18	0.75	0.14
Iaccarino 2018	54	0.265	0.06	54	0.705	0.09
Fixed-effect average		0.30	0.02		0.93	0.04
Random-effect average		0.31	0.01		0.84	0.12
I^2	79%			84%		

SE standard error

[a]Estimated from mean and patient-years of follow-up

mental component score and the EuroQoL 5 Dimension instruments. Scheinberg [8] reported a mean (SD) FACIT-Fatigue score at baseline of 37.6 (3.8), which showed improvement to 48.8 (3.3) at 6 months.

Disease severity

Disease severity outcomes were reported in three studies. Two of these reported improvements in Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) score; this decreased by 9 months and remained low through to 24 months [25, 26]. Collins (2016) reported improvements in physician's assessment of disease severity: at baseline, 2.2, 77.6, and 20.2% of patients were assessed as having mild, moderate, or severe disease, respectively, which improved to 65.0, 33.1, and 1.9% at 24 months, respectively.

DISCUSSION

Consistent with the efficacy findings of randomized controlled trials, the real-world results of key clinical outcomes demonstrate the benefits of treating SLE with belimumab. Reductions in SLEDAI score, prednisone-equivalent dosing, and flare frequency were all apparent within 6–12 months of belimumab treatment across the 17 real-world observational studies evaluated in this analysis.

The baseline patient characteristics extracted from the observational studies were similar to those of patients in the phase 3 belimumab IV clinical trials [12–14]. In these clinical trial populations, nearly all patients were female (range of 93–97% across the three studies) with a mean age range of 32–40 years [12–14]. The present review identified a mean age range of 37–47 years across the observational studies,

while females accounted for over 80% of the population in 15 of the 17 studies included. Mean disease duration was generally lower in the clinical trials than in the observational studies (5–7.9 years for clinical trials, vs. 9–-15.7 years for the observational studies). Mean SELENA-SLEDAI scores within clinical trials ranged between 9.5 and 10, versus 8 and 12.7 for the observational studies. The baseline prednisone dose of 9–30 mg/day for the observational studies was also similar to the values reported in clinical trials [12–14]. The observational studies included a more diverse patient population than those selected for randomized clinical trial inclusion, and this can result in heterogeneity among studies. However, this variation is representative of the real-world patient cohort and is more generalizable to the population with SLE who receive belimumab in clinical practice.

In phase 3 randomized clinical trials investigating the efficacy of belimumab, significantly higher SRI rates were reported with belimumab than placebo at week 52 [12–14]. The observational studies included here also saw a reduction in mean SELENA-SLEDAI score from 10.1 to 4.4 after 6 months, fulfilling the $\geq$ 4-point SELENA-SLEDAI reduction required for an SRI response [35]. This suggests that belimumab can achieve clinically meaningful reductions in disease activity in a real-world setting, as measured by the SELENA-SLEDAI.

A reduction or discontinuation of corticosteroid dose has been demonstrated with belimumab in clinical trials, which is likely of benefit to the patient given that there is little randomized control trial evidence to support a positive effect of corticosteroids on suppression of inflammation in SLE [36]. Corticosteroid use is also not without harm; high doses of corticosteroids in patients with SLE are associated with an increased risk of mortality and organ damage [37, 38]. After 6 months of belimumab treatment, the real-world observational data showed a reduction from mean prednisone-equivalent baseline dose of 12.1 mg/day to an average dose of approximately 7 mg/day; this is below the common clinical 'low dose' threshold of 7.5 mg/day, and supports the 'steroid-sparing' effect of belimumab treatment that was identified in phase 3 clinical trials [12].

Longer-term data (6–24 months) reported for SLEDAI score and for prednisone-equivalent dose indicate that reductions were maintained through to 24 months among patients remaining on therapy, although the magnitude of the monthly reduction was smaller than during the first 6 months. This is consistent with the findings of long-term open-label continuation studies, which reported sustained reduced corticosteroid use with belimumab [39, 40].

The majority of patients with SLE experience symptom exacerbations, or flares, throughout the course of their life, which may impact on both short- and long-term clinical outcomes; thus, the prevention of flares is an important target in the management of the disease [41]. In randomized clinical trials, belimumab was found to reduce the incidence and severity of flares; in BLISS-52, the risk of flare was significantly reduced and median time to first disease flare was significantly increased with belimumab versus placebo [12]. The observational studies evaluated here had varying definitions of flare, making a direct comparison of the results difficult. However, a meta-analysis was performed on data from three studies which reported standardized SELENA-SLEDAI flare index data to determine the overall mean number of flares per patient, per year, over the first 12 and 24 months following belimumab treatment. Mean flare rates for the fixed-effects model were 39 and 30% for the first 12 and 24 months, respectively; for the random-effects model, these values were 38 and 31%, respectively. BLISS-52 and BLISS-76 randomized clinical trials reported varying results for the SELENA-SLEDAI flare index, ranging from 15.7% at 52 weeks, and 71% from 24 to 76 weeks, respectively, so this small sample size meta-analysis is within the range of these findings [12, 13].

Additional evidence of improved outcomes associated with belimumab were reported in only a few real-world studies, ranging from just two with mention of Quality of Life and Global Assessment Score, to three studies reporting disease severity, and six studies detailing clinical response. Therefore, data for these measures

were not meta-analyzed; however, the results summarized from this small sample showed either no worsening, or a general improvement following belimumab treatment, which is consistent with the clinical trial results [12–14].

A strength of this study was the quality of the included studies; the Newcastle–Ottawa Scale indicated that the quality of all of the studies included in this analysis was 'good'. As is common with syntheses of observational data, only limited information exists to evaluate comparability of the identified studies. Statistical heterogeneity was present among nearly all outcomes analyzed, but the potential sources of this heterogeneity could not be explored, as only partial information was available. The sample size of the 17 studies ranged between 10 and 501 patients; this variation reduces the ability to compare individual studies, and may have contributed to the heterogeneity observed between studies. The present study identified trials published up to 2020, excluding potentially relevant studies published later. One publication from July 2020 reported results from the 24-month Argentina OBSErve study of 81 patients with SLE showing that belimumab treatment leads to clinical improvement and reductions in corticosteroid dose, consistent with the findings presented here [42]. Similar results were also reported in a recently published post hoc pooled analysis of real-world data from six OBSErve studies [43], most of which were included in our evaluation.

CONCLUSIONS

In the real-world setting, outcomes with belimumab for the treatment of SLE are consistent with those observed in randomized clinical trials. Belimumab is associated with improvements in SLEDAI score, reductions in daily prednisone-equivalent dose, and flare incidence. Reductions in prednisone-equivalent use and SLEDAI activity with belimumab were maintained over a 24-month period.

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