Within-trial economic analysis of flare data from the BLISS-SC trial of subcutaneous belimumab in systemic lupus erythematosus

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ABSTRACT

Objective The management of systemic lupus erythematosus (SLE) flares can incur substantial healthcare costs. In the phase III BLISS-SC trial, subcutaneous (SC) belimumab 200 mg plus standard therapy was associated with significant reductions in time to severe flare, and risk of flares, versus placebo plus standard therapy, in adults with active SLE. We evaluated whether the reduction in SLE flares with belimumab SC plus standard therapy translated to lower healthcare costs.
Methods A retrospective, post hoc economic analysis of BLISS-SC data was conducted. Unit costs per flare from claims data were estimated and applied to flares observed in BLISS-SC to quantify costs associated with treating severe flares (primary objective) or flares of any severity (secondary objective).
Results Of 836 patients (n=556 belimumab, n=280 placebo) analysed (94.4% female, mean (standard deviation, SD) age 38.6 (12.3) years), 13.2% and 62.8% had experienced a severe or mild/moderate flare, respectively. Mean (SD) unit costs per severe, moderate, mild or mild/moderate flare were US$9273 (38 800), US$3048 (9321), US$1671 (6202) and US$2303 (7821), respectively. Adjusted mean costs of treating flares were significantly lower with belimumab SC plus standard therapy than placebo plus standard therapy (severe flare, US$927 lower, p<0.001; flare of any severity, US$1379 lower, p<0.001).
Conclusions This economic analysis of data from the BLISS-SC trial revealed significant cost reductions were associated with treating SLE flares with belimumab SC plus standard therapy versus placebo plus standard therapy. These findings may help to inform decision making about introducing belimumab to healthcare systems.
Trial registration number NCT01484496.

Key messages

What is already known about this subject?
► Systemic lupus erythematosus (SLE) flares are associated with a substantial financial healthcare burden; patients who experience SLE flares are estimated to have 35% greater annual costs than those who do not experience flares.
► Subcutaneous (SC) belimumab treatment was shown to reduce the risk of SLE flares versus placebo in the BLISS-SC trial.

What does this study add?
► In this retrospective, post hoc economic analysis of the BLISS-SC trial, mean costs associated with treatment of severe flares and flares of any severity were significantly reduced with belimumab 200 mg SC (plus standard therapy) versus placebo (plus standard therapy).

How might this impact on clinical practice or future developments?
► Healthcare providers are interested in quantifying the potential economic impact of the reduction in SLE flares associated with treatments to assist with allocation of resources; these findings may aid decision makers who are considering the introduction of belimumab to their healthcare system.

relapses are characterised by disease flares, often involving different and multiple organs and systems, and an increased clinical and serological activity. Poorly controlled recurrent relapses/flares compromise patient outcomes, including organ damage accrual early in the disease course, placing a significant burden on patients and caregivers.[5 6]

The management of flares is associated with a substantial financial healthcare burden,[7 8] with severe flares being a significant predictor of increased cost.[9] A retrospective cost analysis performed using US Medicaid claims data (2002–2009) found the cost per flare was US$11 716, US$562 and US$129 for severe, moderate, and mild

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disease with a prevalence of 62.2–73 per 100 000 individuals, and an incidence of 4.6–5.6 per 100 000 individuals.[1–3] SLE is characterised by heterogeneous clinical manifestations, chronic inflammation and, in most patients, relapsing and remitting disease activity.[4] SLE

flares, respectively, while the annual total medical cost per patient with severe flares was US$49 754.[8] In the 2-year, retrospective, multicentre, observational LUpus erythematosus Cost of Illness in Europe (LUCIE) study conducted in five European countries (France, Germany, Italy, Spain and the UK) in consecutive patients (n=427) at SLE specialist centres, the occurrence of flares was associated with an average increment in annual cost of 35.0%, compared with the cost of no flares (equivalent of +€399, p=0.03). Severe flares were the strongest predictor of total costs, with each severe flare resulting in a 97.4% (equivalent of +€1,002; p<0.0001) increase in the annual cost of SLE.[10]

Treatment strategies for SLE focus on managing symptoms, reducing disease activity and flares, preventing organ damage, achieving low disease activity or clinical remission and improving health-related quality of life,[11–14] and include a combination of corticosteroids, antimalarials, immunosuppressants and biological agents.[14 15]

Belimumab is a B-cell activating factor (BAFF)-specific inhibitor administered via intravenous (IV) infusion or subcutaneous (SC) injection, and both formulations are indicated in the USA for the treatment of adults with active, autoantibody-positive SLE who are receiving standard therapy.[16] Additionally, the IV formulation is indicated in the USA for children ≥5 years of age.[16] The efficacy and safety of belimumab have been established in four phase III, randomised, placebo-controlled trials (belimumab IV, three trials; belimumab SC, one trial).[17–20] In the BLISS-SC trial, in addition to achieving the primary end point of SLE Responder Index reduction, belimumab SC plus standard therapy was associated with a statistically significant reduction in time to severe flare, and in risk of severe flares and flares of any severity compared with placebo plus standard therapy.[19]

Following the approval of belimumab SC in the USA and Europe in 2017,[16 21] healthcare providers are interested in information that quantifies the potential economic impact of the reduction in SLE flares associated with this treatment, to inform decision-making regarding the allocation of resources. Thus, the aim of this study was to provide data on the impact that treatment with belimumab SC may have on the costs of treating disease flares in patients with SLE, to help inform decision makers who are considering the introduction of belimumab SC to their healthcare system.

The primary objective of this study was to compare the costs associated with treating severe flares in patients who received belimumab 200 mg SC plus standard therapy with those of patients who received placebo plus standard therapy in the BLISS-SC trial. The secondary objective was to compare the costs associated with treating flares of any severity in the belimumab SC plus standard therapy group with those in the placebo plus standard therapy group from the BLISS-SC trial.

METHODS

Study population

The study population included all patients in the intent-to-treat (ITT) population of the 52-week, phase III, multinational, randomised, placebo-controlled BLISS-SC trial (GSK study BEL112341), which enrolled adults ≥18 years of age with a clinical diagnosis of active, autoantibody-positive SLE, who were receiving a stable SLE treatment regimen.[19] Patients were randomised to weekly doses of belimumab 200 mg SC or placebo, plus standard therapy. Time to first severe flare over 52 weeks, as measured by the modified Safety of Estrogens in Lupus Erythematosus-National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) Flare Index, was a major secondary end point in BLISS-SC. Flares were defined (as mild/moderate or severe) and graded according to severity using the SLE Flare Index (criteria shown in online supplemental file 1).

Study design

The current post hoc within-trial economic analysis (GSK study 207134) was conducted in two stages. Stage 1 involved sourcing unit cost data for flares, by severity, from a claims database analysis of the Truven Commercial Claims and Encounters (commercial) (now part of the IBM Watson Health Company) and Medicare Supplemental (Medicare) databases, which include annual medical and drug health insurance claims information from >50 million and ~4.3 million individuals, respectively.[22] Stage 2 was an analysis of the BLISS-SC trial data from all sites and countries included in the trial and was conducted from the US payer's perspective with the time horizon based on the duration of the BLISS-SC trial. The unit costs of flares obtained from stage 1 were applied to the adjusted rates of flares from BLISS-SC (stage 2) to obtain costs associated with treating flares for the BLISS-SC trial population.

For stage 1, commercial and Medicare administrative health insurance claims data from 1 January 2015 to 31 December 2016 were used for the analysis. Unit cost per SLE flare was imputed using a retrospective, cross-sectional, event-based costing methodology, and was defined as the cost to a US payer attributable to the treatment of an SLE flare (valued in 2017 US dollars). Patients with active SLE disease, defined as having ≥1 SLE hospitalisation, ≥1 SLE emergency department visit or ≥2 SLE outpatient visits of ≥30 days apart, and with continuous health plan enrolment (during the calendar years 2015 and 2016), were identified using 2015 data (the pre-index period; figure 1). For this patient population, SLE flare events occurring in 2016 were then determined according to a previously published algorithm which identifies flares in administrative claims data and categorises them by severity (mild, moderate and severe; online supplemental file 2).[23] This algorithm identifies an SLE flare episode based on the Lupus Foundation 2nd International Lupus Flare Conference Definition, consensus of expert clinical opinion and additional criteria of
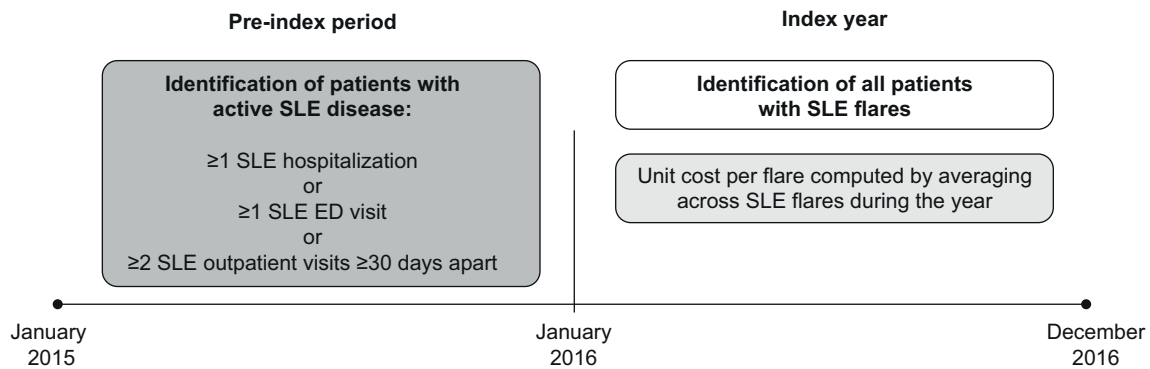
Figure 1 Study design for the assessment of unit cost per flare. ED, emergency department; SLE, systemic lupus erythematosus.

outpatient visits, hospitalisations and emergency room (ER) visits supported by a qualifying SLE diagnosis or SLE-related condition. Costs incurred between the start and end date for each flare episode, including all medical and pharmacy costs from all claims regardless of diagnosis code, procedure or medication, were used to compute the unit cost per SLE flare. The unit costs per SLE flare, by severity, were obtained by averaging across all flares of that severity. The minimum duration of a flare episode was 30 days; however, if a flare of higher severity occurred during those 30 days, the length of the flare was limited to the time between the start of the lower-severity flare and the start of the higher-severity flare episode. For flares based on a hospitalisation, the start date of the flare was the date of inpatient admission, unless the patient was admitted to the ER (with any diagnosis) on the previous day; in this case, the date of the ER visit was considered to be the start date of the flare.

For stage 2, average unit cost per SLE flare, obtained from stage 1 (as described above), was applied to the patient-level flare data observed in the BLISS-SC trial, allowing for a comparison of the costs associated with treating flares (severe and those of any severity) in the belimumab SC plus standard therapy group versus the placebo plus standard therapy group.

Study variables
The primary end point of the within-trial economic analysis was the cost associated with treating severe flares, and the secondary end point was the cost associated with treating flares of any severity (calculated using patients who experienced severe flares plus those who experienced mild/moderate flares). Both end points were evaluated over a 52-week duration (BLISS-SC trial follow-up period).

Additionally, patient characteristics (eg, age, sex, race, ethnicity, country, completers, patient-years contributed) of the BLISS-SC trial population were reported (also published elsewhere)[19]; and the following variables were used as covariates in the multivariable analyses: baseline complement levels (low C3 and/or low C4 vs no low C3 or

C4), race (black African ancestry vs other), and baseline SELENA-SLEDAI score (≤9 vs ≥10).

Data analyses
All sample characteristics, as well as unadjusted outcomes were presented using descriptive statistics (mean, SD, median, percentile, frequency and percentage). Unadjusted differences in costs for severe flares and flares of any severity for the belimumab SC plus standard therapy and placebo plus standard therapy groups were compared via univariate analysis using Student's t-tests.

Multivariable analyses employed generalised linear models with negative binomial distribution to obtain the adjusted rate of severe and mild/moderate flares, respectively. Treatment arm (belimumab SC plus standard therapy vs placebo plus standard therapy) was used to predict the flare rate; other covariates included baseline complement levels (low C3 and/or low C4 vs no low C3 or C4), race (black African ancestry vs other) and baseline SELENA-SLEDAI score (≤9 vs ≥10). Patient follow-up time as $\log_{10}$ (patient-years) was used as an offset variable in the model. The adjusted rates of severe and mild/moderate flares for each patient were computed, and the adjusted costs were obtained by multiplying the adjusted rates by the unit cost per SLE flare obtained from the claims analysis. The 95% confidence intervals (CIs) around adjusted costs were obtained similarly. The mean adjusted costs associated with treating flares of any severity were estimated by adding the adjusted cost of severe and mild/moderate flare for each patient. Student's t-test was then used to test for differences in adjusted costs for treating flares of any severity between belimumab and placebo groups. All statistical tests evaluated a two-sided hypothesis of no difference between treatment arms at a significance level of 0.05.

RESULTS
All 836 patients from the ITT efficacy population of the BLISS-SC trial were included in this within-trial economic analysis (belimumab SC plus standard therapy group: n=556, placebo plus standard therapy group: n=280).

Table 1 Demographics and baseline characteristics of patients from the BLISS-SC trial included in the analysis

| Parameter	Total population (n=836)	Placebo plus standard therapy (n=280)	Belimumab 200 mg SC plus standard therapy (n=556)
Mean (SD) age, years	38.6 (12.3)	39.6 (12.6)	38.1 (12.1)
Age group, years, n (%)			
≤45	596 (71.3)	193 (68.9)	403 (72.5)
45–65	221 (26.4)	80 (28.6)	141 (25.4)
65–75	18 (2.2)	7 (2.5)	11 (2.0)
≥75	1 (0.1)	0 (0)	1 (0.2)
Sex, n (%)			
Female	789 (94.4)	268 (95.7)	521 (93.7)
Race, n (%)			
Black African ancestry	86 (10.3)	30 (10.7)	56 (10.1)
White/Caucasian	502 (60.0)	166 (59.3)	336 (60.4)
Other	248 (29.7)	84 (30.0)	164 (29.5)
Country, n (%)			
USA and Canada	237 (28.4)	84 (30.0)	153 (27.5)
South America	172 (20.6)	57 (20.4)	115 (20.7)
Asia	172 (20.6)	61 (21.8)	111 (20.0)
Eastern Europe	188 (22.5)	59 (21.1)	129 (23.2)
Western Europe/Australia/Israel	67 (8.0)	19 (6.8)	48 (8.6)
Completers,* n (%)	677 (81.0)	214 (76.4)	463 (83.3)
Patient-years contributed, mean (SD)	0.91 (0.2)	0.92 (0.2)	0.89 (0.2)

*All patients who completed all 52 weeks of the planned double-blind treatment period.
SC, subcutaneous; SD, standard deviation.

The mean (SD) age of participants was 38.6 (12.3) years, 94.4% were female, with the largest percentage of patients residing in the USA and Canada (28.4%). The demographics and baseline characteristics of patients in the belimumab SC plus standard therapy and placebo plus standard therapy groups were similar (table 1).

From the claims analysis (stage 1), 20 781 adults with active SLE disease were identified to compute the unit costs of flares by severity. The mean (SD) age of patients with active SLE from the stage 1 sample was 50.8 (13.5) years (median=51 years) as of 2015, and 91.7% were female. The mean (SD) unit costs obtained per severe, moderate and mild flares were US$9273 (38 800), US$3048 (9321) and US$1671 (6202), respectively. The mean (SD) unit cost obtained per mild/moderate flare was US$2303 (7821) (figure 2).

From the trial data (stage 2), severe flares were experienced by 13.2% (n=110) of the total trial population (figure 3). The proportion of patients experiencing a severe flare during the trial period was greater in the placebo plus standard therapy group than the belimumab SC plus standard therapy
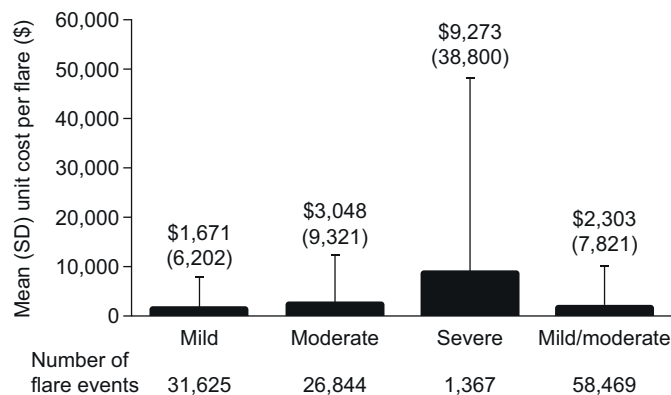
Figure 2 Unit cost per flare from claims data analysis. SD, standard deviation.

group (18.2% (n=51) vs 10.6% (n=59)), and the mean (SD) number of severe flares per patient was also greater in the placebo plus standard therapy group than the belimumab SC plus standard therapy group (0.25 (0.6) vs 0.15 (0.5)). Mild/moderate flares were experienced by 62.8% (n=525) of the trial population. The placebo plus standard therapy group had a greater proportion of patients with mild/moderate flares (67.5% (n=189) vs 60.4% (n=336)), and a higher mean (SD) number of mild/moderate flares per patient (1.69 (1.7) vs 1.51 (1.7)), than the belimumab SC plus standard therapy group. The mean (SD) unadjusted cost associated with treating severe flares in the belimumab SC plus standard therapy group was US$1368 (4382) and was US$951 (note: this value appears higher than the exact mathematical difference between belimumab and placebo costs shown here, due to rounding of decimal places postcalculation) lower than that of the placebo plus standard therapy group (US$2318 (5566)) over the follow-up period (p=0.013). The mean adjusted cost estimate associated with treating severe flares in the belimumab SC plus standard therapy group was US$1484 (95% CI = 1391 to 1484) and was US$927 lower than that of the placebo plus standard therapy group (US$2411 (95% CI = 2318 to 2597)) over the follow-up period (p<0.001) (figure 4).

The mean (SD) unadjusted cost associated with treating flares of any severity in the belimumab SC plus standard therapy group was US$4835 (6761) and was US$1374 lower than that in the placebo plus standard therapy group (US$6209 (7856)) over follow-up (p=0.009). The mean adjusted cost estimate associated with treating flares of any severity in the belimumab SC plus standard therapy group was US$4947 (95% CI = 4820 to 5075) and was US$1379 lower than that in the placebo plus standard therapy group (US$6326 (95% CI = 6080 to 6572)) over follow-up (p<0.001) (figure 4).

DISCUSSION

This post hoc within-trial cost study analysed data from the BLISS-SC trial to compare the costs associated with treating SLE flares (severe and of any severity) in patients treated with belimumab SC plus standard therapy versus those treated with placebo plus standard therapy; the costs associated with
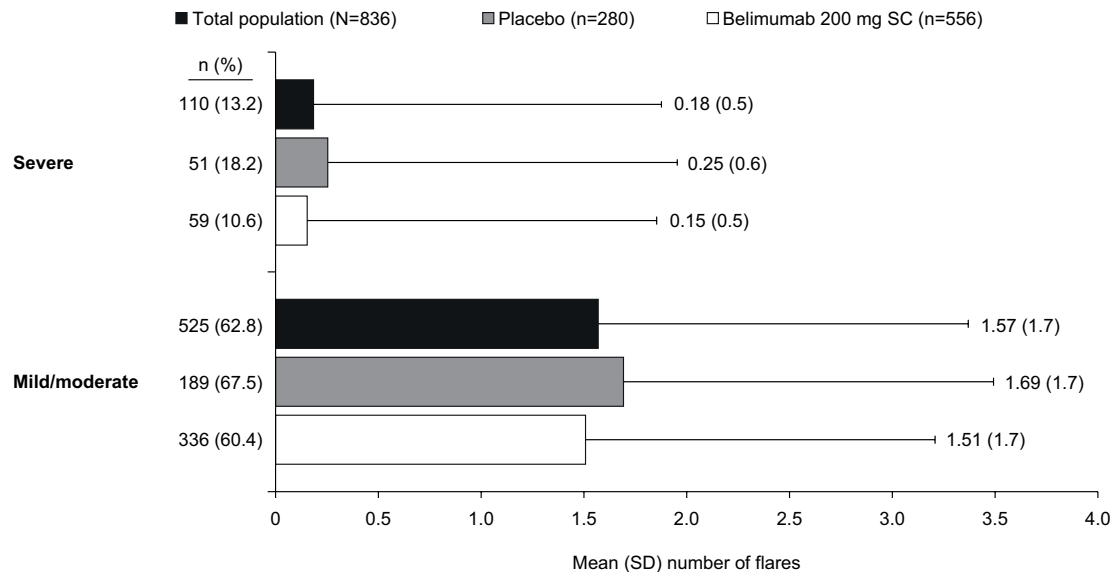
■ Total population (N=836) ▦ Placebo (n=280) ☐ Belimumab 200 mg SC (n=556)

Figure 3 Occurrence of flares by severity in patients receiving belimumab 200 mg SC plus standard therapy versus placebo plus standard therapy. SC, subcutaneous; SD, standard deviation.

treating severe flares and flares of any severity were lower with belimumab SC plus standard therapy than placebo plus standard therapy.

SLE flares are associated with increased use of healthcare resources and significantly higher annual direct and indirect costs, which increase with flare frequency and severity.[7 24 25] In a retrospective assessment of medical charts of consecutive patients (n=109) at three specialist SLE treatment centres in Canada, the 2-year direct medical cost for patients with ≥1 flare was significantly higher than for patients without flares (US$22 633 vs US$11 113; p=0.028). The mean incremental annual cost was US$7007 (95% CI = 3487 to 13 048) for patients with severe disease, and the 2-year mean incremental cost was US$5848 (95% CI = 2919 to 8777) for each additional severe flare.[24] In a 2-year, retrospective, multicentre, observational study in Italy in patients with active SLE (n=96), the annual medical cost, assessed from the Italian National Health Insurance perspective, was 1.6 times higher in patients with severe SLE than in those with non-severe disease (€2101 vs €1,320; p=0.031), while the cost of medication was also 2.5 times higher (€1101 vs €445; p=0.007). Furthermore, each severe flare was associated with an incremental annual cost of €465 (p=0.02).[7]
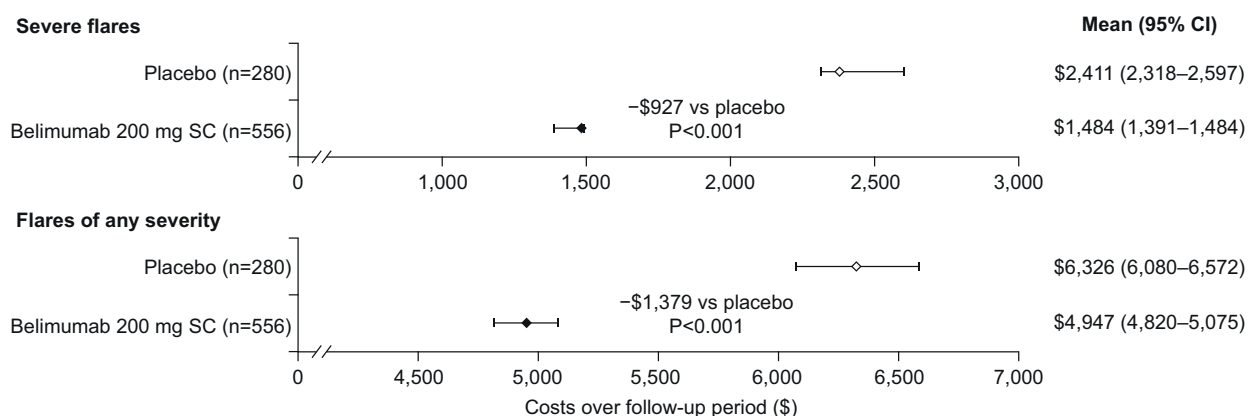

Figure 4 Adjusted costs associated with treating severe flares and flares of any severity with belimumab 200 mg SC plus standard therapy versus placebo plus standard therapy. Adjusted cost estimates were obtained as follows: GLMs with negative binomial distribution were used to obtain the adjusted rate of severe flare. Treatment arm (belimumab 200 mg SC vs placebo) was the primary independent variable, and other covariates included baseline complement levels (low C3 and/or low C4 vs no low C3 or C4), race (black African ancestry vs other), and baseline SELENA-SLEDAI score (≤9 vs ≥10). Patient follow-up time as $\log_{10}$ (patient-years) was used as an offset variable in the model. The adjusted rates of severe and mild/moderate flare for each patient were computed, and the costs of severe and mild/moderate flare were estimated using the unit cost from the claims study multiplied by the adjusted rates from the GLM model. The mean and 95% CI were then computed for each arm. The mean and 95% CI for costs associated with treating flares of any severity was estimated by adding the adjusted cost of severe and mild/moderate flare for each patient. Student's t-test was used to test for differences in estimated costs. CI, confidence interval; GLM, generalised linear model; SC, subcutaneous; SD, standard deviation; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Activity Index.

Because flares, particularly severe ones, present a considerable economic burden, SLE treatment approaches that prevent or reduce the severity of flares may result in significant cost savings for the healthcare system. Indeed, a budget impact analysis conducted in Italy demonstrated that over 3 years, belimumab (administered via IV infusion) prevented 3631 flares, including 1111 that were severe, for a total saving of approximately €6.2 million. Healthcare budget savings associated with the introduction of belimumab ranged from €4.4 million in the first year to €20.3 million in the third year.[26] Furthermore, flares have been associated with organ damage; a case-crossover study of 251 patients with SLE in nine Latin American countries found that the number of flares, regardless of their severity, was an independent predictor of increased risk of damage accrual.[6] Thus, prevention of flares may lead to a reduction in organ damage over time, which could facilitate further economic benefits of treating SLE.

In the present study, the mean (SD) unit cost per severe flare was US$9273 (38 800) and per mild/moderate flare was US$2303 (7821). As expected, the costs increased with flare severity, which is consistent with similar economic analyses of the burden of SLE.[8 10 23 27] In the USA, one economic analysis of the claims data for the US Medicaid population (n=14 777) estimated mean (SD) cost per SLE flare as US$11 716 (29 141) for severe, US$562 (2275) for moderate and US$129 (702) for mild flares.[8] While costs of treating severe flares were similar to those in our findings, the study found much lower costs of treating mild and moderate flares. Another US study also reported lower average adjusted mean (SD) costs per mild and moderate flares (US$909 (2584) and US$1539 (3263), respectively), but higher costs per severe flares (US$17 059 (40 988)).[23] As all three studies used similar flare definitions, these differences could be reflective of time periods for which the data were analysed (2008 for Garris et al and 2009 for Kan et al vs 2017 in the current study), that is, before the widespread use of biologics, which could have influenced treatment costs. Furthermore, Garris et al and Kan et al reported total (payer and patient) costs, while our study reports costs from the payer's perspective only. Finally, the sample size of Garris et al was much smaller (n=2990 vs n=20 781 in the current study) and included only patients enrolled in commercial health plans, while in Kan et al, medical claims data for patients enrolled in Medicaid were analysed. As SLE prevalence rates may vary between populations such as patients enrolled in commercial health plans or Medicare/Medicaid, and as our study combined these health plans (commercial plus Medicare), our findings are more representative of the majority of care populations on a national level than either of these other studies alone.

The multinational, retrospective, observational European LUCIE study showed that each severe flare was associated with a €1002 increase in the annual cost of SLE,[10] with occurrence of a new severe flare in the Italian or French populations associated with an incremental annual cost of €465[7] or €1330,[27] respectively. However, the differences reported for the European and US studies can be attributed to variation in study design (retrospective, observational study vs post hoc analysis of clinical trial data), patient population (real-world patients with SLE vs those included in a clinical trial), cost analysis methods (medical hospital costs from payers' perspective vs medical hospital and non-hospital costs from claims databases) and healthcare and medical care plan systems (national healthcare system vs claims database of commercially insured patients) and the associated treatment costs, as well as different flare definitions (not specified vs prespecified algorithm for identifying flares in claims data).

Limitations

There were some limitations of the present analysis. As this was a within-trial cost analysis, the findings are not generalisable to the use of belimumab SC plus standard therapy in a real-world setting. The rate of SLE flares is representative of a select clinical trial population with moderate-to-severe SLE, and this rate may differ from that observed in real-world patients who may have SLE of varying severity, as well as comorbidities. The BLISS-SC trial population and the population from which the unit cost of SLE flares was derived were different; the results should be interpreted with this caveat in mind. In particular, the average age of the claims data population used to derive the unit costs of flares was 10 years older than that of the BLISS-SC clinical trial population. This study employed an algorithm to identify and categorise the severity of flares,[23] as no specific diagnosis codes for SLE flares currently exist in administrative claims data. The use of the algorithm is not precise and may result in the underestimation/overestimation of the identification of flares and the subsequent costing of flares. A recent study has evaluated a portion of the algorithm (ie, the identification of mild, moderate and severe disease activity) and compared the algorithm-predicted disease severity with clinical SLE disease activity as measured by the SLEDAI-2K.[28] The algorithm was associated with sensitivity of 85.7%, specificity of 67.6%, positive predictive value of 81.8% and negative predictive value of 73.5%. A further disadvantage of this method is that administrative data are not collected/designed for research purposes and may be subject to coding errors. Important clinical parameters that may be associated with flare severity are also unavailable in administrative claims data and the presence of a prescription claim does not guarantee that the patient took the medication as prescribed. Alternatively, patients may have received drug samples, over-the-counter medication or prescriptions outside of their insurance/pharmacy systems, in which case those data will not be available in the claims. The algorithm also heavily relies on the utilisation of healthcare services and medications for SLE. The higher costs of severe flares may be driven in part due the definition used to identify severe flares using inpatient admissions and the cost of a flare may have included costs due to other non-related treatments/visits since all costs over the 30-day period were included. Finally, the unit cost of SLE flares may not accurately reflect the cost of treating flares for all patients because the cost data were derived from a commercially insured population and assumed a fixed episode-of-care time period for flares (ie, 30 days). Furthermore, as flares have been associated with an increased risk of damage accrual, our study

may not fully illustrate the economic benefit of flare prevention, as it does not account for the benefits of reducing organ damage.

This within-trial economic analysis of data from the BLISS-SC phase III trial demonstrated a significant reduction in the costs associated with treating disease flares in patients with SLE treated with belimumab 200 mg SC plus standard therapy, compared with placebo plus standard therapy. Although the study is representative of a select clinical trial population and may differ from the experiences of real-world patients with SLE, these findings may help inform decision makers who are considering the introduction of this treatment to their healthcare system.

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