Rheumatology, 2025, **64**, 276–282
https://doi.org/10.1093/rheumatology/kead696
Advance access publication 15 March 2024
Original Article

British Society for Rheumatology RHEUMATOLOGY OXFORD

Clinical science

Thorough assessment of the effectiveness of belimumab in a large Spanish multicenter cohort of systemic lupus erythematosus patients

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Abstract

Objectives: To provide an overview on the current use of belimumab (BLM) in SLE patients in clinical practice and to examine its efficacy in terms of standardized outcomes, drug survival, as well as patient and safety profiles.

Methods: A longitudinal retrospective multicenter cohort including SLE patients treated with BLM at 18 Spanish centers. Data was collected upon initiation of BLM, at 6 and 12 months after initiation, and at the last recorded visit. Changes in SLEDAI-2K, the proportion of patients who

Received: 24 August 2023. **Accepted:** 5 November 2023

achieved LLDAS and DORIS 2021, and number of flares were compared between visits. Changes in damage, glucocorticoids use and employment status pre-BLM and post-BLM were also assessed.

Results: A total of 324 patients were included with a mean follow-up of 3.8 (±2.7) years. LLDAS was attained by 45.8%, 62% and 71% of patients, and DORIS by 24%, 36.2% and 52.5% on successive visits, respectively. A total of 27.2% of patients were in DORIS ≥50% of the visits and 46% in LLDAS-50. Flares and number of flares were significantly lower one year after treatment with BLM and no changes in damage accrual were observed. Mean (±SD) prednisone dose was significantly reduced over time, with 70 (24%) patients discontinuing GC.

Conclusion: Our study not only demonstrates belimumab's efficacy in attaining treat-to-target goals in SLE patients, but also confirms its GC-sparing effect, and its prevention of flares and organ damage accrual.

Keywords: systemic lupus erythematosus, belimumab, biologics, remission, DORIS, LLDAS, target, Spanish, cohort, effectiveness.

Rheumatology key messages

- Belimumab is effective in attaining treat-to-target goals in clinical practice.
- Belimumab has a steroid-sparing effect and prevents flares and organ damage accrual.
- Belimumab shows a good safety profile in the clinical setting and a possible positive effect on employment status of SLE patients after it is used.

Introduction

Belimumab (BLM) is a monoclonal antibody that works by inhibiting the production of BAFF (B-cell activating factor), previously known as BlyS (B-lymphocyte stimulator), a cytokine that drives the survival and maturation of B cells. Since its approval by the US Food and Drug Administration (FDA) in 2011 for the treatment of systemic lupus erythematosus (SLE), and more recently in 2019 for the treatment of lupus nephritis (LN) in combination with standard of care, BLM has been extensively studied in clinical trials [1–5] and observational studies [6–10] and has shown positive results in reducing disease activity, improving quality of life in SLE patients, and preventing organ damage and flares.

Our study aim is to provide an overview of its current use to treat SLE patients in clinical practice based on a large Spanish multicenter cohort. Specifically, we examine its efficacy in terms of standardized outcomes and drug survival, as well as patient and safety profiles.

Methods

Study design

This was a national longitudinal retrospective multicenter cohort study of SLE patients treated with BLM. Eighteen Spanish rheumatology departments in tertiary university hospitals with physicians experienced both in the management of SLE patients and in the clinical research on the subject were invited to participate.

Patients

We included all SLE patients who met the revised 1997 American College of Rheumatology (ACR) classification criteria [11] and who were being actively treated or who had previously been treated with BLM in a clinical setting (intravenous or subcutaneous). Patients treated between the approval of BLM use in Spain (July 2011) and June 2022 were included. Approval was obtained from the Ethics Committee (CEIM) of University Hospital of Gran Canaria Dr Negrín.

Our Registry was approved by the Research Ethics Committee of Dr Negrín University Hospital and by the Ethics Committees of the participating centers, when required. It was carried out in accordance with the Declaration of Helsinki's guidelines for research on humans, as well as with the Oviedo Convention. Data protection was respected in accordance with Spanish law. Our current study did not require patient consent because data was collected retrospectively.

Data collection

Data were collected retrospectively upon initiation of BLM, at 6 and 12 months after initiation, and at the last recorded visit. At baseline, data on demographic characteristics, SLE criteria and previous therapies before onset of BLM were collected. Disease activity was measured in all visits using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)-2K, based on the previous 30 days [12], and the 28 tender/swollen joint count. Physician Global Assessment (PGA) scores were obtained by asking physicians to rate disease activity on a scale of 0–3 during all visits. Laboratory parameters that were collected at every visit consisted of the following: complete blood cell count, creatinine, estimated glomerular filtration rate (eGFR) according to Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and 24-h proteinuria as available, levels of anti-double-stranded DNA (anti-dsDNA) antibodies (EIA), C3 and C4, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) within 30 days of the visit. Organ damage was assessed using the SLICC/ACR Damage Index (SDI) [13]. Additionally, physicians were asked if they observed a global clinical response of >25% or >50%. Flares between visits were captured by the SELENA-SLEDAI flare index (SFI). Employment status pre-BLM and post-BLM was also assessed [14].

Concomitant medications included current use and doses of antimalarials, glucocorticoids, immunosuppressive treatments and biologic agents.

Outcomes

Standardized outcomes were measured at all visits. For remission, we used the Definition Of Remission In SLE (DORIS) 2021 [15] and for low disease activity the Lupus Low Disease Activity State (LLDAS) as defined by the Asia-Pacific Lupus Collaboration (APLC) [16]. The DORIS 2021 is defined via the following criteria: clinical SLEDAI = 0 irrespective of serology; PGA <0.5; prednisone dose up to 5 mg/day and well-tolerated standard maintenance doses of immunosuppressive drugs and approved biologic agents and

antimalarials. In contrast, the LLDAS was defined using the following criteria: (i) SLE Disease Activity Index (SLEDAI)-2K ≤4, with no activity in major organ systems [renal, central nervous system (CNS)], cardiopulmonary, vasculitis, fever and no hemolytic anaemia or gastrointestinal activity; (ii) no new lupus disease activity compared with the previous assessment; (iii) a Physician Global Assessment (PGA) (scale 0–3) ≤1; (iv) a current prednisolone (or equivalent) dose ≤7.5 mg daily; and (v) well-tolerated standard maintenance doses of immunosuppressive drugs and approved biological agents. We also evaluated the time spent in these states during the first year and classified various subgroups (DORIS6M, DORIS12M, DORIS 6M-12M, LLDAS6M, LLDAS12M, LLDAS 6M-12M) according to the number of visits that the patients persisted in those particular states.

All researchers were requested to provide the number and type (mild-moderate or severe) of flares that occurred between visits based on the SELENA-SLEDAI Flare Index (SFI).

Damage was evaluated according to SDI at baseline, at 12 months and at the last visit.

Safety and BLM discontinuation

All discontinuations of BLM were recorded. Reasons for discontinuation were grouped as follows: inefficacy, adverse events, non-adherence or other. The types of adverse events were compiled by the centers, with particular focus on depression and severe infection. The latter was defined as the patient requiring hospitalization or dying due to infection.

Statistical analysis

We carried out a descriptive analysis of the complete cohort. Numerical variables are expressed as means, medians and standard deviations, while categorical variables are expressed as frequencies and percentages.

A *t* test or Wilcoxon test for numerical variables and the Fisher test for categorical variables have been used to detect differences. *P*-values <0.05 were considered statistically significant. All analyses were performed using R statistical software, version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics of the cohort

We included 324 SLE patients treated with BLM. Mean follow-up until start of BLM was 10.9 (±9.07) years, and mean follow-up since BLM initiation was 3.8 (±2.7) years. Mean time between the 12 months visit after initiation of BLM and the last recorded visit was 26.2 (±20.9) months. Patient demographic and clinical characteristics are shown in Table 1.

Baseline treatments and reasons for prescribing BLM

Most patients had undergone other treatments before being prescribed BLM (89.2%; $n = 289$). Conventional disease-modifying anti-rheumatic drugs (cDMARDs) were used in 87% of patients, with methotrexate being the most common, administered to 127 (44.4%) patients. Biologic DMARDs (bDMARDs) were used in 22.8% of cases. The most frequent bDMARD used was rituximab, in 80% ($n = 60$) of cases. Most patients had received antimalarials (83.2%). Glucocorticoids (GC) were used in the majority of patients (91.2%), with a mean dose of 12.3 mg/day at onset of BLM. More detailed information about treatments is shown in Table 2.

A total of 215 patients (66.35%) received intravenous (i.v.) BLM and 110 (33%) subcutaneously. BLM was used in monotherapy in 47 (14.5%) subjects. BLM was mainly initiated due to disease activity (95%). Other concurrent reasons

Table 1. Patient demographics and disease characteristics

	Number (%) or mean (± SD) ($n = 324$ patients)
Female	295 (91%)
Mean age (±SD) at diagnosis	31.3 (± 11.9)
Disease duration at enrolment (years) (±SD)	8.7(± 9.0)
Mean (±SD) follow-up	3.8 (±2.7)
Smoker	76 (23.6%)
Ethnicity	
−Caucasian	274 (84.8%)
−Black	4 (1.2%)
−Hispanic	34 (10.5%)
−Asian	4 (1.2%)
−Arabic	7 (2.2%)
Number of patients meeting 1997 ACR criteria for SLE	304 (93.8%)
Number of patients meeting 1997 ACR criteria or SLICC 2012	319 (98.45%)
Number of ACR criteria for SLE	5.9 (±1.6)
Number of patients anti-dsDNA positive	217 (68.2%)
Number of patients with low complement levels	224 (69.8%)
SLEDAI-2K score at enrolment	10.4 (±5.25)
Mean SLICC/ACR-DI score at enrolment	0.83(±1.2)
Damage present at enrolment	152 (47.5%)
PGA at enrolment; median IQR	1.76 (1.3–2)

Table 2. Treatments received prior to initiation of BLM

Treatments	Number (%), mean (± SD) or median (IQR) ($n = 324$ patients)
cDMARDs	282 (87%)
Number of cDMARDs prior to Belimumab	2 (1–3)
0	21 (6.6%)
1	131 (41.5%)
>1	164 (46.2%)
Methotrexate	127 (44.4%)
Leflunomide	29 (10.32%)
Azathioprine	91 (32.38%)
Mycophenolate mofetil	104 (37.01%)
Ciclosporin	7 (2.48%)
Tacrolimus	6 (2.12%)
Cyclophosphamide	28 (9.92%)
bDMARDs	74 (22.8%)
Rituximab	60 (81%)
Abatacept	3 (4%)
Anti-TNF	1 (1.3%)
Other	13 (17.5%)
Hydroxychloroquine (HCQ)	271 (83.2%)
Mean dose of HCQ (±SD)	287.55 (101.14)
Glucocorticoids (GC)	292 (91%)
Mean dose of GC	12.3 (±12.16)
>5 mg/day of prednisone	209 (67.9%)
>7.5 mg/day of prednisone	180 (58.4%)

for its prescription were for use as a maintenance treatment (61% of cases) and as a GC sparing agent (59% of cases).

The main drivers of BLM prescription were arthritis in 212 (65.4%) patients, cutaneous activity in 132 (40.7%), both simultaneously in 124 (38%), hematological activity in 60 (18.5%), serositis in 47 (14.5%), fatigue in 15 (4.6%), neurological activity in 5 (1.5%), constitutional in 5 (1.5%), vasculitis in 3 (0.92%) and pulmonary involvement in 1 (0.3%) patient. Renal involvement at the time of BLM initiation, with proteinuria >0.5 g/24 h, was present in 58 patients (17.9%) with media (±SD) of 0.62 g/24 h (±1.32). However, no patient received BLM specifically as an induction treatment for lupus nephritis in this analysis.

Response rates

SLEDAI-2K, anti-dsDNA levels, number of swollen and painful joints, PGA, ESR and CRP significantly decreased over the studied period. We also observed an increase in C3 and C4 levels. Mean (±SD) prednisone dose (or equivalent) was significantly reduced over the visits: 12.3 (±12.16); 7.42 (±5.36); 5.8 (±4.42) and 4.7 (±3.7) mg/day at baseline, 6 and 12 months and at the last visit, respectively (Table 3). At 6 months, the dose of GC with respect to baseline was reduced in 58.9% ($n = 155$) of patients, while 72.8% ($n = 131$) did so at the last visit. A total of 70/292 (24%) patients discontinued GC. The percentage of patients taking ≤5 mg/day of prednisone increased over the successive visits. At baseline, 38.6% of patients ($n = 121$) were taking 5 mg or less of prednisone, at 6 months, 63.5% ($n = 176$) and at 12 months, 84.7% ($n = 178$) [Supplementary Table S1 (available at *Rheumatology* online)].

Target goals

Rates of achievement of LLDAS and DORIS-21 significantly increased from baseline to 6, 12 months, and at the last visit (Fig. 1). DORIS-21 remission rates were as follows: 24%, 36.3% and 52.5% at 6, 12 months and at the last visit, respectively. In turn, LLDAS rates were: 45.8%, 62% and 71% at 6, 12 months and at the last visit, respectively.

Rates of sustained LLDAS and DORIS-21 were also analysed. A total of 94 patients (34.2%) maintained LLDAS at 6 and 12 months; 118 patients (50.6%) maintained it from the 12-month visit to their last one, and 80 patients (29.6%) maintained this state during the entire period. For DORIS-21, 56 patients (19%) maintained at 6 and 12 months, 68 (27.4%) from 12 months to the last visit and 44 patients (15%) during the entire follow-up period. A total of 88 patients (27.2%) maintained DORIS in >50% of the visits; and 149 patients (46%) did so in the case of LLDAS (Table 4). The only factors we found associated with reaching LLDAS and DORIS, during any of the visits, were low levels of C3 and C4 at baseline ($P < 0.05$).

Flares

During the year before initiation of BLM, 86.5% ($n = 249$) of patients had suffered at least one flare of lupus activity. Of these, 89 patients (29.3%) had a severe flare.

At 12 months after initiation of BLM, 28.8% ($n = 62$) of patients had flared and 7.4% ($n = 15$) had experienced a severe flare (Supplementary Table S2, available at *Rheumatology* online).

Damage

Mean SDI score at the end of the observation period did not change from the baseline visit. A total of 26 patients (11.2%) presented new damage at 12 months with respect to the baseline visit and 28 (12%) at the last evaluation of the study with respect to baseline (Table 5).

We found that risk factors for organ damage included the presence of neurological, serositis, renal and discoid lupus. Other risk factors for damage were a higher SLEDAI score, low C3 and C4 levels at baseline and age. In addition, the use of GC at baseline and flares at 12 months were found to be factors associated with damage. We determined that LLDAS at 12 months and sustained LLDAS at 6–12 months were protective against damage at 12 months. In terms of DORIS-21, although this state at 6 months was protective against damage, statistical significance was not reached at 12 months.

Safety and discontinuation

A total of 71 adverse events (AE) were registered during the study. Supplementary Table S3 (available at *Rheumatology* online). There was one death in the studied population, but the cause was not specified.

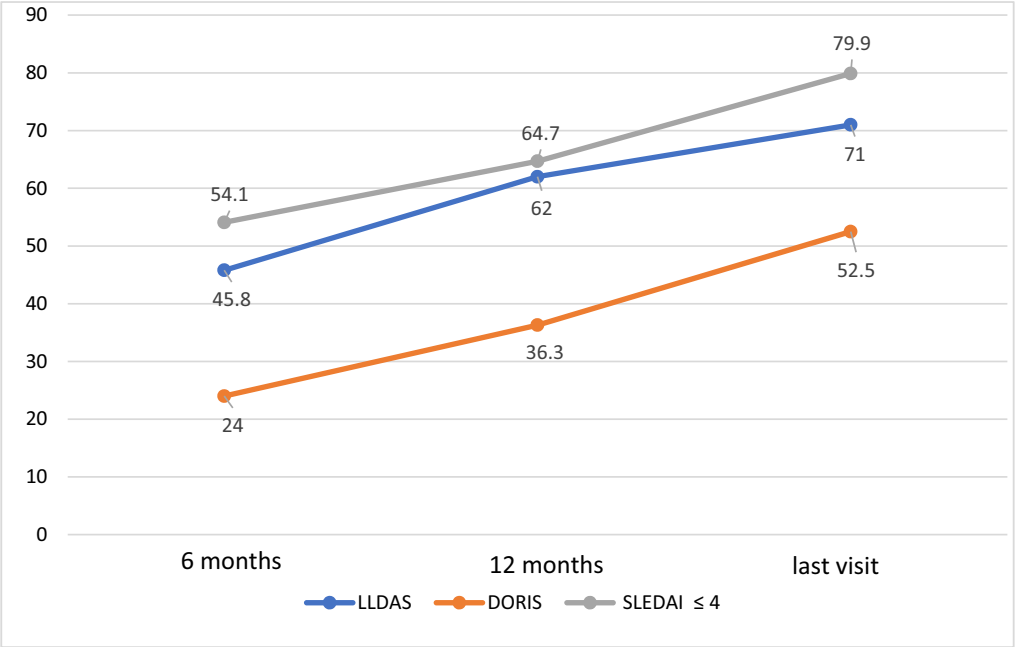
Drug discontinuation was observed in 106 (34%) patients. Median (IQR) time to discontinuation was 0.7 IQR (0.5–1.8) years. Reasons for discontinuation were: inefficacy in 80 (60.5%) patients; adverse events in 25 (23.5%); non-adherence in 3 (2.8%) patients; and other reasons in 14 (13.2%) [Supplementary Table S4 (available at *Rheumatology* online)].

Table 3. Clinical, serological and laboratory responses

	Baseline	6 months	12 months	Last visit
Mean (±SD) SLEDAI reduction	10 (± 5.25)	5.0 (± 5.1)*	6.1 (± 5.5)*	7.13 (± 5.3)*
Response according to physician	—	212 (65.4%)*	185 (57.1%)*	165 (50.9%)*
Number of swollen joints; mean (±SD)	3.3 (±3.6)	1.2 (±2.8)*	0.7 (±1.9)*	0.5 (±1.8)*
Number of painful joints; mean (±SD)	4.4 (±5.1)	1.5 (±3.3)*	1.0 (±2.7)*	0.92 (±2.7)*
C3; median (IQ)	79 (63.4–106)	91.9 (71.5–110)*	90 (73.62–109)*	96 (79–116)*
C4; median (IQ)	12.5 (8–18)	15 (10.4–22)*	16.5 (11.7–23)*	19 (14–26)*
Anti-dsDNA; median (IQ)	100.7 (22–339)	52.85 (13–261)*	52 (10.6–210.75)*	30.2 (7–93)*
ESR; median (IQ)	24 (11.4–42)	18 (8–30)*	13 (7–27)*	12 (6–22)*
CRP; median (IQ)	3.07 (1–8.8)	2.4 (1–6.9)*	2 (0.81–4.4)*	2.3 (0.88–4.9)*
Prednisone dose (mg/day); mean (±SD)	12.3 (±12.16)	7.4 (±5.36)*	5.8 (±4.42)*	4.75 (±3.74)*

anti-dsDNA: anti-double-stranded DNA; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

* $P < 0.05$, compared with previous visit.



	6 months	12 months	Last visit, mean (±SD) time 26 (±20.9) months
Discontinued	45	69	106
Ongoing	279	255	218

Figure 1. Rates of therapeutic targets attained over time by patients being treated with BLM

Table 4. Sustained LLDAS and DORIS-21 states

Period	6–12 months	12 months–last visit	Entire period (6m–12m–last visit)
Sustained LLDAS *n* (%)	94 (34.2%)	118 (50.6%)	80 (29%)
Sustained DORIS-21 N (%)	56 (19%)	68 (27.4%)	44 (15%)

DORIS: definition of remission in SLE; LLDAS: lupus low disease activity state.

Table 5. Damage accrual

SDI	Baseline	12 months	last
n (%)	68/329 (21%)	44/251 (17.5%)	41/217 (18.9%)
mean (± SD)	0.8 (±1.2)	0.8 (±1.1)	0.8 (±1.1)

SDI: SLICC/ACR Damage Index.

Most patients ($n = 45$, 13.9%) discontinued BLM during the first 6 months following treatment initiation; 24 (7.4%) discontinued during the period of 6–12 months and 37 (11.4%) patients discontinued it during the period from 12 months to the last recorded visit.

Infections

Only severe infections were recorded. A total of 54 (16.6%) patients presented a severe infection and 51 (15.7%) presented >1 severe infection at some point. Only four patients discontinued BLM due to serious infections, none of them opportunistic. There were no deaths due to infection.

Depression

A total of 35 (10.8%) patients were newly diagnosed with depression after onset of BLM; 31 of them started new pharmacological therapy for it. Distribution of new episodes of depression during the analysed visits were as follows: 13 patients at 6 months, 9 patients at 12 months and 13 patients at the last visit. No patients committed suicide. In four patients, BLM was withdrawn due to depression and in another two cases due to suicidal ideation.

Discussion

Our study describes the current use of BLM in a large Spanish cohort. We evaluated the indications, effectiveness, safety and attainment of treat-to-target (T2T) strategy goals. The main reason for prescribing BLM in our cohort was for controlling disease activity (95%), mainly joint and/or skin manifestations. Simultaneously, it was also considered as a maintenance treatment and as a corticosteroid-sparing agent in 61% and 59% of cases, respectively. However, rheumatologists do not prescribe BLM solely to prevent flares or as a sparing corticosteroid agent. BLM is mainly used after DMARD failures (87%) and in most cases concomitantly with DMARDs (85%). Only 15% of patients received BLM as monotherapy. At the time of data collection, we did not include patients who had received BLM for lupus nephritis; however, 44 (13.7%) patients had proteinuria at baseline, media (±SD) 0.62 (±1.32) g/24 h.

On the other hand, our data confirm the consistent effectiveness of BLM at multiple levels. This is evident by the

response in global disease activity, serological response, clinical response according to physician assessment and laboratory parameters, as well as by the number of swollen and painful joints, which were consistent with the results of BLM clinical trials [1, 2] and other observational studies [7, 10].

In terms of therapeutic strategies, BLM managed to achieve the recommended therapeutic objectives (LLDAS/DORIS) beginning at 6 months (45%/24%), which continued to increase throughout the time studied (71%/52%). In addition, we observed that the objective of both LLDAS and DORIS in >50% of the visits was obtained in 46% and 27% of cases, respectively. Our results are similar to other European cohorts [10] despite the differing definitions of remission and low disease activity (LDA). However, in post-hoc analysis of BLM clinical trials [1, 2] the rates of LLDAS were much lower: 12–14% at 52 weeks. It should be noted that in terms of global activity, more than half of the patients obtained an SLEDAI ≤4 early, and this percentage continued to increase over the time studied, with up to 80% of the patients reaching this goal by the end of the study. This confirms BLM's role in controlling disease activity.

According to the T2T strategy for SLE [17], 'lupus maintenance treatment should aim for the lowest GC dosage needed to control disease, and if possible, GCs should be withdrawn completely'. Despite the fact that clinical trials did not demonstrate significant results in the BLM GC-sparing effect, our data showed that 33% of patients were able to discontinue corticosteroids at the end of the study. In addition, 84.7% and 73.6% of patients managed to reduce their dose by 5 mg/day or less, at 12 months and at the end of the period studied, respectively. This data arguably supports the use of BLM in those patients who are unable to reduce GC below 7.5 mg/day.

BLM also demonstrated the ability to prevent severe flares, as has been shown in previous clinical trials [1, 2]. We have also observed its preventative effects in mild-moderate flares, which could have implications for lessening damage accrual [18]. Interestingly, BLM has recently been shown to play an important role in the early treatment of SLE patients, given that it can delay or reduce the severity of the first SLE flare, which can result in lower organ damage accrual and better outcomes [19].

The use of BLM has demonstrated its role in the prevention of long-term damage [20]. In our study, we did not observe any significant changes in the rates of damage, whether in terms of early damage (assessed in the first year) or at the end of follow-up (mean time 3.8 years). We found that patients with more severe manifestations at the beginning of treatment (neurological, renal, serositis or discoid lupus) were those who experienced greater damage accrual. On the other hand, both LLDAS and DORIS played protective roles in preventing damage, as has been previously demonstrated [21–26].

Severe infections and depression were evaluated as adverse effects of particularly important interest. A total of 16% of patients presented a severe infection and only four patients discontinued treatment for this reason, rates which are lower than those described in other cohorts [10].

Data in the current literature on the use of BLM vis-à-vis depression are controversial. A recent metanalysis [27] demonstrated that BLM did not increase the risk of depression and suicide. Otherwise, in the BASE study, the incidence of depression and serious depression was slightly higher in the BLM group *vs* placebo. In addition, a greater proportion of patients in the BLM arm committed suicide or self-injury [0.75% ($n = 15/2002$) *vs* 0.25 ($n = 5/2001$)] [28]. In our cohort, 10% of patients presented a new diagnosis of depression after initiating BLM, with most starting a new pharmacological therapy for this reason. We did not document any cases of suicide in our cohort, although four patients withdrew from treatment due to depression or suicidal ideation.

About 1/3 of the patients in our cohort discontinued BLM. Interestingly, our data show that most rheumatologists' decisions to withdrawal BLM mainly stemmed from inefficacy during the period from 0 to 6 months, a strategy most likely adopted based on their experience with other rheumatic diseases. However, similar to the results reported in the BeRLISS study [10], we observed that the majority of patients achieved higher rates of response at around 12 months of treatment and thereafter. Therefore, this should be considered the optimal time to assess response in order to avoid early withdrawal, given that SLE is a disease with scarce therapeutic options.

In summary, our study revealed the current use of BLM in Spain, with outstanding rates of DORIS-21 remission and LLDAS, as well as an adequate safety profile. Our study also confirms belimumab's GC-sparing role, prevention of flares and organ damage accrual. Based on our data, this may mean that BLM is being prematurely withdrawn in real-world clinical practice due to lack of efficacy during the first 6 months. Finally, the use of BLM could also have cost-effective benefits, as more patients remain active in the workforce when they are undergoing BLM treatment.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Funding

Funding was received from GlaxoSimthKline to support the statistical analysis of this work.

Disclosure statement: I.A-G.: received payments for educational talks from: GSK, AstraZeneca. J.M.P-R.: member of speakers' bureau: Advisory boards for GSK, Otsuka, Astrazeneca, Gebro. Received grants/research support: Investigator Sponsorized Study Grant from GSK. Research support from Pfizer International (Competitive International Grants for Learning and Change). T.C.S-M.: received payments for educational talks and consulting activities from: GSK, Otzuka, Vifor. Received grants/research support: Investigator Sponsorized Study Grant from GSK. J.A.G-P.: received payments for educational talks from Abbvie, Astra Zeneca, GSK, Janssen, Lilly, Pfizer, Galápagos and Otsuka. B.F-S.: received payments for educational talks from Abbvie, Astrazeneca, MSD and BMS for presentations. I.J.R-F.: received honoraria as speaker in GSK scientific meetings and as a member of advisory boards.

Acknowledgements

The authors thank all medical staff at all participating institutions for providing the data. All authors approved the final

version to be published. The authors thank the Spanish Foundation of Rheumatology for providing medical writing/editorial assistance during the preparation of the manuscript (FERBT2023). I.A-G. is supported by ACI/FER(21/CONV/02/1266).

References

1. Navarra SV, Guzmán RM, Gallacher AE *et al.*; BLISS-52 Study Group. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet 2011;377:721–31.
2. Furie R, Petri M, Zamani O *et al.*; BLISS-76 Study Group. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. Arthritis Rheum 2011;63:3918–30.
3. Stohl W, Schwarting A, Okada M *et al.* Efficacy and safety of subcutaneous belimumab in systemic lupus erythematosus: a fifty-two-week randomized, double-blind, placebo-controlled study. Arthritis Rheumatol 2017;69:1016–27.
4. Brunner HI, Abud-Mendoza C, Viola DO *et al.* and the Pediatric Rheumatology Collaborative Study Group (PRCSG). Safety and efficacy of intravenous belimumab in children with systemic lupus erythematosus: results from a randomised, placebo-controlled trial. Ann Rheum Dis 2020;79:1340–8.
5. Furie R, Rovin BH, Houssiau F *et al.* Two-year, randomized, controlled trial of belimumab in lupus nephritis. N Engl J Med 2020;383:1117–28.
6. Collins CE, Dall'Era M, Kan H *et al.* Response to belimumab among patients with systemic lupus erythematosus in clinical practice settings: 24-month results from the OBSErve study in the USA. Lupus Sci Med 2016;3:e000118.
7. Cortés J, Andreu JL, Calvo J *et al.* Evaluation of use of belimumab in clinical practice settings (observe study) in Spain: health resource utilization and labour absenteeism. Value Health 2014;17:A534.
8. Touma Z, Sayani A, Pineau CA *et al.* Belimumab use, clinical outcomes and glucocorticoid reduction in patients with systemic lupus erythematosus receiving belimumab in clinical practice settings: results from the OBSErve Canada Study. Rheumatol Int 2017;37:865–73.
9. Fernandes BM, Barreira S, Fonseca JE *et al.* Belimumab in the treatment of Portuguese Systemic Lupus Erythematosus patients: a real-life multicenter study. Acta Reumatol Port 2020;45:170–6.
10. Gatto M, Saccon F, Zen M *et al.* Early disease and low baseline damage as predictors of response to belimumab in patients with systemic lupus erythematosus in a real-life setting. Arthritis Rheumatol 2020;72:1314–24.
11. Tan EM, Cohen AS, Fries JF *et al.* The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271–7.
12. Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. J Rheumatol 2002;29:288–91.
13. Gladman DD, Goldsmith CH, Urowitz MB *et al.* The Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index for Systemic Lupus Erythematosus International Comparison. J Rheumatol 2000;27:373–6.
14. Petri MA, Merrill JT, Maciuca R, Davis JC Jr, Kennedy W. FRI0293 validation of the revised selena flare index in systemic lupus erythematosus. Ann Rheum Dis 2013;72:A473–4.
15. van Vollenhoven RF, Bertsias G, Doria A *et al.* 2021 DORIS definition of remission in SLE: final recommendations from an international task force. Lupus Sci Med 2021;8:e000538.
16. Franklyn K, Lau CS, Navarra SV *et al.*; Asia-Pacific Lupus Collaboration. Definition and initial validation of a Lupus Low Disease Activity State (LLDAS). Ann Rheum Dis 2016;75:1615–21.
17. van Vollenhoven RF, Mosca M, Bertsias G *et al.* Treat-to-target in systemic lupus erythematosus: recommendations from an international task force. Ann Rheum Dis 2014;73:958–67.
18. Ugarte-Gil MF, Acevedo-Vásquez E, Alarcón GS *et al.*; GLADEL. The number of flares patients experience impacts on damage accrual in systemic lupus erythematosus: data from a multiethnic Latin American cohort. Ann Rheum Dis 2015;74:1019–23.
19. Langham J, Barut V, Samnaliev M *et al.* Disease severity, flares and treatment patterns in adults with systemic lupus erythematosus in the UK: a real-world observational retrospective cohort analysis. Rheumatol Adv Pract 2021;5:rkab061.
20. Urowitz MB, Ohsfeldt RL, Wielage RC *et al.* Organ damage in patients treated with belimumab versus standard of care: a propensity score-matched comparative analysis. Ann Rheum Dis 2019;78:372–9.
21. Tsang-A-Sjoe MW, Bultink IE, Heslinga M, Voskuyl AE. Both prolonged remission and Lupus Low Disease Activity State are associated with reduced damage accrual in systemic lupus erythematosus. Rheumatology (Oxford) 2017;56:121–8.
22. Ugarte-Gil MF, Wojdyla D, Pons-Estel GJ *et al.*; GLADEL. Remission and Low Disease Activity Status (LDAS) protect lupus patients from damage occurrence: data from a multiethnic, multinational Latin American Lupus Cohort (GLADEL). Ann Rheum Dis 2017;76:2071–4.
23. Alarcón GS, Ugarte-Gil MF, Pons-Estel G *et al.* Remission and low disease activity state (LDAS) are protective of intermediate and long-term outcomes in SLE patients. results from LUMINA (LXXVIII), a multiethnic, multicenter US cohort. Lupus 2019;28:423–6.
24. Zen M, Iaccarino L, Gatto M *et al.* Lupus low disease activity state is associated with a decrease in damage progression in Caucasian patients with SLE, but overlaps with remission. Ann Rheum Dis 2018;77:104–10.
25. Sharma C, Raymond W, Eilertsen G, Nossent J. Association of achieving lupus low disease activity state fifty percent of the time with both reduced damage accrual and mortality in patients with systemic lupus erythematosus. Arthritis Care Res (Hoboken) 2020;72:447–51.
26. Petri M, Magder LS. Comparison of remission and lupus low disease activity state in damage prevention in a United States systemic lupus erythematosus cohort. Arthritis Rheumatol 2018;70:1790–5.
27. Xie W, Huang H, Zhan S, Zhang Z. Risk of psychiatric disorders and all-cause mortality with BLM therapy in patients with systemic lupus erythematosus: a meta-analysis of randomised controlled trials. Lupus Sci Med 2021;8:e000534.
28. Sheikh SZ, Scheinberg MA, Wei JCC *et al.* Mortality and adverse events of special interest with intravenous belimumab for adults with active, autoantibody-positive systemic lupus erythematosus (BASE): a multicentre, double-blind, randomised, placebo-controlled, phase 4 trial. Lancet Rheumatol 2021;3:e122–30.