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Efficacy of belimumab in patients with SLE and haematological manifestations: retrospective analysis from the BeRLiSS 2.0 cohort

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ABSTRACT

Objective To assess the effectiveness of belimumab (BEL) in improving anaemia, thrombocytopenia, lymphopenia and leucopenia in patients with SLE.

Methods The BeRLiSS (Belimumab in Real Life Setting Study) 2.0 cohort included patients with SLE from 14 Italian referral centres treated with BEL for active joint or skin involvement, based on physician judgement, between June 2013 and May 2024. Clinical and laboratory parameters were recorded at baseline and every 6 months. Patients were eligible if they had baseline haematological abnormalities defined according to British Isles Lupus Assessment Group (BILAG) (grade C or higher): haemoglobin (Hb) ≤10.9 g/dL, platelets (Plts) ≤149×10^9/L, lymphocytes (Lym) ≤1.0×10^9/L or leucocytes (Leuc) ≤3.0×10^9/L. Follow-up data up to month 48 were available for 33 patients with anaemia, 20 with thrombocytopenia, 44 with lymphopenia and 18 with leucopenia.

Results At baseline, 76 patients had anaemia, 44 thrombocytopenia, 107 lymphopenia and 53 leucopenia. Hb levels increased significantly from 9.9±0.6 g/dL to 11.7±1.4 g/dL at month 48 (p<0.001). Platelet counts rose from 110.2±38.1×10^9/L to 176.6±88.7×10^9/L (p=0.004), Lym counts from 0.72±0.21×10^9/L to 1.14±0.45×10^9/L (p<0.001) and leucocyte counts from 2.437±0.533×10^9/L to 4.732±1.897×10^9/L at 48 months (p<0.001). Improvement in Hb (p=0.97), Plts (p=0.12), Lym (p=0.86) and Leuc (p=0.73) was similar regardless of the use of concomitant immunosuppressants. Glucocorticoid (GC) doses decreased significantly across all manifestations, except for leucopenia: anaemia (12.9±12.1 to 3.6±4.9 mg/day, p=0.003), thrombocytopenia (10.8±9.6 to 4.4±5.5 mg/day, p=0.004), lymphopenia (10.6±8.6 to 3.1±3.2 mg/day, p<0.001). Proportion of GC users declined over 48 months: anaemia 96.1–60.7%, thrombocytopenia 93.1–80%, lymphopenia 96.3–70.3% and leucopenia 95.3–80%.

Conclusion In this real-world cohort, BEL treatment was associated with improvement in anaemia, thrombocytopenia, lymphopenia and leucopenia with over half of patients achieving normalisation of blood counts. Haematological responses were similar regardless of

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Haematological manifestations are common in SLE, but evidence on the efficacy of belimumab for anaemia, thrombocytopenia, lymphopenia and leucopenia is limited to small case series or post hoc analyses not designed to assess these outcomes. No large real-life studies have specifically evaluated belimumab's effect on distinct haematological abnormalities.

WHAT THIS STUDY ADDS

⇒ This study provides the first real-life evidence in a large Caucasian cohort showing that belimumab significantly improves anaemia, thrombocytopenia, lymphopenia and leucopenia, with more than half of patients achieving normalisation of blood counts. It also identifies baseline predictors of response for anaemia and lymphopenia and confirms a robust glucocorticoid-sparing effect.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Belimumab emerges as a valuable therapeutic option for patients with SLE and haematological involvement. These findings support its use beyond cutaneous and articular disease and highlight the need for prospective studies specifically addressing haematological outcomes.

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concomitant immunosuppressive therapy, supporting the role of BEL as a therapeutic option for haematological abnormalities in SLE.

INTRODUCTION

SLE is a chronic systemic autoimmune disease characterised by inflammation and immune-mediated injury to multiple organ systems, frequently involving the mucocutaneous, musculoskeletal, haematological and kidney systems.[1]

Anaemia is commonly observed in SLE, affecting approximately 50% of patients.[2] The most common type is anaemia of chronic disease, driven by inflammatory cytokines such as interleukin (IL)-6, followed by iron deficiency anaemia, often due to chronic blood loss.[3 4] Autoimmune haemolytic anaemia, although less common (10–12% of patients),[5] represents a clinically distinct anaemia phenotype in SLE and is associated with increased disease severity, reduced survival and higher organ damage accrual.[2 6] Other causes—including drug-induced cytopenias, bone marrow suppression, pernicious anaemia and microangiopathic haemolytic anaemia—are much less frequent and generally contribute minimally to the overall anaemia burden in SLE.[7–12] This study therefore focuses on the most common non-haemolytic forms of anaemia, which account for the majority of cases encountered in routine clinical practice.

Thrombocytopenia is a common haematological manifestation of SLE, affecting 10–40% of patients, with severe forms (<50×10⁹/L) reported in 3–20%.[13] It is linked to higher disease activity and comorbid burden. Thrombocytopenia is considered a marker of poor prognosis in SLE and is associated with increased mortality and cumulative organ damage.[13] The pathogenesis is multifactorial: it includes peripheral destruction via autoantibodies and immune complexes, reduced bone marrow production, cell-mediated mechanisms, such as CD8+ T cell-induced platelet (Plt) lysis, and microvascular sequestration. While antiphospholipid antibodies (aPL) have been linked to Plt clearance, other immunological pathways—such as anti-Plt antibodies and Plt desialylation—also contribute, although their exact role in SLE remains less well defined.[13 14] Treatment follows principles similar to those of immune thrombocytopenia (ITP) management but is individualised according to SLE activity. Glucocorticoids (GCs) remain the first-line therapy, though they often fail to maintain sustained responses. Other options include IVIG, HCQ, immunosuppressants (eg, mycophenolate mofetil (MMF), azathioprine (AZA), cyclophosphamide (CYC)), rituximab and thrombopoietin receptor agonists.[15 16] Emerging treatments include agents that target novel mechanisms, such as Plt desialylation with oseltamivir and differentiation induction with all-trans retinoic acid, although evidence specific to SLE remains limited.[17 18] Splenectomy is now reserved for refractory cases due to its inconsistent efficacy and risk of complications.[19]

Leucopenia is a common manifestation in SLE, reported in 22–42% of patients.[20] It is often secondary to lymphopenia, neutropenia or a combination of both, with lymphopenia being the most frequent leucocyte abnormality, affecting 20–75% of patients.[7 20] Risk factors include younger age, elevated disease activity, hypocomplementaemia, anti-double-stranded DNA (dsDNA) positivity and immunosuppressive (IS) therapy, whereas antimalarials (AM) and azathioprine appear protective.[2 20] Lymphopenia is not clearly linked to increased organ damage or mortality.[2] Pathogenetic mechanisms encompass anti-lymphocyte autoantibodies targeting T and B cells, decreased complement regulatory proteins (CD55, CD59), enhanced Fas ligand-mediated apoptosis, impaired lymphopoiesis mediated by cytokines (interferon (IFN)-γ, IL-6) and lymphocyte sequestration at inflammatory sites. Iatrogenic lymphopenia is common, related to immunosuppressants and corticosteroids.[21 22] Clinically, lymphopenia is rarely severe but may predispose to infections, notably herpes zoster and bacterial infections, although data are inconclusive.[23] It often reflects underlying disease activity and tends to improve with its control. Therapeutic approaches focus on controlling disease activity; specific treatments for lymphopenia are lacking. Prophylactic antimicrobial therapy may be considered in patients on prolonged high-dose corticosteroids.[24 25]

Belimumab (BEL) is a monoclonal antibody that antagonises the B-lymphocyte stimulator (BLyS) molecule.[26] It has demonstrated efficacy in SLE therapy, particularly for cutaneous, articular and renal manifestations; however, evidence supporting its use in haematological involvement remains limited.

Our aim was to analyse and describe the effect of BEL on anaemia, thrombocytopenia, lymphopenia and leucopenia in a large Italian multicentre cohort of patients with SLE.

MATERIALS AND METHODS

Data from the Belimumab in Real Life Setting Study (BeRLiSS) 2.0 cohort were retrospectively analysed. The BeRLiSS 2.0 study included patients with joint or skin involvement requiring BEL therapy, as determined by physician judgement, across 14 Italian SLE referral centres. BeRLiSS 2.0 inclusion criteria were: (1) Fulfilment of American College of Rheumatology (ACR) 1997 revised criteria or the Systemic Lupus International Collaborating Clinics (SLICC) 2012 criteria or European Alliance of Associations for Rheumatology (EULAR)/ACR 2019 classification criteria; (2) Treatment with intravenous (10 mg/kg on days 0, 14 and 28, and then every 28 days) or subcutaneous (200 mg/week) BEL for at least 6 months; (3) Active disease, that is, clinical SLE Disease Activity Index-2000 (cSLEDAI-2K)>0 despite GC and AM, with or without IS agents; (4) Positive serology (anti-dsDNA antibodies and low C3 or C4 serum levels).[27]

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Table 1 Baseline demographic, clinical and serological variables in patients with anaemia, thrombocytopenia, lymphopenia and leucopenia in BeRLiSS 2.0 cohort

	Anaemia	Thrombocytopenia	Lymphopenia	Leucopenia
Demographics and disease characteristics				
Total patients, n	76	44	107	53
Females, n (%)	72 (94.7)	34 (77.3)	95 (88.8)	49 (92.5)
Age at diagnosis, mean±SD	30.7±12.4	27.8±19.5	31.6±13.1	30.2±11.9
Age at baseline, mean±SD	49.2±12.2	48.8±12.3	49.6±11.7	46.7±11.4
Disease duration, mean±SD (years)	12.2±9.9	15.5±18.9	11.3±8.4	10.8±6.4
Early belimumab use (<3 years since diagnosis)	15 (20)	11 (25.6)	23 (21.5)	9 (16.9)
Follow-up duration (mean±SD) (months)	30.2±17.9	19.3±9.5	31.1±16.3	31.2±15.2
Previous haematological involvement, n (%)	41 (53.9)	34 (77.3)	69 (64.5)	35 (66)
SDI, median (IQR)	1(0;2)	1(0;2)	1(0;1)	1.0 (0;2)
SLEDAI-2K, mean±SD	10.4±4.8	9.77±5.3	9.7±3.9	10.4 (4.5)
Chronic-active pattern, n (%)	26 (35.1)	18 (43.9)	36 (33.6)	23 (42.6)
Relapsing-remitting pattern, n (%)	50 (65.8)	26 (59.1)	73 (68.2)	31 (58.5)
PGA, mean±SD	2.6±2	2.5±1.8	2.3±1.5	2.6±2.0
Fatigue (VAS 0–10), mean±SD	5.2±2.4	4.8±2.4	5.0±2.6	5.0±2.6
APS, n (%)	20 (26.7)	16 (37.2)	16 (15)	11 (20.4)
People who smoke, n (%)	14 (18.4)	7 (15.9)	19 (17.9)	8 (14.8)
Serology				
Anti-dsDNA, n (%)	63 (85.1)	31 (70.5)	86 (80.4)	49 (92.5)
Anti- Sm, n (%)	19 (25.3)	12 (27.9)	36 (33.6)	20 (37.0)
Anti- SSA, n (%)	35 (46.7)	18 (41.9)	61 (57)	23 (42.6)
Anti- SSB, n (%)	10 (13.3)	0 (0)	17 (15.9)	5 (9.3)
Anti- U1RNP, n (%)	27 (36)	14 (32.6)	42 (39.3)	21 (38.9)
Anti- P-ribosomal, n (%)	4 (5.4)	4 (9.3)	17 (13.2)	6 (11.3)
Anti-phospholipid, n (%)	34 (44.7)	19 (43.2)	41 (38.3)	24 (45.3)
C3 mg/dL, mean±SD	64.2±19.9	64.5±20.8	65.6±16.8	62.6±18.3
C4 mg/dL, mean±SD	11.7±8.3	9.9±6.6	10±5.3	10.0±5.6
Concomitant therapy				
Glucocorticoid users, n (%)	73 (96.1)	41 (93.2)	103 (96.3)	50 (95.3)
Low-dose (≤5 mg/day) PDN users, n (%)	24 (31.6)	16 (36.4)	33 (30.8)	21 (39.6)
PDN daily dose (mg) mean±SD	12.9±12	10.9±9.6	10.6±8.6	10.2±8.6
Antimalarials, n (%)	40 (52.6)	27 (61.4)	50 (46.7)	30 (56.6)
Immunosuppressants, n (%)	51 (67.1)	25 (56.8)	73 (68.2)	39 (73.6)

Anti-dsDNA, anti-double-stranded DNA; APS, antiphospholipid syndrome; PDN, prednisone; PGA, Physician Global Assessment; SDI, SLE Damage Index; SLEDAI-2K, SLE Disease Activity Index 2K; VAS, Visual Analogue Scale.

The study period spans from June 2013 to May 2024. Clinical and laboratory variables were collected at baseline and every 6 months. They included SLEDAI-2K, daily prednisone (PDN) intake, complete blood count, anti-dsDNA antibodies, C3, C4, concomitant medications, fatigue (Visual Analogue Scale (VAS) 0–10) and Physician Global Assessment (PGA, scale 0–3).

For our study, we considered patients from the BeRLiSS 2.0 cohort who, at baseline, had anaemia, thrombocytopenia, lymphopenia or leucopenia. To define these laboratory anomalies, we used British Isles Lupus Assessment Group (BILAG)-2004 cut-offs for grade C haematology manifestations, that is, anaemia, thrombocytopenia, lymphopenia and leucopenia were defined respectively as haemoglobin (Hb) ≤10.9 g/dL, Plts ≤149×10^9/L, lymphocytes (Lym) ≤1.0×10^9/L and leucocytes (Leuc) ≤3.0×10^9/L.

Outcome measures included Hb, Plts, Lym and Leuc values and the rate of patients with anaemia, thrombocytopenia, lymphopenia and leucopenia during follow-up.

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Table 2 Number of patients with SLE and anaemia, thrombocytopenia, lymphopenia and leucopenia considered in the analyses at different time points and number (%) of patients in whom Hb, Plts, Lym and Leuc values improved beyond cut-offs for anaemia, thrombocytopenia, lymphopenia and leucopenia, respectively

	Anaemia resolution		Thrombocytopenia resolution		Lymphopenia resolution		Leucopenia resolution	
Time points	n	Pts with Hb >10.9 g/dL, n (%)	n	Pts with Plts >150×10^9/L n (%)	n	Pts with Lym >1×10^9/L, n (%)	n	Pts with Leuc >3×10^9/L, n (%)
Baseline	76	0 (0)	44	0 (0)	107	0 (0)	53	0 (0)
Month 6	71	37 (52)	40	21 (53)	104	13 (13)	49	30 (61)
Month 12	67	42 (63)	39	23 (59)	99	35 (35)	47	27 (57)
Month 24	49	30 (61)	32	18 (56)	77	37 (48)	39	31 (80)
Month 36	40	28 (70)	26	17 (65)	55	26 (47)	26	22 (85)
Month 48	33	21 (64)	20	11 (55)	44	28 (64)	18	14 (78)

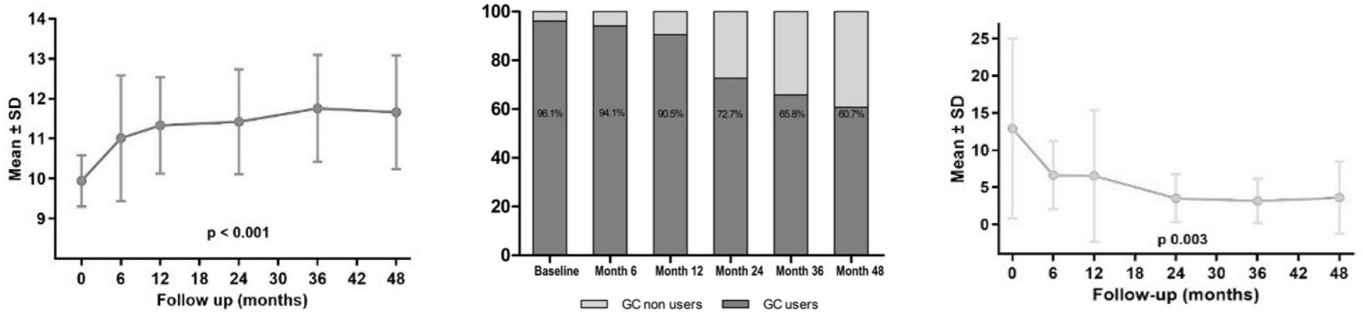
Hb, haemoglobin; Leuc, leucocytes; Lym, lymphocytes; Plts, platelets.

Anaemia/thrombocytopenia/lymphopenia/leucopenia responders were defined as patients with SLE showing an increase in Hb, Plts, Lym and Leuc, respectively, over the following values: Hb >10.9 g/dL, Plts >150×10^9/L, Lym >1×10^9/L, Leuc 3×10^9/L.

Similarly, GC daily dose (in terms of PDN equivalents), the rate of GC users and low-dose PDN users (defined as patients on a PDN dose ≤5 mg/day) were calculated during follow-up. The number of patients who discontinued BEL throughout the follow-up was also recorded.

Parametric and non-parametric tests were used according to the types of variables. Comparisons of continuous data with parametric distribution were performed using t-test, t-test for paired data and one-way analysis of covariance with Bonferroni's post hoc analysis, and repeated measures analysis of variance. Continuous data with non-parametric distribution were analysed using Wilcoxon's rank-sum test and Wilcoxon's test for paired data. Comparisons of categorical data were performed using χ^2 test (Pearson test if indicated); p values less than 0.05 were considered as significant.

The following variables, collected at baseline, were included in the univariate analyses: age at BEL initiation, gender, smoking status (yes/no), disease activity pattern (chronic active vs relapsing-remitting pattern),[28] concomitant IS therapy (yes/no); PDN-equivalent dose, GC use and low dose PDN use (yes/no); SLEDAI-2K score, anti-dsDNA, anti-Sm, anti-SSA, anti-SSB, anti-U1RNP antibodies seropositivity (yes/no); complement levels (C3 and C4), SLICC damage index (SDI) (categorised into >0, >1, >2); Hb, Plts, Lym and Leuc values for patients with anaemia, thrombocytopenia and lymphopenia, respectively. However, while the collection of abnormal values was extremely accurate, normal values were often approximated to prespecified thresholds: 13 g/dL for Hb, 150×10^9/L for Plts, 1.2×10^9/L for Lym and 3×10^9/L for Leuc. Variables with a p value <0.2 at univariate analysis were included in the multivariate models. Backward stepwise logistic regression was employed to identify predictors of response at 12 months and 24 months, with significance set at 5%. Statistical analyses were performed using the SPSS (V.28.0) software (Chicago, Illinois, USA).



A B C

Figure 1 (A) Hb values (g/dL) during follow-up among patients with anaemia at baseline; (B) GC users during follow-up among patients with anaemia at baseline; (C) Mean GC daily dose (PDN equivalents, mg/day) among patients with anaemia at baseline. Note: normal values were often approximated to prespecified thresholds: 13 g/dL for Hb, 150×10^9/L for Plts, 1.2×10^9/L for Lym and 3×10^9/L for Leuc. GC, glucocorticoid; Hb, haemoglobin; Leuc, leucocytes; Lym, lymphocytes; PDN, prednisone; Plts, platelets.

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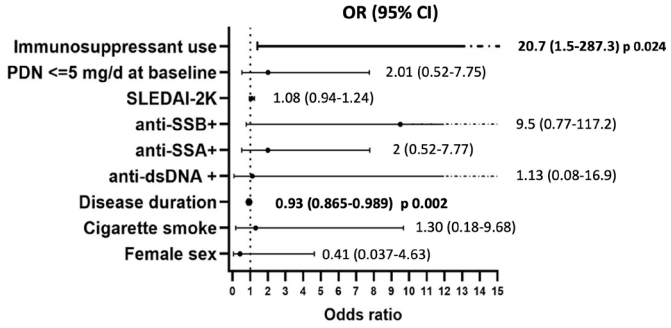


Figure 2 Multivariate regression analysis was performed for anaemia responders at 12 months. Variables included in the model were cigarette smoking, SLEDAI-2K score, complement C3 and C4 levels, baseline prednisone dose ≤5 mg/day, seropositivity for anti-dsDNA, anti-SSA and anti-SSB antibodies, sex, use of immunosuppressants and disease duration. dsDNA, double-stranded DNA; PDN, prednisone; SLEDAI-2K, SLE Disease Activity Index-2000.

RESULTS

The BeRLiSS 2.0 cohort included 443 patients with SLE and joint or skin manifestations. Among these, haematological involvement—defined according to BILAG-C criteria—was observed at baseline in 76 patients with anaemia, 44 with thrombocytopenia, 107 with lymphopenia and 53 with leucopenia. All these patients were included in the present analysis.

Demographic, clinical and serological variables of the included patients are reported in table 1.

During treatment with BEL, we observed a significant increase in Hb, Plts, Lym and Leuc values, along with a significant decrease in PDN use across all manifestations, except for leucopenia.

Table 2 reports the number of patients with anaemia, thrombocytopenia, lymphopenia and leucopenia at baseline and reaching 6, 12, 24, 36 and 48 months of follow-up. The number (%) of patients whose Hb, Plts, Lym and Leuc values improved beyond the cut-off thresholds is also reported.

Anaemia

Among the 76 patients with anaemia, data regarding Hb levels at month six were available for 71 patients; complete follow-up at month 48 was available for 33 patients (43.4%). Clinical and laboratory data at baseline and at follow-up are reported in online supplemental table S1.

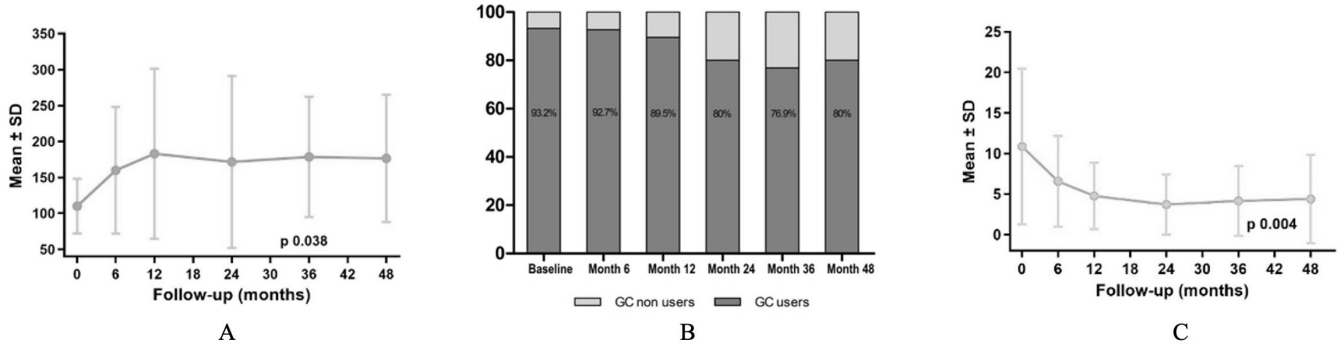
Hb values increased significantly from a mean±SD of 9.9±0.6 g/dL at baseline to 11.33±1.2 g/dL at 12 months, 11.42±1.3 g/dL at 24 months, 11.76±1.34 g/dL at 36 months, 11.7±1.4 g/dL at 48 months (p=0.005) (figure 1A) and the percentage of patients with anaemia decreased to 36.4% at 48 months (table 2). GC users decreased from 96.1% at baseline to 94.1% at 6 months (p=0.003), 90.5% at 12 months (p=0.008), 72.7% at 24 months, 65.8% at 36 months and 60.7% at 48 months (figure 2B). Additionally, the percentage of low-dose PDN users increased progressively from 31.6% at baseline to 89.3% at month 48 (calculated among GC users only). The mean GC dose significantly decreased from 12.9±2.1 mg/day at baseline to 6.63±4.56 mg/day at 6 months, 6.52±8.86 mg/day at 12 months, 3.51±3.23 mg/day at 24 months, 3.15±2.99 mg/day at 36 months, 3.57±4.88 mg/day at 48 months (p=0.003) (figure 1C).

At univariate analysis, anaemia responders had a higher proportion of IS users (p=0.049), shorter disease duration (p=0.02) and higher baseline C4 values (p=0.017) compared with non-responders at 12 months. At 24 months, anaemia responders showed a significantly lower proportion of anti-SSA positive patients (p=0.015), while anti-SSB positive patients were found to be numerically but not significantly lower (p=0.062).

At multivariate regression analysis, baseline predictors of anaemia resolution at 12 months were a shorter disease duration (OR 0.93, CI 0.87 to 0.99, p=0.022) and concomitant IS use (OR 20.7, CI 1.45 to 287.26, p=0.024) (figure 2).

Thrombocytopenia

According to the inclusion criteria, 44 patients with thrombocytopenia were included at baseline; complete



A B C

Figure 3 (A) Platelet count (×10^9/L) during follow-up among patients with thrombocytopenia at baseline; (B) GC users during follow-up among patients with thrombocytopenia at baseline; (C) Mean GC daily dose (PDN equivalents, mg/day) among patients with thrombocytopenia at baseline. Normal values were often approximated to prespecified thresholds: 13 g/dL for Hb, 150×10^9/L for Plts, 1.2×10^9/L for Lym and 3×10^9/L for Leuc. GC, glucocorticoid; Hb, haemoglobin; Leuc, leucocytes; Lym, lymphocytes; PDN, prednisone; Plts, platelets.

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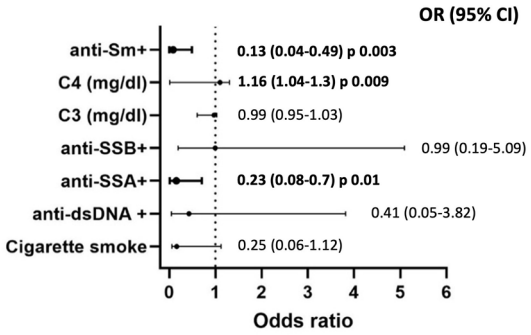


Figure 4 Multivariate regression analysis was performed for lymphopenia responders at 12 months. Variables included in the model were C3 and C4 levels, seropositivity for anti-dsDNA, anti SSA and anti SSB, anti Sm and cigarette smoking. dsDNA, double-stranded DNA.

follow-up at month 48 was available for 20 patients (45.5%). Clinical and laboratory data at baseline and at follow-up are reported in online supplemental table S1.

Plt values increased significantly from a mean±SD of 110.2±38.1×10^9/L at baseline to 159.9±88.1×10^9/L at 6 months, 183.1±118.4×10^9/L at 12 months, 171.6±119.7×10^9/L at 24 months, 178.5±83.9×10^9/L at 36 months, 176.6±88.7×10^9/L at 48 months (p=0.038) (figure 3A) and the rate of patients with thrombocytopenia decreased to 45% at 48 months (table 2).

GC users decreased numerically, but not significantly, from a baseline value of 93.2–92.7% at 6 months, 89.5% at 12 months, 80% at 24 months, 76.9% at 36 months and 80% at 48 months (figure 3B); in contrast, the percentage of low-dose PDN users increased from 36.4% at baseline to 90% at 48 months. Mean GC dose declined significantly from a baseline value of 10.8±9.6 mg/day to 6.56±5.6 mg/day at 6 months, 4.75±4.11 mg/day at 12 months, 3.71±3.71 at 24 months, 4.16±4.33 at 36 months and 4.4±5.5 mg/day at 48 months (figure 4C) (p=0.004).

Neither univariate nor multivariate analysis identified any predictor of thrombocytopenia resolution at 12 and 24 months among patients with thrombocytopenia at baseline.

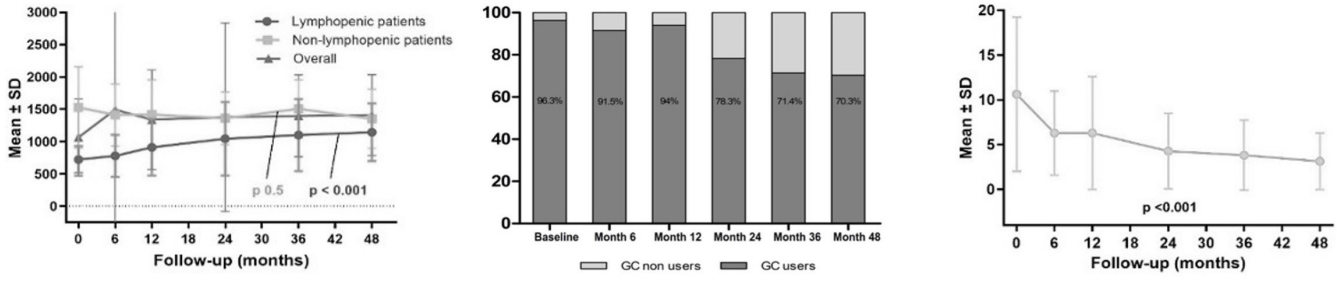
Lymphopenia

According to the inclusion criteria, 107 patients with lymphopenia were included at baseline; complete follow-up at month 48 was available for 44 patients (41.1%). Clinical and laboratory data at baseline and at follow-up are reported in online supplemental table S1.

Among patients with lymphopenia at baseline, lymphocyte values increased significantly (p<0.001) from a mean±SD baseline of 0.72±0.208×10^9/L to 0.778±0.447×10^9/L at 6 months, 0.91±0.325×10^9/L at 12 months, 1.042±0.436×10^9/L at 24 months, 1.099±0.57×10^9/L at 36 months and 1.144±0.558×10^9/L at 48 months (figure 5A), and the percentage of patients with lymphopenia decreased to 36.4% at 48 months (table 2).

GC users decreased from a baseline value of 96.3–91.5% at 6 months, 94% at 12 months, 78.3% at 24 months, 71.4% at 36 months and 70.3% at 48 months (p<0.001) (figure 5B). Compared with baseline values, rates of GC users were significantly lower at 24 months (p<0.001), at 36 months (p<0.001) and 48 months (p<0.001). During follow-up, mean PDN daily dose decreased significantly (p<0.001) from a baseline value of 10.6±8.6 mg/day to 6.3±4.7 mg/day at 6 months, 6.29±6.3 mg/day at 12 months, 4.26±4.2 mg/day at 24 months, 3.8±3.91 at 36 months and 3.1±3.2 mg/day at 48 months (*figure 5C*). The percentage of low-dose PDN users increased from a baseline value of 30.8–56.6% at 6 months, 62% at 12 months, 82.6% at 24 months, 81.6% at 36 months and 89.2% at month 48; statistical significance was found at every time point, compared with baseline (p<0.001 for all).

At univariate analysis at 12 months, lymphopenia responders had a lower rate of anti-Sm seropositive patients (17.1% vs 42.2%, p=0.011), higher mean C4 values (11.7±6.2 vs 8.8±4.5 mg/dL, p<0.05) and higher mean±SD baseline lymphocyte counts (0.768±0.195 vs 0.679±0.208 x 10^9/L, p<0.05) compared with lymphopenia non-responders; lower rates of anti-SSA seropositive patients were found among responders, although this difference narrowly missed statistical significance (45.7% vs 65.6%, p=0.055). At 24 months, lymphopenia



A B C

Figure 5 (A) Lym count over time in patients lymphopenic at baseline; (B) GC users during follow-up among patients with lymphopenia at baseline; (C) Mean GC daily dose (PDN equivalents, mg/day) among patients with lymphopenia at baseline. Normal values were often approximated to prespecified thresholds: 13 g/dL for Hb, 150×10^9/L for Plts, 1.2×10^9/L for Lym and 3×10^9/L for Leuc. GC, glucocorticoid; Hb, haemoglobin; Leuc, leucocytes; Lym, lymphocytes; PDN, prednisone; Plts, platelets.

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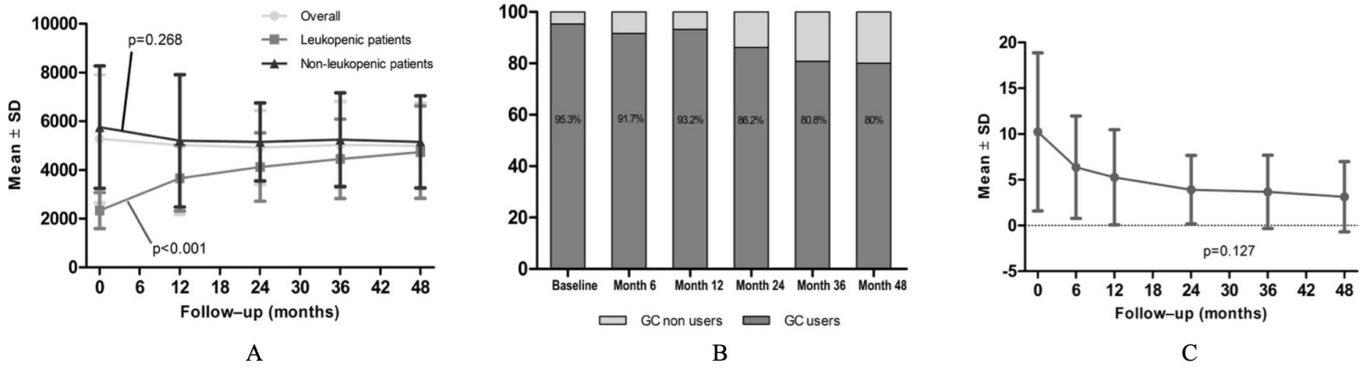


Figure 6 (A) Leuc count over time in patients with leucopenia at baseline; (B) GC users during follow-up among patients with leucopenia at baseline; (C) Mean GC daily dose (PDN equivalents, mg/day) among patients with leucopenia at baseline. Note: normal values were often approximated to prespecified thresholds: 13 g/dL for Hb, 150×10^9/L for Plts, 1.2×10^9/L for Lym and 3×10^9/L for Leuc. GC, glucocorticoid; Hb, haemoglobin; Leuc, leucocytes; Lym, lymphocytes; PDN, prednisone; Plts, platelets.

responders showed significantly higher mean baseline C3 values (72.1±16 vs 64.1±15.3 mg/dL, p<0.05).

At multivariate regression analysis for lymphopenia responders at 12 months (figure 4), baseline factors significantly associated with lymphopenia resolution at 12 months were anti-Sm (OR 0.132, CI 0.035 to 0.491, p=0.003), anti-SSA seropositivity (OR 0.23, CI 0.075 to 0.702, p=0.01) and C4 values (OR 1.162, CI 1.037 to 1.301, p=0.009). No predictors of lymphopenia resolution at 24 months were identified.

Leucopenia

According to the inclusion criteria, 53 patients with leucopenia were included at baseline; complete follow-up at month 48 was available for 18 patients (34%). Clinical and laboratory data at baseline and at follow-up are reported in online supplemental table S1.

Among patients with leucopenia at baseline, leucocyte values increased significantly (p<0.001) from a mean±SD baseline of $2.437\pm0.533\times10^9$/L to $3.845\pm1.773\times10^9$/L at 6 months, $3.614\pm1.322\times10^9$/L at 12 months, $4.048\pm1.340\times10^9$/L at 24 months, $4.452\pm1.630\times10^9$/L at 36 months and $4.732\pm1.897\times10^9$/L at 48 months (figure 6A), and the percentage of patients with leucopenia decreased to 22% at 48 months (table 2). GC users decreased from a baseline value of 95.3–91.7% at 6 months, 93.2% at 12 months, 86.2% at 24 months, 80.8% at 36 months and 80% at 48 months (figure 6B). During follow-up, mean PDN daily dose decreased from a baseline value of 10.23±8.64 mg/day to 6.37±5.59 mg/day at 6 months, 5.27±5.20 mg/day at 12 months, 3.91±3.74 mg/day at 24 months, 3.67±4.00 mg/day at 36 months and 3.14±3.84 mg/day at 48 months (p=0.127) (figure 6C). The percentage of low-dose PDN users increased from a baseline value of 39.6–56.2% at 6 months, 68.2% at 12 months, 82.8% at 24 months, 84.6% at 36 months and 86.7% at month 48.

At 12-month univariate analysis, leucopenia responders had a lower rate of anti-SSA-positive patients compared with leucopenia non-responders (28.6% vs 60%, p=0.033).

In the multivariate regression analysis, baseline factors significantly associated with leucopenia resolution at 12 months were anti-SSA seropositivity (OR 0.07, 95% CI 0.01 to 0.52, p=0.009) and disease duration (OR 1.10, 95% CI 1.01 to 1.54, p=0.003). At 24 months, baseline factors significantly associated with leucopenia resolution were anti-SSA seropositivity (OR 0.05, 95% CI 0.00 to 0.54, p=0.014) and age at diagnosis (OR 0.85, 95% CI 0.74 to 0.97, p=0.015).

New onset cytopenias during belimumab treatment

New onset cytopenias were rarely observed. Anaemia occurred in 4.95% of patients at month 6, 2.26% at month 12, 4.79% at month 24, 3% at month 36 and 2.45% at month 48. Thrombocytopenia was observed in 2.74% at month 6, 4.32% at month 12, 3.06% at month 24, 5.00% at month 36 and 2.47% at month 48. Lymphopenia occurred in 1.78% at month 6, 1.11% at month 12, 2.09% at month 24, 1.03% at month 36 and 1.88% at month 48. Leucopenia occurred in 4.47% at month 6, 6.22% at month 12, 3.42% at month 24, 5.53% at month 36 and 6.13% at month 48. Detailed numbers for each timepoint are provided in online supplemental table 3.

Use of immunosuppressants

Hb, Plts, Lym and Leuc counts did not significantly differ during follow-up between patients on IS (previous or concomitant) in addition to BEL, compared with those on BEL alone (p=0.97, p=0.12; p=0.86, p=0.73 respectively) (figure 7A-D). Moreover, no significant differences were found regarding mean GC daily dose between patients with or without IS, in addition to BEL, in those with anaemia, thrombocytopenia, lymphopenia and leucopenia (p=0.68, p=0.33, p=0.49, p=0.99, respectively) (online supplemental table S2).

Clinical and laboratory trends

During the 48-month follow-up period, patients presenting with anaemia, thrombocytopenia, lymphopenia and leucopenia showed a reduction in SLEDAI-2K, PGA, VAS fatigue and anti-dsDNA seropositivity, alongside an

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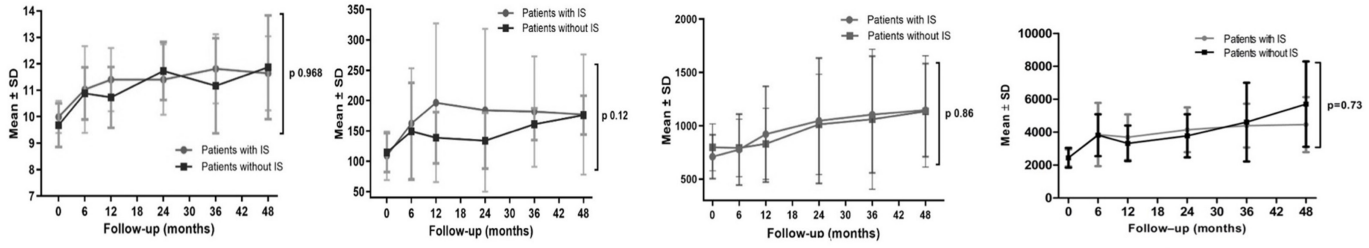


Figure 7 (A) Hb values in patients with baseline anaemia treated with belimumab: comparison between those with and without IS. (B) Plt values in patients with baseline thrombocytopenia treated with belimumab: comparison between those with and without IS. (C) Lym values in patients with baseline lymphopenia treated with belimumab: comparison between those with and without IS. (D) Leuc values in patients with baseline leucopenia treated with belimumab: comparison between those with and without IS. Note: normal values were often approximated to prespecified thresholds: 13 g/dL for Hb, 150×10^9/L for Plts, 1.2×10^9/L for Lym and 3×10^9/L for Leuc. Hb, haemoglobin; IS, immunosuppressant; Leuc, leucocytes; Lym, lymphocytes; Plts, platelets.

increase in complement levels (C3 and C4). Of note, VAS fatigue scores improved significantly during follow-up among patients with anaemia (p<0.001). Moreover, patients with leucopenia showed a significant reduction in SLEDAI-2K (p<0.001), PGA (p=0.011), VAS fatigue (p<0.001) and anti-dsDNA seropositivity, along with a significant increase in complement levels (C3; p<0.001) (online supplemental figure S1).

DISCUSSION

Our study demonstrates the efficacy of BEL in improving anaemia, thrombocytopenia, lymphopenia and leucopenia in patients with SLE. Evidence regarding BEL's effect on haematological manifestations remains limited, mostly based on small case series or post hoc analyses of registration trials. The BLISS-NEA study showed efficacy in an Asian population, while pooled post-hoc data from BLISS-52 and BLISS-76 in Caucasians failed to demonstrate improvement in haematological domains.[29] Notably, neither trial was designed to assess haematological outcomes, nor did they distinguish between anaemia, thrombocytopenia and leucopenia. In contrast, our study specifically differentiates these manifestations. To our knowledge, this is the first real-world analysis on a large cohort evaluating BEL's efficacy on haematological SLE features, also identifying baseline predictors of anaemia or lymphopenia resolution.

In our work, BEL proved effective in increasing mean Hb values in a large Caucasian cohort. This result confirms previous Asian studies, which, however, were conducted on relatively small case series and generally followed for a short period of time.[29–31] Anaemia in SLE has multiple causes, including chronic systemic inflammation related to disease activity. Since BEL reduces overall disease activity, the observed Hb improvement may partly result from decreased inflammation.[29 32–34]

We aimed to identify predictive factors for anaemia resolution among several baseline variables. Shorter disease duration and IS use were associated with a higher probability of resolution at the evaluated timepoints. Higher baseline C4 and anti-SSA positivity correlated with anaemia resolution at 12 and 24 months, respectively, in univariate but not multivariate analysis. Longer disease duration, often linked to organ damage accrual,[35] was more frequent among non-responders, consistent with previous data showing that anaemia is the only cytopenia associated with damage accrual in SLE.[2] This may reflect the greater efficacy of BEL in patients with early disease and less accumulated damage. The role of IS use in anaemia resolution may involve two distinct mechanisms. First, ISs may contribute to improved global disease activity control, thereby improving anaemia of chronic disease through the reduction of systemic inflammation. Anti-SSA autoantibodies have been shown to be associated with a more pronounced IFN-signature in SLE.[36] When SLE disease activity is driven by IFN, it has been shown to be less prone to BEL immunomodulation, thus explaining our findings.[37] Finally, in patients with anaemic SLE, VAS-fatigue scores significantly decreased during follow-up. This result may be due both to a better disease control and to the improvement in Hb values, as both higher SLE disease activity and anaemia are associated with greater fatigue scores.[38]

Several therapies have been studied for SLE-related thrombocytopenia, but no direct comparison data exist. Management of thrombocytopenia is generally derived from strategies developed for ITP, in which maintenance therapy is not always required after induction. By contrast, patients with SLE and thrombocytopenia often show a steroid-dependent disease and the need for long-term immunosuppression.[39] Rituximab and immunosuppressants, particularly MMF, are used for maintenance in primary ITP and SLE but carry a significant infection risk,[35 40] further increased by prolonged GC use.[41] Elevated circulating levels of BLyS have been demonstrated both in SLE and in ITP.[42] This may constitute the pathophysiological rationale for BEL use in SLE-related thrombocytopenia. Furthermore, previous studies have shown that BEL is not burdened by an increased infection rate when added to background therapy,[43] differently from other IS drugs used to treat SLE.[40] In our work, patients treated with BEL showed a significant increase in

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Plt values during follow-up. This increase was both early, already appreciable at month 6, and long-lasting, as Plt values did not decrease during the observation period. This finding is coherent with previous reports of thrombocytopenia in patients with SLE, mostly conducted on small case series, often consisting of patients with multirefractory disease.[29 44–46]

The neutral effect of BEL on lymphocyte counts in patients without lymphopenia aligns with previous evidence. In the BLISS-52 and BLISS-76 trials, lymphopenia rates were comparable between the BEL and placebo groups.[29] Similarly, a large retrospective SLE cohort found no association between BEL exposure and lymphopenia after adjusting for disease activity.[20] Altogether, these data indicate that BEL may improve lymphopenia through disease activity control, while remaining safe in patients with normal baseline lymphocyte counts. We investigated predictors of lymphopenia resolution and found that complement levels and baseline lymphocyte counts were positively associated, suggesting greater efficacy in patients with milder baseline serological activity. Anti-Sm and anti-SSA seropositivity were associated with a poorer response to BEL, likely due to an IFN-driven disease less responsive to its effects.[36 37] Smoking, which is known to reduce BEL efficacy,[47] was similarly linked to lower lymphopenia resolution in multivariate analysis.

Leucocyte counts improved over time, similarly to what was observed in the other haematological groups, with the proportion of patients with leucopenia decreasing at each follow-up timepoint. As observed for lymphopenia, anti-SSA seropositivity was associated with a lower probability of leucopenia resolution in both univariate and multivariate analyses, suggesting that BEL may be more effective in patients without these autoantibodies. Overall, these findings reinforce the idea that SLE manifestations driven by IFN may be less responsive to BEL,[37] which could help explain the associations observed in our study. During follow-up, all four groups showed a reduction in PDN use, as early as at 6 months in patients with anaemia and thrombocytopenia. The observed reduction in GC use aligns with previous findings from both registration trials and real-world studies, which demonstrated a GC-sparing effect of BEL.[33 48–51] At the end of follow-up, the mean PDN dose was below the target maintenance dose of ≤5 mg/day, as recommended in the latest EULAR guidelines as a key long-term treatment goal in SLE.[41] As IS use is concerned, no differences were observed in terms of disease efficacy and PDN use between patient on-IS or off-IS. These results suggest that BEL is effective for haematological manifestations and has a steroid-sparing effect regardless of background therapy.

LIMITATIONS OF OUR STUDY

It must be noted that, although the BeRLiSS 2.0 database allowed us to analyse a substantial number of patients, it was not specifically designed to investigate the haematological domain of SLE. All patients included in our cohort had joint or skin involvement at baseline; therefore, the collected data did not allow us to characterise patients with isolated haematological manifestations. Another limitation is the lack of a control group, which prevents us from isolating BEL's net effect on haematological manifestations, free from confounding biases.

CONCLUSIONS

Our study demonstrates the efficacy of BEL in improving anaemia, thrombocytopenia and lymphopenia in patients with SLE, regardless of IS use, along with a notable GC-sparing effect. Data on BEL's impact on haematological SLE manifestations remains limited; to our knowledge, this is the first real-life study in a large Caucasian cohort addressing this issue. compared with other treatments, BEL offers a favourable risk-benefit profile. Notably, the low incidence of new onset cytopenias during follow-up further supports the haematological safety of BEL in this population.

However, due to limited clinical and laboratory data, we could not assess the underlying aetiology of cytopenia or explore specific pathophysiological mechanisms. Moreover, since BEL was initiated for articular or cutaneous symptoms in the BeRLiSS 2.0 cohort, its effect on haematological abnormalities was not the primary treatment goal. Nonetheless, the results obtained from our work are encouraging and could serve as a starting point for further dedicated studies.

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authors approved the final version of the manuscript and gave their agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. MZ had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. MZ is the named guarantor.

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

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