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ORIGINAL RESEARCH

Efficacy of Belimumab on Different Joint and Skin Manifestations of Systemic Lupus Erythematosus: Real-Life Data from a New Multicentric, Nationwide Italian Cohort (BeRLiSS-JS 2.0)

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Objective: To evaluate the effectiveness of belimumab in different joint and skin phenotypes of systemic lupus erythematosus (SLE).

Methods: The BeRLiSS-JS 2.0 is a decade-long observational study including adult SLE patients from 14 Italian Centers treated with belimumab (intravenous/subcutaneous) stratified by articular (nondeforming nonerosive arthritis -NDNE-, Jaccoud's arthropathy, Rhupus) and cutaneous phenotypes (acute -ACLE-, subacute -SCLE-, and chronic cutaneous lupus erythematosus -CCLE-, and nonspecific manifestations). Outcome variables measured every 6 months up to 36 months included Disease Activity Score-28 joints (DAS28) and Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) scores, remission rates (DAS28<2.6; CLASI-A=0), and prednisone intake (mg/day).

Results: Of 443 patients, 221 (49.9%) had NDNE, 30 (6.8%) Jaccoud's arthropathy, 21 (4.7%) rhupus, 112 (25.3%) had ACLE, 54 (12.2%) SCLE, and 18 (4.1%) CCLE. At 6 months a significant decrease of DAS28 was observed in NDNE ($p<0.001$) and by CLASI-A in ACLE and SCLE (both $p<0.001$). Non-specific cutaneous manifestations did not improve significantly. CLASI-D scores remained stable over 36 months. Remission rates were higher in NDNE and ACLE patients (at 6 months: NDNE 59.6%, Jaccoud's 18.8%, rhupus 30.3% - p=0.002; at 18 months: ACLE 75.9%, SCLE 56.4%, CCLE 33.3% - p=0.018). Daily prednisone dosage decreased in all organ-specific phenotypes, but more pronouncedly in patients with NDNE, ACLE, and SCLE. Higher baseline CLASI-A and DAS28 and CLASI-D were associated with lower remission rates.

Conclusion: Treatment with belimumab was associated with reduced disease activity and increased remission especially in NDNE and ACLE patients. Glucocorticoid-sparing effect was also found.

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Plain Language Summary: Belimumab is known to be an effective treatment for systemic lupus erythematosus (SLE), achieving the highest level of recommendation for non-responders to hydroxychloroquine/immunosuppressive agents (1a/A), while reaching a level B for active cutaneous involvement (1a/B) in the latest EULAR recommendations. On the other hand, belimumab effectiveness across different joint and skin phenotypes of SLE had not been thoroughly evaluated. This study was necessary to understand how belimumab performs in specific SLE phenotypes, such as nondeforming nonerosive arthritis (NDNE), Jaccoud's arthropathy, rhupus, and various cutaneous manifestations (acute, subacute, chronic, and nonspecific) by using disease specific and validated clinimetric measures, such as DAS28 and CLASI.

Belimumab significantly decreased disease activity and improved remission rates especially in NDNE and acute cutaneous lupus erythematosus (ACLE) patients while also highlighting a glucocorticoid-sparing effect particularly in NDNE, ACLE, and subacute cutaneous lupus erythematosus (SCLE) patients.

Therefore, these findings suggest that belimumab could be more beneficial for patients with NDNE and ACLE than other phenotypes, potentially guiding more personalized treatment approaches in clinical practice.

Keywords: systemic lupus erythematosus, skin manifestations, joint manifestations, belimumab, remission

Introduction

Over 15 years after the publication of the first Phase I clinical trial of belimumab for the treatment of systemic lupus erythematosus (SLE),[1] an extensive body of research has now been gathered backing up its use,[2] culminating in belimumab being featured both in the 2019 and in the 2023 updates of the EULAR recommendations for the management of SLE.[3,4]

Indeed, belimumab has achieved the highest level of recommendation in the latest update for renal involvement (1a/A) and non-responders to hydroxychloroquine/immunosuppressive agents (1a/A), while reaching a level B for active cutaneous involvement (1a/B).[4]

Along the disease course, joint manifestations can affect 69% to 95% of patients and skin manifestations between 70% and 85% of patients, bearing a strong correlation with the deterioration of quality of life.[5–9] On the other hand, data from real-world settings are scarce and a sizeable gap of knowledge still remains regarding its varying degrees of efficacy on distinct joint and skin phenotypes.[10,11]

Stemming from the previous study "Belimumab in Real Life Setting Study - Joint and Skin" (ie "BeRLiSS-JS")[10] that explored belimumab efficacy on joint and skin manifestations and its glucocorticoid-sparing effect, especially in the context of early use, our current work aims to further characterize the response to belimumab by performing an analysis on a new cohort (BeRLiSS-JS 2.0) with a special focus on specific articular and skin phenotypes in a real-life setting.

Patients and Methods

Inclusion Criteria

The BeRLiSS-JS 2.0 is an observational study carried out in Italy, enrolling adult SLE patients (≥18 years old) from 14 national referral centers with expertise in SLE management. Prospectively collected data from anonymized patient records since the time of belimumab initiation were retrospectively analyzed. The inclusion and follow-up of patients in this study were carried out without disrupting daily clinical practice. The study period spans from June 2013 to May 2024.

Inclusion Criteria Were the Following

1. Fulfillment of American College of Rheumatology (ACR) 1997 revised criteria for SLE,[12] Systemic Lupus International Collaborating Clinics (SLICC) 2012 classification criteria for SLE[13] or the 2019 European Alliance of Associations for Rheumatology/American College of Rheumatology (EULAR/ACR) classification criteria;[14]
2. Treatment with belimumab for a period of at least 6 months, both via intravenous (IV) and subcutaneous (SC) route of administration (IV: 10 mg/kg on days 0, 14, and 28, and then every 28 days; SC: 200 mg/week). The

comparability of the SC route of administration to the IV in terms of efficacy and safety has already been corroborated by several studies.[15–19]

3. Active disease such as clinical SLE Disease Activity Index-2000 (cSLEDAI-2K) >0 despite glucocorticoids and antimalarials, with or without immunosuppressive agents. Joint, skin, and other involvements were identified by the fulfillment of each individual SLEDAI-2K item.

Exclusion and Discontinuation Criteria

All data were systematically evaluated to find inconsistencies or missing information leading to a request of data amendment by the participating centers. Patients who still had insufficient data entry were excluded from the study. A gap in the follow-up greater than 6 months was considered equivalent to drug discontinuation for the purpose of this study.

Study Variables

All investigators were required to collect the following baseline data: sex, date of diagnosis, age at diagnosis, age at belimumab initiation, duration of SLE prior to belimumab, and the pattern of disease before starting belimumab (categorized as chronic active or relapsing-remitting as defined by Zen et al).[20] Additionally, the following data regarding the serologic profile (ANA, anti-dsDNA, anti-Sm, anti-SSA, anti-SSB, anti-U1RNP, anti-P ribosomal, anti-phospholipid antibodies), co-existence of antiphospholipid syndrome (APS), overlap with other autoimmune diseases, and previous therapies (ie hydroxychloroquine (HCQ), methotrexate (MTX), azathioprine (AZA), cyclophosphamide (CYC), cyclosporine A (CsA), mycophenolate mofetil (MMF), rituximab (RTX), and others) were collected. Finally, previous organ involvement (ie articular, cutaneous, renal, neurological, serositis, and hematological involvement), comorbidities (ie diabetes, hypertension, dyslipidemia, neoplasms, vasculopathy, ischemic heart disease, osteoporosis, smoking, and menopause before 40 years), and concomitant therapy at the start of belimumab (including MMF, MTX, AZA, CsA, HCQ) were recorded.

The following variables were collected every 6 months: daily prednisone intake, levels of anti-dsDNA, complete blood cell count, C3 and C4 serum levels, 24-hour proteinuria, urine sediment, and creatinine.

Patients with joint involvement at baseline were stratified into the following phenotypes: non-deforming non-erosive arthritis (NDNE), Jaccoud's arthropathy, and rhupus ie deforming and erosive arthritis. Patients with skin active disease were classified into acute (ACLE), subacute (SCLE), and chronic cutaneous lupus erythematosus (CCLE); non-specific SLE cutaneous manifestations were categorized into cutaneous vasculitis, livedo reticularis, and alopecia/lupus hair.

Clinimetric data included global activity indices such as SLEDAI-2K, Physician's Global Assessment (PGA), and organ-specific activity indices, with a particular emphasis on articular manifestations using the Disease Activity Score-28 joints -based on C reactive protein- (DAS28) and cutaneous manifestations using the Cutaneous Lupus Erythematosus Disease Area and Severity Index Activity (CLASI-A) and Damage (CLASI-D) scores. Damage accrual was measured by the Systemic Lupus International Collaborating Clinics Damage Index (SLICC-DI). These variables were examined at baseline and every 6 months until 36 months after the initiation of belimumab.

Outcome Measures

The BeRLiSS-JS 2.0 study examined the trajectory of DAS28 scores across various joint phenotypes, and CLASI-A and CLASI-D scores across different cutaneous phenotypes.

This study also assessed DAS28 remission (defined as DAS28 <2.6) and CLASI-A remission rate (defined as CLASI-A=0)[21,22] using an *intention-to-treat* approach to mitigate attrition bias. Of note, when analyzing for non-specific cutaneous manifestations of SLE, we only considered patients exhibiting these manifestations in isolation as the considerable overlap with ACLE, SCLE, or CCLE was deemed a potentially relevant confounding factor.

Additionally, the study analyzed the variation in daily prednisone intake alongside the proportion of patients who discontinued glucocorticoids.

Statistical Analysis

The χ^2-test with Bonferroni correction was utilized to compare groups for categorical dichotomous variables. The Shapiro–Wilk normality test determined whether quantitative continuous variables followed a parametric or non-parametric distribution. Consequently, comparisons between two groups were conducted using the Wilcoxon signed-rank test for non-parametric data and the paired *t*-test for parametric data. For comparisons among three or more groups, Friedman's two-way analysis of variance by ranks was applied for non-parametric variables, while repeated-measures ANOVA was used for parametric variables. *p*-values less than 0.05 were considered significant. Quantitative continuous variables are expressed as median (IQR). All analyses were conducted using SPSS software version 29.0 (Chicago).

Ethics

Informed consent was obtained from all participants prior to enrollment. This study received approval from the University of Padova Ethics Committee (3806/AO/16) and was conducted in accordance with the Declaration of Helsinki.

Results

Characteristics of the BeRLiSS-JS 2.0 Cohort

A total of 443 patients were enrolled (females = 394; 88.9%), with a median age at diagnosis of 28.2 years (20.8–37.1) and a median disease duration at enrollment of 9.9 years (4.0–18.2). At belimumab initiation, 272 patients (61.4%) had joint involvement: 221 NDNE arthritis (50.7%), 30 Jaccoud's arthropathy (6.9%), and 21 rhupus (4.8%). On the other hand, 242 patients (54.6%) had skin manifestations: 112 ACLE (25.3%), 54 SCLE (12.1%), 18 CCLE (4.1%), 48 cutaneous vasculitis (10.8%), 23 livedo reticularis (5.2%), and 79 alopecia/lupus hair (17.8%). The nonspecific cutaneous manifestations tended to overlap considerably with the specific ones: only 22 patients (5.0%) with cutaneous vasculitis, 12 patients (2.7%) with livedo reticularis, and 22 patients (5.0%) with alopecia/lupus hair exhibited these conditions without any association with specific skin manifestations. Considering the whole cohort, 404 patients were in follow-up at 6 months, 356 at 12 months, 301 at 18 months, 266 at 24 months, 230 at 30 months, and 193 at 36 months. Considering patients with joint involvement, 194 were in follow-up at 6 months, 173 at 12 months, 146 at 18 months, 134 at 24 months, 120 at 30 months, and 97 at 36 months. Finally, considering patients with skin manifestation, 154 were in follow-up at 6 months, 139 at 12 months, 118 at 18 months, 107 at 24 months, 91 at 30 months, and 75 at 36 months.

The demographic and serologic features of the cohort are reported in Table 1, while the baseline clinical and clinimetric features are reported in Table 2.

Of note, patients with Jaccoud's arthropathy or rhupus had longer disease duration before initiating belimumab compared to those with NDNE - 9.5 (3.3–16.3) years for NDNE, 22.9 (11.3–26.2) years for Jaccoud's, and 13.6 (4.7–16.8) years for rhupus ($p = 0.003$).

No difference in the duration of the disease at baseline was found in patients with different skin subtypes.

Table 1 Description of the Baseline Cohort Characteristics

Variables	Results
Demographic characteristics	
Patients, n (%)	443 (100%)
Female patients, n (%)	394 (88.9%)
Male patients, n (%)	49 (11.1%)
Age at SLE diagnosis, years, median (IQR)	28.2 (20.8–37.1)
Age at the first infusion years, median (IQR)	42.0 (32.7–49.8)
Disease duration at recruitment, years, median (IQR)	9.9 (4.0–18.2)
Duration of treatment with belimumab, months, median (IQR)	30.0 (12.0–60.0)

(*Continued*)

Table 1 (Continued).

Variables	Results
Serologic profile	
ANA, n (%)	441 (99.5%)
Anti-DNA, n (%)	397 (89.6%)
Anti-Sm, n (%)	122 (27.7%)
Anti-SSA, n (%)	199 (45.3%)
Anti-SSB, n (%)	69 (15.7%)
Anti-U1RNP, n (%)	139 (31.6%)
Anti-Ribosomal P Protein, n (%)	30 (7%)
Anti-Phospholipids, n (%)	141 (32.1%)
APS, n (%)	59 (13.5%)
Concomitant treatment	
PDN (mg/die), median (IQR), (%)	8.0 (5.0–12.5), (94.6%)
MMF (g/day), median (IQR), (%)	2.0 (1.0–2.0), (30.2%)
MTX (mg/week), median (IQR), (%)	11.3 (7.5–15.0), (11.7%)
AZA (mg/day), median (IQR), (%)	100 (50.0–100.0), (16.7%)
HCQ (mg/day), median (IQR), (%)	300.0 (200–400), (69.8%)
Belimumab monotherapy, n (%)	183 (41.4%)
Previous treatments	
MMF, n (%)	201 (45.4%)
MTX, n (%)	196 (44.2%)
AZA, n (%)	194 (43.8%)
CsA, n (%)	115 (26.0%)
HCQ, n (%)	245 (55.3%)
CYF, n (%)	76 (17.2%)
RTX, n (%)	50 (11.3%)
Previous clinical manifestations	
Arthritis, n (%)	388 (87.0%)
Cutaneous, n (%)	315 (71.3%)
Renal, n (%)	166 (37.5%)
Class, n (%):	
• II	17 (3.8%)
• III	23 (5.2%)
• IV	63 (14.2%)
• V	16 (3.6%)
Neurologic, n (%)	57 (13.0%)
Serositis, n (%)	131 (29.6%)
Hematological, n (%)	235 (53.0%)
Baseline biohumoral parameters	
C3 (mg/dl), median (IQR)	72.0 (60.0–85.0)
C4 (mg/dl), median (IQR)	10.0 (7.0–15.0)
GB (mmc), median (IQR)	4500 (3520–6500)
Lymphocytes (mmc), median (IQR)	1200 (935–1450)
Hb (g/dl), median (IQR)	12.2 (11.3–13.0)
Platelets (el/uL), median (IQR)	210,000 (160,000–281,000)
24h proteinuria (g/die), median (IQR)	0.1 (0.0–0.3)
Active sediment, n (%)	70 (19%)
eGFR, median (IQR)	90.0 (84.0–100.0)

Notes: Quantitative continuous variables are reported as the median and interquartile range (IQR). Qualitative data are reported as the numerosity and percentage relative to the total number of patients.

Abbreviations: ANA, Antinuclear Antibodies; Anti-DNA, Anti-Double Stranded; DNA Antibodies; Anti-Sm, Anti-Smith Antibodies; Anti-SSA, Anti-Sjögren's Syndrome A; Anti-SSB, Anti-Sjögren's Syndrome B Antibodies; Anti-U1RNP, Anti-U1 Ribonucleoprotein Antibodies; Anti-Ribosomal P Protein, Antibodies against Ribosomal P Proteins, Anti-Phospholipid: Antibodies against Phospholipids, APS, Antiphospholipid Syndrome; PDN, Prednisone; MMF, Mycophenolate Mofetil; MTX, Methotrexate; AZA, Azathioprine; CsA, Cyclosporine; HCQ, Hydroxychloroquine; CYF, Cyclophosphamide; RTX, Rituximab; C3, Complement Component 3; C4, Complement Component 4; GB, Granulocytes; Hb, Hemoglobin; eGF, Estimated Glomerular Filtration Rate.

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Table 2 Description of the Baseline Clinical Characteristics of the Cohort

Variables			Results
Articular involvement	Overall, n (%)		272 (61.4%)
	NDNE, n (%)		221 (49.9%)
	Jaccoud's arthropathy, n (%)		30 (6.8%)
	Rhupus, n (%)		21 (4.7%)
Cutaneous involvement	Overall		242 (52.1%)
	Specific	ACLE, n (%)	112 (25.3%)
		SCLE, n (%)	54 (12.2%)
		CCLE, n (%)	18 (4.1%)
	Non-specific	Cutaneous vasculitis, n (%)	48 (10.8%)
		Livedo reticularis, n (%)	23 (5.2%)
		Alopecia/lupus hair, n (%)	79 (17.8%)
Hematological involvement, n (%)			152 (34.3%)
Renal involvement, n (%)			106 (23.9%)
Serositis, n (%)			43 (9.7%)
Constitutional involvement, n (%)			191 (43.1%)
Relapsing-remitting disease, n (%)			270 (61.0%)
Chronic-active disease, n (%)			173 (39.0%)
Baseline clinimetric scores			
SLEDAI-2K, median (IQR)			8.0 (6.0–10.0)
PGA, median (IQR)			2.0 (1.3–2.0)
Fatigue (VAS 0–10), median (IQR)			5.0 (3.0–7.0)
SLICC-DI, median (IQR)			1.0 (0.0–1.0)
DAS28, median (IQR)			3.8 (3.0–4.6)
CLASIa, median (IQR)			3.0 (1.0–6.0)
CLASId, median (IQR)			0.0 (0.0–0.0)

Notes: Qualitative data are reported as the numerosity and percentage relative to the total number of patients. Quantitative continuous variables are reported as the median and interquartile range (IQR). For every concomitant medication the percentage of patients is also shown.

Abbreviations: NDNE, Non-Deforming Non-Erosive; ACLE, Acute Cutaneous Lupus Erythematosus; SCLE, Subacute Cutaneous Lupus Erythematosus; CCLE, Chronic Cutaneous Lupus Erythematosus; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; PGA, Physician Global Assessment; VAS, Visual Analogue Scale; SLICC-DI, Systemic Lupus International Collaborating Clinics Damage Index, DAS28: Disease Activity Score in 28 Joints; CLASIa, Cutaneous Lupus Erythematosus Disease Area and Severity Index (activity), CLASId, Cutaneous Lupus Erythematosus Disease Area and Severity Index (damage).

Activity Score Trajectories Measured by DAS28 and CLASI-A

As shown in Figure 1 and in Supplementary Table 1, only NDNE patients experienced a significant decrease in DAS28 scores already at 6 months ($p < 0.001$). However, both NDNE and Jaccoud's patients exhibited significant DAS28 score decrease throughout the 36-month treatment period, ($p < 0.001$ for NDNE, $p = 0.007$ for Jaccoud's arthropathy, and $p = 0.102$ for rhupus).

As illustrated in Figure 1 and in Supplementary Table 1, patients with ACLE and SCLE exhibited a prominent and swift decrease in CLASI-A scores within 6 months of treatment initiation ($p < 0.001$ for both). In contrast, CCLE patients did not show a significant decrease in CLASI-A scores at this time point. Nonetheless, when evaluating the entire 36-month treatment period, all specific cutaneous manifestations exhibited a significant reduction in CLASI-A scores, including in the case of CCLE ($p < 0.001$ for both ACLE and SCLE; $p = 0.005$ for CCLE).

Non-specific cutaneous manifestations typically co-occurred with specific cutaneous manifestations which acted as a confounding factor in evaluating CLASI trajectory. When evaluating only patients with non-specific manifestations alone, non-specific manifestations did not demonstrate a statistically significant reduction in CLASI-A scores at any time point.

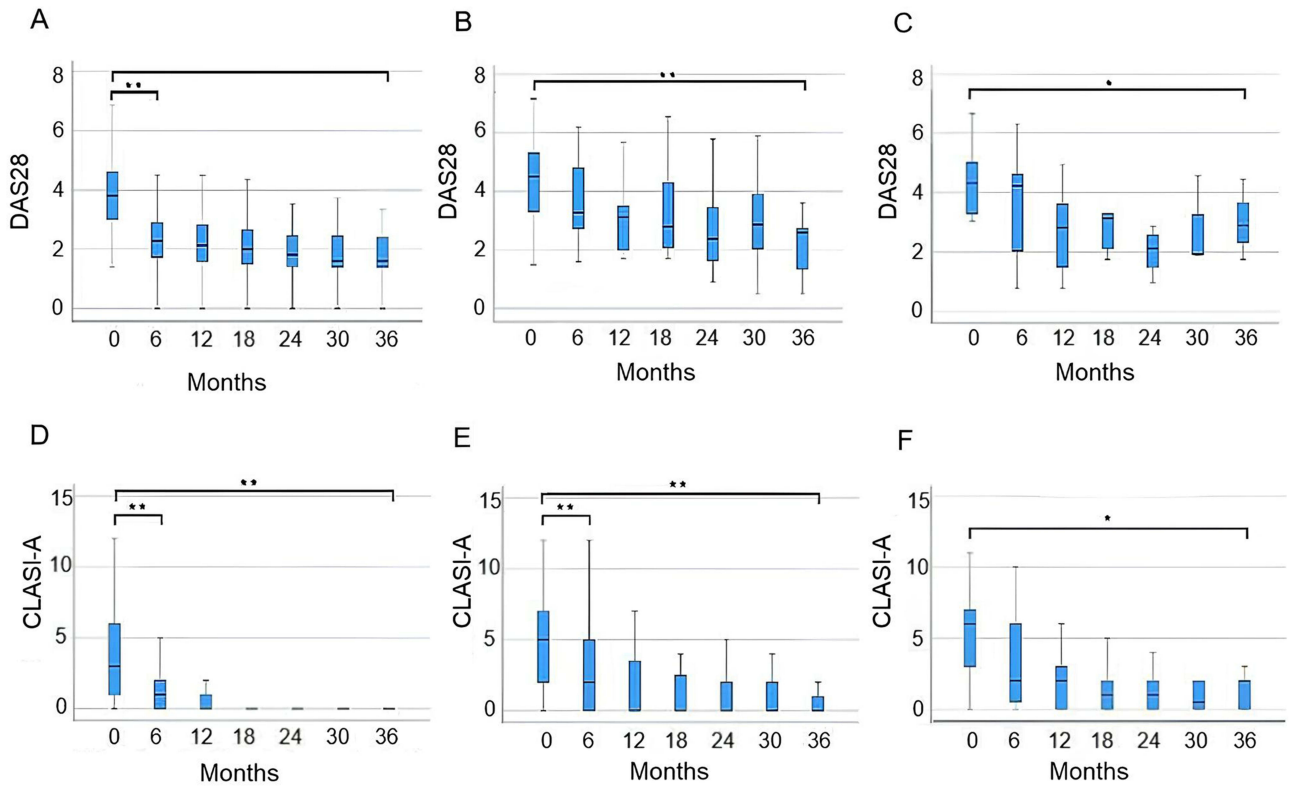

Figure 1 Boxplot chart of DAS28 and CLASI-A reduction over time across different joint and skin phenotypes. DAS28 (top) and CLASI-A scores (bottom) are shown at each timepoint (months) for each articular (**A–C**) and cutaneous (**D–F**) phenotype, respectively. (**A**) NDNE; (**B**) Jaccoud's arthropathy; (**C**) Rhupus; (**D**) ACLE; (**E**) SCLE; (**F**) CCLE. The statistical significance of the score comparisons between each pair of timepoints was assessed using Wilcoxon signed-rank test ($\alpha = 0.0$) ** $p < 0.001$ * $p < 0.05$.
Abbreviations: NDNE, Non-Deforming Non-Erosive arthropathy; ACLE, Acute Cutaneous Lupus Erythematosus; SCLE, Subacute Cutaneous Lupus Erythematosus; CCLE, Chronic Cutaneous Lupus Erythematosus; DAS28, Disease Activity Score in 28 Joints; CLASIa, Cutaneous Lupus Erythematosus Disease Area and Severity Index (activity).

Variation of CLASI-D and Onset of New Joint Deformities

The analysis of variance of CLASI-D scores over the 36-month period on belimumab revealed no significant increase for either specific or non-specific cutaneous manifestations ($p = 0.508$ for ACLE, $p = 1.000$ for SCLE, $p = 0.770$ for CCLE, and $p = 1.000$ for cutaneous vasculitis, livedo reticularis, and alopecia/lupus hair, data not shown).

Furthermore, assuming that joint deformities could be considered as an expression of damage, no patients with NDNE arthritis developed Jaccoud's features during follow-up.

Remission by DAS28 and CLASI-A Scores

In Figure 2 and in Supplementary Table 2, the trajectories of remission rates among different subtypes of joint and skin involvement are depicted.

At 6 months, NDNE phenotypes showed significantly higher remission rates compared to Jaccoud's and rhupus phenotypes ($p = 0.002$), but no significant difference among the three phenotypes were found at other timepoints.

On the other hand, ACLE consistently showed higher remission rates compared to other phenotypes at 18, 24, and 36 months ($p = 0.018$, $p = 0.006$, $p = 0.015$, respectively).

Reduction in Daily Prednisone Oral Intake and Glucocorticoid Discontinuation

The median dosage and the percentage of patients with joint and skin phenotypes stratified into different tiers of daily prednisone intake at each timepoint is reported in Figure 3 and Supplementary Table 3 and 4.

A significant decrease in daily prednisone intake by 6 months was observed in patients with NDNE ($p < 0.001$) while a trend of daily dose reduction was observed in patients with Jaccoud's arthropathy ($p = 0.053$); no difference was

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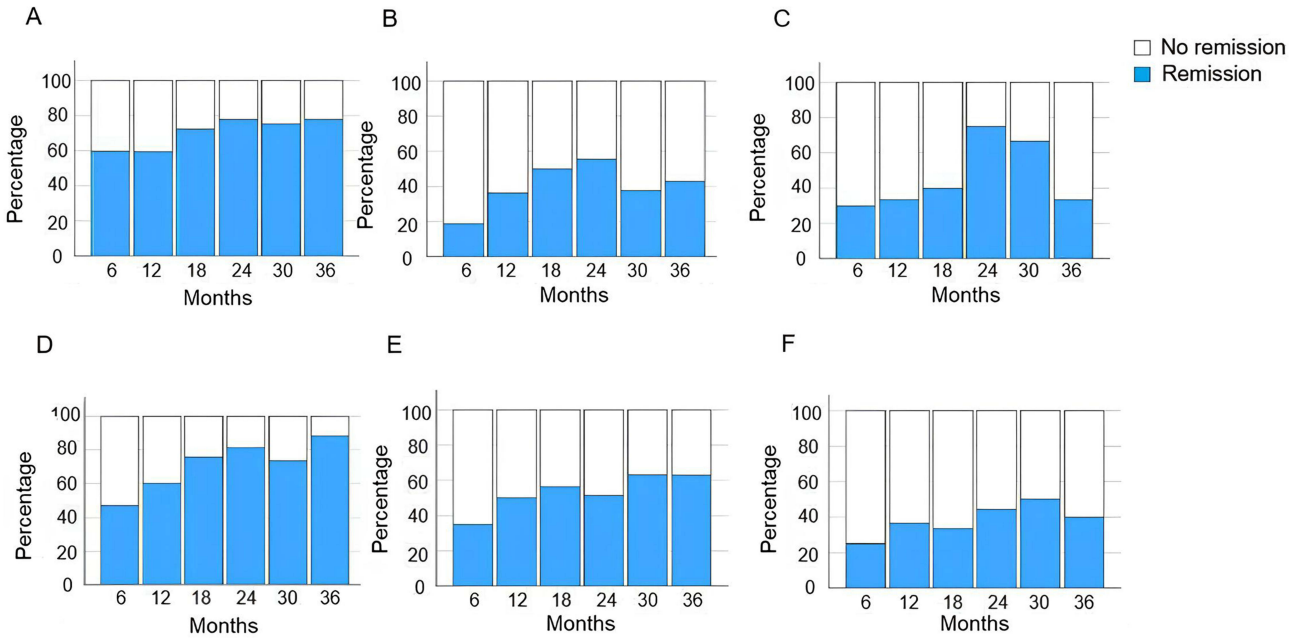

Figure 2 Stacked bar chart illustrating DAS28-remission and CLASI-A remission rates stratified for joint and skin phenotype, respectively. The blue bars depict the percentage of joint (**A–C**) and skin (**D–F**) patients who achieved remission by DAS28 (top) and CLASI-A (bottom) score at any specific timepoint (months), as shown in the legend above to the right. (**A**) NDNE; (**B**) Jaccoud's arthropathy; (**C**) Rhupus; (**D**) ACLE; (**E**) SCLE; (**F**) CCLE.
Abbreviation: NDNE: Non-Deforming Non-Erosive arthropathy, ACLE: Acute Cutaneous Lupus Erythematosus, SCLE: Subacute Cutaneous Lupus Erythematosus, CCLE: Chronic Cutaneous Lupus Erythematosus.

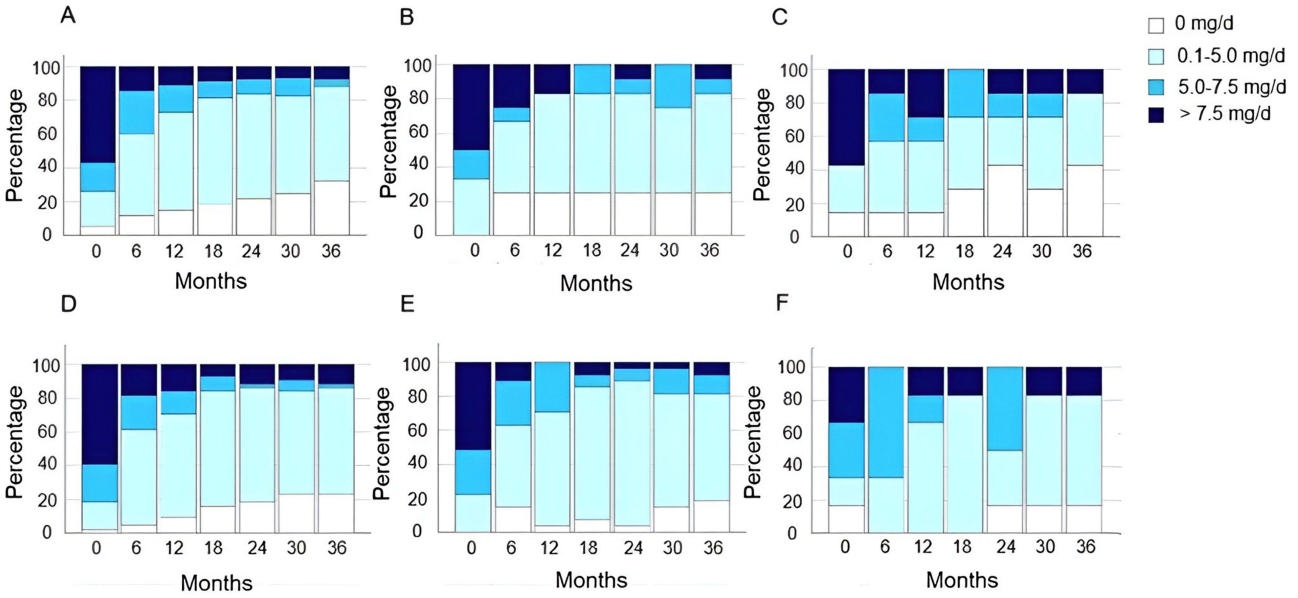

Figure 3 Stacked bar chart illustrating the reduction in daily prednisone oral intake over time across various joint and skin phenotypes. The bars depict the percentage of patients stratified into different tiers of daily prednisone intake at each timepoint (months) for both joint (**A–C**) and skin (**D–F**) phenotypes. Each tier is represented by a different shade of blue, as shown in the legend above to the right. (**A**) NDNE; (**B**) Jaccoud's arthropathy; (**C**) Rhupus; (**D**) ACLE; (**E**) SCLE; (**F**) CCLE.
Abbreviations: NDNE, Non-Deforming Non-Erosive arthropathy; ACLE, Acute Cutaneous Lupus Erythematosus; SCLE, Subacute Cutaneous Lupus Erythematosus; CCLE, Chronic Cutaneous Lupus Erythematosus.

observed in patients with rhupus (p = 0.353) (Supplementary Table 3). On the other hand, patients with all joint phenotypes exhibited significant PDN dose reduction throughout the entire 36-month treatment period (rhupus p = 0.002; NDNE and Jaccoud's arthropathy $p < 0.001$ for both).

A significant decrease in daily prednisone intake was also observed in patients with either ACLE or SCLE as early as 6 months ($p < 0.001$ and $p = 0.002$, respectively), but not in patients with CCLE ($p = 0.947$). Furthermore, analysis of variance did not reveal a statistically significant decrease over the entire 36-month treatment period in patients with CCLE ($p = 0.418$), in contrast to ACLE and SCLE, which both showed significant decrease ($p < 0.001$ for both) (Supplementary Table 3).

Baseline Predictors of DAS28 and CLASI Remission at 6, 12, 24, and 36 months

In patients with NDNE, higher baseline DAS28 scores were associated with lower remission rates at 6 ($p < 0.001$) and 12 months ($p = 0.003$). Smoking was associated with lower remission at 12 months ($p = 0.003$), while higher baseline prednisone intake was associated with remission at 12 months ($p = 0.046$). Prior methotrexate treatment had a negative impact on remission at 6 and 24 months ($p = 0.006$ and $p = 0.027$), whereas concurrent methotrexate treatment did not significantly affect remission rates.

In patients with Jaccoud's arthropathy baseline DAS28 scores were not associated with remission outcomes (data not shown). However, prior methotrexate use was associated with poorer remission rates at 12 months ($p = 0.027$) and 36 months ($p = 0.022$).

In patients with rhupus arthropathy, higher baseline DAS28 scores were associated with lower remission rates only at 6 months ($p = 0.016$).

In patients with ACLE, the age at the initiation of belimumab treatment was associated with lower CLASI remission at 6 ($p = 0.047$) and 12 months ($p = 0.015$). Moreover, high baseline CLASI-A scores was associated with lower remission rates at 6 ($p < 0.001$), 12 ($p = 0.003$), and 24 months ($p = 0.002$), but not at 36 months ($p = 0.082$). Similarly, high baseline CLASI-D scores were associated with lower remission rates at 6 ($p = 0.002$), 12 ($p = 0.030$), and 24 months ($p < 0.001$).

Likewise, in patients with SCLE high baseline CLASI-A scores were negatively associated with remission at 6 ($p < 0.001$), 12 ($p = 0.001$), and 24 months ($p < 0.001$). High baseline CLASI-D scores were associated with lower remission rates at 6 ($p = 0.049$), 12 ($p = 0.005$), and 24 months ($p = 0.026$). Interestingly, the presence of anti-SSB antibodies at baseline was also negatively associated with remission at 6 ($p = 0.025$) and 24 months ($p = 0.012$).

In patients with CCLE high baseline CLASI-A scores negatively impacted remission at 24 months ($p = 0.016$). Finally, baseline CLASI-D scores showed no significant association with remission in this subset of patients.

Discussion

Belimumab effectiveness and safety has been proven in patients with joint and skin manifestations by both randomized controlled trials[11] and real word studies.[10] However, evidence on its efficacy on different joint and skin phenotypes still remains elusive. For this reason, the present study analyzes belimumab's effectiveness in a new BeRLiSS-JS cohort (2.0) focused on different joint and skin phenotypes.

The major finding of this study was that patients with NDNE, ACLE, and SCLE experienced a more rapid decrease in disease activity, and those with NDNE and ACLE exhibited also a better remission rate measured by DAS28 and CLASI-A, respectively, compared to patients with other joint and skin subtypes. On the other hand, a consistent decrease in disease activity and a significant achievement of remission was observed in patients with Jaccoud's arthropathy and CCLE over a longer-term period. In addition, we did not find an overall significant effect in non-specific cutaneous manifestations of SLE after belimumab treatment. However, it is necessary to underline that in our cohort non-specific skin manifestations were associated with specific skin features in more than 50% of cases which led to a curtailed sample size of patients available for the analysis.

Notably, patients treated with belimumab did not experience a significant increase of CLASI-D scores over 36 months across all cutaneous phenotypes, including the non-specific ones and, most importantly, in the CCLE phenotype as well which notoriously drives skin scarring and no patients developed Jaccoud's features during follow-up. These results corroborate previous findings showing that belimumab is able to reduce damage accrual even in the long-term follow-up.[23–31]

Moreover, our findings confirmed the glucocorticoid-sparing effects of belimumab in all subtypes of joint and skin phenotypes; however, this effect seems to be more pronounced in patients with NDNE, ACLE, and SCLE than in other

phenotypes. Interestingly, over 80% of patients in our nationwide cohort was able to achieve the daily oral prednisone intake in accordance with the 2023 EULAR/ACR reccomendations[4] or discontinue glucocorticoid treatment altogether during belimumab treatment. This marks a significant turning point compared to the pre-biologic era, during which less than 60% of patients by real-world data achieved glucocorticoid levels below the recommended threshold.[32]

The heterogeneity in the response to belimumab across different subset of joint and skin manifestations could at least in part be explained by the growing body of evidence which supports the notion that substantial etiopathogenetic differences exist among the various phenotypes often categorized under the generic terms of joint or skin involvement in SLE.[33–35] For instance, numerous studies have highlighted the pivotal role of the interferon signature in the development of skin involvement in SLE patients, identifying it as a primary molecular driver.[36–39] This aligns with the well-documented efficacy of anifrolumab in treating cutaneous manifestations of the disease, with case series supporting its effectiveness even in refractory cases of CCLE.[38,40]

Conversely, emerging evidence indicates that CCLE tends to exhibit suboptimal responsiveness to B-cell depleting therapies, which have demonstrated remarkable efficacy in ACLE and, to a lesser extent, in SCLE.[41–44] Thus, it could be speculated that CCLE relies more on interferon signaling while ACLE could depend more heavily on a B cell-mediated response. It has also been hypothesized that CCLE may often be the expression of a localized, rather than systemic, inflammatory process, consistent with the reduced antibody production and the epidemiology of this phenotype, which is frequently found without systemic involvement.[41]

Analyzing the variables potentially associated with remission among different joint and skin phenotypes in our cohort, the major finding is that the higher the disease activity in both joint and skin disease, the lower is the probability of achieving remission. Similar results had been found in a previous paper[10] suggesting that an early use of belimumab, when the organ specific disease activity is still mild,[45,46] may increase the chances of achieving remission, especially in patients with NDNE and ACLE. In line with this, similarly to previous studies,[27] we found that prior use of MTX is in some cases negatively associated with remission. Another interesting finding is the negative correlation between anti-SSB and remission. This result is difficult to clearly explain; however, one could hypothesize that this autoantibody, is primarily found in patients with Sjögren's syndrome and, unlike anti-SSA, is not clearly associated with SCLE. Therefore, this correlation, observed in a clinical practice setting, needs to be confirmed by further investigation. This study has strengths and limitations. The primary strength of this study lies in the large size of the nationwide cohort, which is one of the largest in Europe with a consistent duration of follow-up (36 months); in addition, all patients were followed-up and treated homogeneously since all the centers involved in the BeRLiSS-JS 2.0 project are requested to follow the EULAR guidelines.[3,4,47]

Among the limitations, first and foremost is the observational retrospective design and the lack of a control arm. Additionally, the limited number of patients with some uncommon forms of joint and skin involvement (eg, rhupus, CCLE, and non-specific cutaneous manifestations) may affect comparability with more common phenotypes. Finally, the homogeneity in the ethnic composition of our cohort may limit the generalizability of our findings to other populations.

Conclusions

In our cohort of SLE patients with joint and skin manifestations, those with NDNE, ACLE, and SCLE experienced a more rapid response and those with NDNE and ACLE showed also a higher rate of organ specific remission than those with other subtypes. In addition, a glucocorticoid-sparing effect was found, with most patients achieving the threshold daily dosage of prednisone suggested by the latest EULAR recommendations. Finally, the negative association between high disease activity and remission supports once again the early use of belimumab in our cohort of patients.

Data Sharing Statement

All data relevant to the study are included in the article or uploaded as online supplemental information.

Ethics Approval

This study was performed in line with the principles of the Declaration of Helsinki. This study received approval from the University of Padova Ethics Committee (3806/AO/16). Informed consent was obtained from all individual participants included in the study. No personal or identifiable data were collected during the conduct of this study.

Author Contributions

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

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Disclosure

Luca Iaccarino: GSK, AstraZeneca, Novartis - Speaker/Honoraria (includes speakers bureau, symposia, and expert witness).
Margherita Zen: GSK, AstraZeneca - Speaker/Honoraria (includes speakers bureau, symposia, and expert witness).
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Giovanni Orsolini: GSK, AstraZeneca, Blueprint - Fee - Speaker/Honoraria (includes speakers bureau, symposia, and expert witness).
The authors report no other conflicts of interest in this work.

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