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Early Disease and Low Baseline Damage as Predictors of Response to Belimumab in Patients With Systemic Lupus Erythematosus in a Real-Life Setting

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Objective. To investigate predictors of response, remission, low disease activity, damage, and drug discontinuation in patients with systemic lupus erythematosus (SLE) who were treated with belimumab.

Methods. In this retrospective study of a multicenter cohort of SLE patients who received intravenous belimumab, the proportion of patients who achieved remission, low disease activity, and treatment response according to the SLE Responder Index 4 (SRI-4) was determined, and the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) was used to score disease damage yearly over the follow-up. Predictors of outcomes were analyzed by multivariate logistic regression with the results expressed as odds ratios (ORs) and 95% confidence intervals (95% CIs).

Results. The study included 466 patients with active SLE from 24 Italian centers, with a median follow-up period of 18 months (range 1–60 months). An SRI-4 response was achieved by 49.2%, 61.3%, 69.7%, 69.6%, and 66.7% of patients at 6, 12, 24, 36, and 48 months, respectively. Baseline predictors of response at 6 months included a score of ≥10 on the SLE Disease Activity Index 2000 (SLEDAI-2K) (OR 3.14 [95% CI 2.033–4.860]) and a disease duration of ≤2 years (OR 1.94 [95% CI 1.078-3.473). Baseline predictors of response at 12 months included a score of ≥10 on the SLEDAI-2K (OR 3.48 [95% CI 2.004–6.025]) and an SDI score of 0 (OR 1.74 [95% CI 1.036–2.923]). Baseline predictors of response at 24 months included a score of ≥10 on the SLEDAI-2K (OR 4.25 [95% CI 2.018–8.940]) and a disease duration of ≤2 years (OR 3.79 [95% CI 1.039–13.52]). Baseline predictors of response at 36 months included a score of ≥10 on the SLEDAI-2K (OR 14.59 [95% CI 3.54–59.79) and baseline status of current smoker (OR 0.19 [95% CI 0.039–0.69]). Patients who were in remission for ≥25% of the follow-up period (44.3%) or who had low disease activity for ≥50% of the follow-up period (66.1%) accrued significantly less damage (P = 0.046 and P = 0.007). A baseline SDI score of 0 was an independent predictor of achieving low disease activity in ≥50% of the follow-up period and remission in ≥25% of the follow-up period. Our findings suggest that the lower the baseline damage, the greater the probability of achieving remission over the course of ≥25% of the follow-up. Further, there was a negative association between the number of flares reported prior to belimumab initiation and the frequency of belimumab discontinuation due to inefficacy (P = 0.009).

Conclusion. In patients with active SLE and low damage at baseline, treatment with belimumab early in the disease may lead to favorable outcomes in a real-life setting.

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INTRODUCTION

Since its approval for the treatment of systemic lupus erythematosus (SLE) in 2011, belimumab has been progressively introduced into the drug treatment regimen in clinical practice, despite some variable indications across countries (1). Since then, improvement has been demonstrated in real-life settings, showing overall consistent results in terms of efficacy and safety (2–6). Better clinical responses were observed in patients with higher disease activity, while long-standing disease, chronic manifestations, and former use of immunosuppressants negatively impacted clinical response (2–4). Importantly, belimumab was shown to decrease disease activity, glucocorticoid intake, and flare rates, thereby hindering damage progression (2–4).

Belimumab has been included in the updated 2019 European League Against Rheumatism (EULAR) recommendations on SLE management as an approved biologic drug to be used in patients with a refractory response to a standard of care regimen (7), which typically includes glucocorticoids and hydroxychloroquine with or without previously unsuccessful treatment with an immunosuppressant.

Remission and low disease activity have recently emerged as desirable therapeutic targets in SLE as they are associated with a decreased risk of organ damage and a better prognosis (8–11), especially if achieved early during treatment (12), and should therefore be among the ultimate goals of any therapeutic strategy.

We previously evaluated predictors of response to belimumab in a multicenter cohort of SLE patients (3), which is, to date, the largest European nationwide cohort of SLE patients investigating the effects of belimumab on disease activity, damage progression, remission, and low disease activity, having increased from 188 participants in the previous cohort to 466 participants in the present study. The present study extends those findings by evaluating the effects of belimumab treatment in the early stages of SLE disease in the same cohort.

PATIENTS AND METHODS

In Italy, intravenous (IV) belimumab can only be prescribed in reference centers selected by Health Regional Authorities based on their experience in the management of SLE. The Belimumab in Real Life Setting Study (BeRLiSS) is a national multicenter cohort study, wherein physicians working in Italian reference centers were invited to participate without any financial support.

Inclusion criteria. Inclusion criteria were as follows: 1) fulfillment of the American College of Rheumatology (ACR) 1982 revised criteria for SLE (13) or the Systemic Lupus International Collaborating Clinics (SLICC)/ACR classification criteria for SLE (14); 2) active disease, defined by a clinical SLE Disease Activity Index (SLEDAI) score of >0, that is refractory to a standard of care regimen (7); 3) IV belimumab (10 mg/kg on days 1, 14, and 28, and then every 28 days) as adjunct therapy; and 4) monthly follow-up due to infusion schedule. Standard of care was defined according to the 2019 EULAR recommendations for the management of SLE (7) as glucocorticoids and antimalarials (if not absolutely contraindicated), with or without immunosuppressive agents. Patients were considered to have early lupus if they had a disease duration of ≤2 years at baseline. SLE patients who were treated between January 1, 2013 and March 31, 2019 were included. Inclusion and follow-up of patients in this study did not interfere with clinical practice.

Data collection and management. Patients were followed up in a prospective manner according to EULAR recommendations (15,16). Anonymized patient data were collected in an ad hoc database since belimumab initiation and were regularly updated. Clinical and laboratory variables collected at baseline and every 6 months were as follows: SLEDAI 2000 (SLEDAI-2K) score (17), fatigue (0–10 on a visual analog scale), daily prednisone intake, complete blood cell count, 24-hour proteinuria, levels of anti–double-stranded DNA (anti-dsDNA) antibodies, levels of C3

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and C4, and concomitant medications (3). All compiled data were systematically and regularly evaluated. In cases of inconsistencies or missing information, centers were required to amend the data. Patient data that did not fulfill inclusion and qualitative control criteria were excluded.

The study was approved by the University of Padua Ethics Committee (approval no. 3806/AO/16) and was carried out in accordance with the Declaration of Helsinki. Informed consent was obtained from each patient regarding personal data treatment.

Outcome measures. All centers were requested to provide the SLE responder index 4 (SRI-4) response (18) for each patient at 6, 12, 24, 36, and 48 months.

Organ-specific activity measures included the Disease Activity Score in 28 joints (DAS28) (19) in patients with musculoskeletal involvement and the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) (20) in patients with skin involvement (3).

Damage was assessed at baseline and annually by the SLICC/ACR Damage Index (SDI) (21), and disease flares were assessed using the Safety of Estrogens in Lupus Erythematosus National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index (SELENA–SLEDAI) flare index (22). All centers were requested to provide the number of flares experienced by each patient up to 5 years before belimumab initiation, when available.

Remission was defined as having a clinical SLEDAI score of 0 and receiving no more than 5 mg of prednisone each day with immunosuppressants and antimalarials at a stable dose, according to Zen and colleagues (23,24), while low disease activity was defined as having a clinical SLEDAI score of ≤2 regardless of treatment, according to Tselios et al (25). Moreover, we evaluated the cumulative time spent either in remission or low disease activity by each patient after belimumab initiation, and classified 4 subgroups (0–24%, 25–49%, 50–74%, and 75–100% of follow-up time) according to the proportion of follow-up time spent in remission or low disease activity.

Safety and discontinuation. Discontinuation was defined as an interruption of belimumab for more than 6 months. Among other reasons for discontinuation, inadequate response was defined by physician judgment as the presence of flares and/or the persistence of moderate/high disease activity.

Adverse events (AEs) and severe AEs (SAEs) (3) were recorded at each clinical evaluation during the follow-up.

Statistical analysis. Data are expressed as the mean ± SD, except for CLASI score and anti-dsDNA antibody levels, which were expressed as the median (interquartile range [IQR]) due to nonparametric distribution. Continuous data with a parametric distribution were compared by *t*-test, *t*-test for paired data,

Table 1. Demographic, clinical, and serologic features of the 466 patients with SLE treated with belimumab*

Sex	
Female	427 (91.6)
Male	39 (8.4)
Ethnicity, white	450 (96.6)
Age, mean ± SD years	
At baseline	41.4 ± 11.2
At diagnosis	29.8 ± 11.9
Patients with antiphospholipid syndrome	70 (15.0)
Patients with concomitant rheumatic disease	71 (15.2)
Disease duration, mean ± SD years	11.6 ± 8.8
Follow-up duration, median (IQR) months†	18 (1–60)
SLEDAI-2K score, mean ± SD (range)	9.3 ± 3.3 (2–42)
SLEDAI-2K score ≥10	183 (39.4)
CLASI activity score, median (IQR)†	1 (0–4)
CLASI damage score, median (IQR)†	0 (0–0)
DAS28, mean ± SD	3.8 ± 1.3
Fatigue, mean ± SD score on 10-cm VAS	5.1 ± 2.7
SDI score, median (IQR)†	1 (0–2)
Clinical SLE manifestations at baseline	
Musculoskeletal	330 (70.8)
Constitutional	209 (44.8)
Cutaneous	211 (45.3)
Hematologic	162 (34.8)
Renal	102 (21.9)
Serosal	46 (9.9)
Neurologic	11 (2.4)
>1 organ affected by SLE	338 (72.5)
>2 organs affected by SLE	184 (39.5)
>3 organs affected by SLE	68 (14.6)
>4 organs affected by SLE	15 (3.2)
Serology at baseline	
ANA titer >1:80	466 (100)
Anti-dsDNA antibodies	378 (81.1)
Anti-Sm antibodies	125 (26.8)
Anti-SSA antibodies	203 (43.6)
Anti-SSB antibodies	82 (17.6)
Anti–U1 RNP antibodies	139 (29.8)
Antiphospholipid antibodies	165 (35.4)
Low serum C3 and/or C4 levels	395 (84.8)
Concomitant treatment	
Oral glucocorticoids	443 (95.1)
Total daily intake, mean ± SD (min.–max.) prednisone equivalent dose in mg	10.6 ± 8.6 (0–60)
Daily intake >5 mg	293 (64.4)
Daily intake >7.5 mg	233 (51.2)
Antimalarials	327 (70.2)
Immunosuppressants	312 (66.9)
Mycophenolate mofetil	136 (29.2)
Methotrexate	66 (14.2)
Azathioprine	70 (15.0)
Cyclosporin A	37 (7.9)
Others (i.e., leflunomide, tacrolimus)	3 (0.01)

* Except where indicated, values are the number (%). SLE = systemic lupus erythematosus; SLEDAI-2K = SLE Disease Activity Index 2000; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; DAS28 = Disease Activity Score in 28 joints; VAS = visual analog scale; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; ANA = antinuclear antibody; anti-dsDNA = anti–double-stranded DNA; min. = minimum; max. = maximum.
† Variables reported as the median (interquartile range [IQR]) due to nonparametric distribution of data.

and one-way analysis of variance (ANOVA) with the Bonferroni post hoc correction for multiple comparisons. CLASI score and anti-dsDNA antibody levels were analyzed by Wilcoxon's rank sum test, Wilcoxon's test for paired data, and ANOVA on ranks (followed by Friedman's test for repeated measures). We investigated predictors of an SRI-4 response, remission, low disease activity, damage, and discontinuation for inefficacy (tested variables are reported in Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41253/abstract). Backward stepwise multiple logistic regression analyses were performed and included variables with a *P* value of less than 0.2 in univariate analysis. SPSS software (version 25.0) was used for statistical analysis. *P* values less than 0.05 were considered significant.

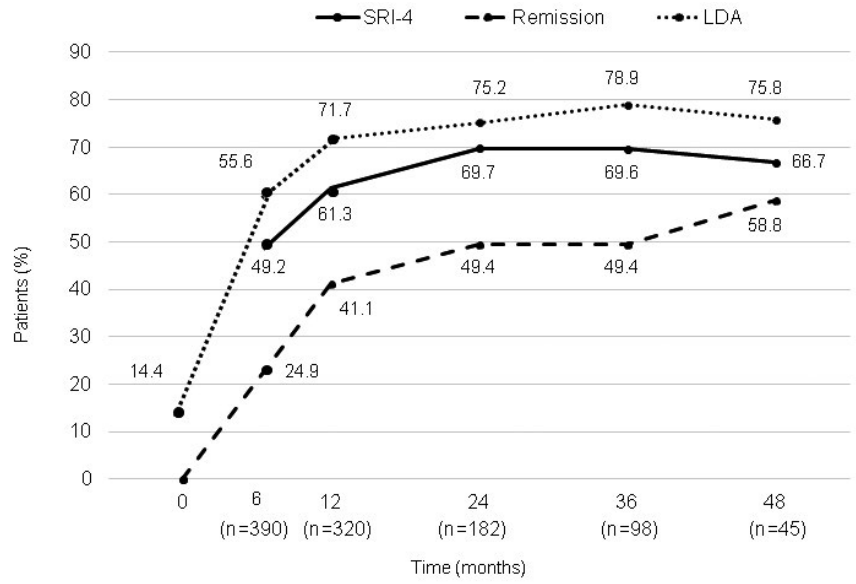
RESULTS

Baseline patient characteristics. The BeRLiSS project included a total of 466 SLE patients from 24 Italian centers, with a median follow-up period of 18 months (range 1–60 months). Demographic, clinical, and serologic features and concomitant treatments are summarized in Table 1.

Manifestations that necessitated belimumab as adjunct therapy were as follows: musculoskeletal in 200 patients (42.9%), mucocutaneous in 110 (23.6%), glomerulonephritis in 56 (12.0%), hematologic in 50 (10.7%), constitutional in 27 (5.8%), and serosal in 23 (4.9%). Renal involvement at the time of belimumab initiation was classified as persistent proteinuria levels of >0.5 grams/day following induction treatment for lupus nephritis or requirement for a high threshold dosage of prednisone (≥7.5 mg/day) in order to control proteinuria. Belimumab was never used as induction treatment for lupus glomerulonephritis.

Seventy-seven patients (16.5%) had a duration of SLE of ≤2 years at baseline. As expected, compared to patients with longer disease duration, patients with early SLE were younger at baseline (mean ± SD age 38.18 ± 10.78 years versus 41.96 ± 11.2 years; $P = 0.007$), had fewer organs previously affected by SLE (mean ± SD number of involved organs 2.86 ± 1.28 versus 3.2 ± 1.18; $P = 0.023$), and had lower baseline SDI scores (mean ± SD score 0.8 ± 1.1 versus 1.2 ± 1.6; $P = 0.044$). Patients with early SLE also had a lower prevalence of antiphospholipid antibody syndrome (7.9% versus 17.2%; $P = 0.026$) and a higher prevalence of serum positivity for anti-Sm antibodies (42.1% versus 23.8%; $P = 0.001$). No significant differences were observed

A



B

	6 months	12 months	24 months	36 months	48 months
Discontinued	37	75	112	147	155
Ongoing but with a still shorter follow-up from baseline	39	71	172	221	266

Figure 1. Rates and timing of therapeutic targets attained by patients with systemic lupus erythematosus (SLE) undergoing belimumab therapy. **A**, Proportion of patients achieving SLE Responder Index 4 (SRI-4) response, remission, and low disease activity (LDA) at different time points. **B**, Number of patients not included in the analysis at a given time point according to the reason. Remission was defined as having a clinical SLE Disease Activity Index (SLEDAI) score of 0 and receiving no more than 5 mg of prednisone each day (refs. 23 and 24), while low disease activity was defined as having a clinical SLEDAI score of ≤2 regardless of treatment (ref. 25).

Table 2. Independent predictors of SRI-4 response in SLE patients*

	SRI-4 response at 6 months (n = 192 assessed)		SRI-4 response at 12 months (n = 193 assessed)		SRI-4 response at 24 months (n = 122 assessed)		SRI-4 response at 36 months (n = 55 assessed)	
Baseline variable	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
SLEDAI-2K score of ≥10	3.14 (2.033–4.860)	<0.001	3.48 (2.004–6.025)	<0.001	4.25 (2.018–8.940)	<0.001	14.59 (3.54–59.79)	<0.001
SLE duration of ≤2 years	1.94 (1.078–3.473)	0.027	1.59 (0.732–3.433)	0.242	3.79 (1.039–13.52)	0.044	2.01 (0.41–9.85)	0.39
SDI score of 0	–	–	1.74 (1.036–2.923)	0.036	–	–	–	–
Musculoskeletal involvement	1.48 (0.868–2.512)	0.151	1.98 (1.146–3.406)	0.014	1.43 (0.671–3.056)	0.35	1.25 (0.29–5.32)	0.75
Skin involvement	0.42 (0.250–0.689)	0.001	–	–	–	–	–	–
Current smoker status	–	–	–	–	–	–	0.19 (0.039–0.69)	0.014

* Variables assessed with multivariate analysis at 6 months included a SLEDAI-2K score of ≥10, SLE duration of ≤2 years, musculoskeletal involvement, skin involvement, kidney involvement, and age at baseline. Variables assessed at 12 months included a SLEDAI-2K score of ≥10, SLE duration of ≤2 years, musculoskeletal involvement, kidney involvement, baseline SDI score of 0, and immunosuppressant use. Variables assessed at 24 months included a SLEDAI-2K score of ≥10, SLE duration of ≤2 years, musculoskeletal involvement, and antimalarial use. Variables assessed at 36 months included a SLEDAI-2K score of ≥10, SLE duration of ≤2 years, musculoskeletal involvement, and current smoker status. Variables that were not considered statistically significant according to univariate analysis ($P < 0.2$) were not included in the multivariate analysis. SRI-4 = SLE Responder Index 4; OR = odds ratio; 95% CI = 95% confidence interval (see Table 1 for other definitions).

in terms of current organ involvement, SLEDAI-2K score, and concomitant treatment at baseline.

Activity indices. SLEDAI-2K scores, fatigue, anti-dsDNA levels, DAS28 scores, CLASI activity, 24-hour proteinuria levels, and daily prednisone intake were significantly decreased among SLE patients treated with belimumab, while serum levels of C3 and C4 were increased during treatment (Supplementary Table 2, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41253/abstract).

In patients with positive anti-dsDNA levels at baseline, data on anti-dsDNA values were available for 261 patients at 12 months and 138 patients at 24 months. Among these, 142 (54.4%) of the 261 patients were seronegative at 12 months, and 46 (33.3%) of the 138 patients were seronegative at 24 months.

Response indices. Rates and timing of therapeutic targets attained by patients are reported in Figure 1.

SRI-4. Once achieved, SRI-4 response was steadily maintained over time in most patients. Notably, 60 (38.2%) of 157 patients who were nonresponders at 6 months became responders at 12 months, suggesting that 6 months may not be a long enough period of time to evaluate the response to belimumab. Among those who were nonresponders at 6 months, 81.8% of patients with early lupus versus 44.7% of patients with long-term lupus became responders at 24 months ($P = 0.022$).

Independent predictors of SRI-4 response are listed in Table 2. Using multivariate logistic regression analysis, an SLEDAI-2K score of ≥10 at baseline predicted SRI-4 response at 6, 12, 24, and 36 months ($P < 0.001$ for all); an SLE duration of ≤2 years predicted SRI-4 response at 6 and 24 months ($P = 0.027$ and $P = 0.044$, respectively); and an SDI score of 0 predicted an SRI-4 response at 12 months ($P = 0.036$). Musculoskeletal involvement predicted an SRI-4 response at 12 months ($P = 0.014$), while skin involvement was negatively associated with predicting an SRI-4 response at 6 months ($P = 0.001$).

Interestingly, current smoker status emerged as being negatively associated with predicting late response ($P = 0.014$).

Remission and low disease activity. Proportions of patients achieving remission and low disease activity at 6, 12, 24, 36, and 48 months during the follow-up period are shown in Figure 1. Notably, ≥90% of patients who achieved low disease activity at any time point received ≤7.5 mg of prednisone each day after 6 months of belimumab therapy.

Of note, a substantial proportion of patients had low disease activity for ≥50% of the follow-up time (66.1% of patients) or disease remission for ≥25% of the follow-up time (44.3% of patients) (Supplementary Figure 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41253/abstract). One-third of patients (49 of 158) who achieved remission for ≥25% of the follow-up period completely stopped glucocorticoid treatment, achieving remission without glucocorticoid therapy.

Independent predictors of remission and low disease activity are listed in Table 3. By multivariate logistic regression analysis, a SLEDAI-2K score of <10 at baseline and an SDI score of 0 predicted achievement of remission for ≥25% of follow-up time ($P = 0.047$ and $P < 0.001$, respectively) and low disease activity for ≥50% of follow-up time ($P < 0.001$ and $P = 0.024$, respectively).

A high number of flares prior to belimumab initiation decreased the likelihood of achieving remission for ≥25% of follow-up time ($P = 0.005$) and also had a negative trend toward the achievement of low disease activity for ≥50% of follow-up ($P = 0.086$). Except for renal involvement at baseline that was negatively associated with predicting remission ($P = 0.034$), no other organ involvement influenced the achievement of remission or low disease activity.

A second multivariate analysis was performed to evaluate the effect of different levels of baseline damage on remission, with the results expressed as odds ratios (ORs) and 95% confidence intervals (95% CIs). We found that the OR for the likelihood of remission decreased as the amount of damage increased—using an SDI score of ≥3 as a reference, an SDI score of 0 had an OR of 12.641 (95% CI 3.739–42.557) ($P < 0.001$), an SDI score of 1 had an OR of 5.720 (95% CI 1.662–19.678) ($P = 0.006$), and an SDI score of 2 had an OR of 3.976 (95% CI 1.023–15.460) ($P = 0.046$))—meaning that the lower the baseline damage, the more probable it would be to achieve remission for ≥25% of the follow-up period.

Disease flares. Among 466 patients, 164 experienced ≥1 flare (35.2%) after belimumab initiation. Overall, 260 flares were observed: 92 (35.4%) with musculoskeletal involvement, 84 (32.3%) with mucocutaneous involvement, 27 (10.4%) with hematologic involvement, 23 (8.9%) with renal involvement, 18 (6.9%) with serosal involvement, 9 (3.5%) with constitutional involvement, and 7 (2.7%) with neurologic involvement. Seven severe flares were observed in 7 patients: 3 characterized by hematologic involvement (hemolytic anemia, severe lymphopenia, and severe neutropenia), 2 characterized by renal involvement (nephrotic flare and nephritic flare with acute kidney injury), 1 characterized by neurologic involvement (polyradiculopathy), 1 characterized by inflammatory myopathy, and 1 characterized by severe flare of skin vasculitis.

We observed a significant decrease in the incidences of flares at 12, 24, 36, and 48 months during belimumab treatment compared to the corresponding period before belimumab initiation ($P < 0.001$) (Figure 2).

Damage accrual. Data on damage accrual after belimumab initiation were available for 309 patients. Over 7,983 person-months of follow-up, we recorded 36 new damage events in 29 patients (9.4%), corresponding to 0.54 events per 10 person-years.

Table 3. Independent predictors of remission and low disease activity*

Baseline variable	Remission for ≥25% of follow-up (n = 368 assessed)		Low disease activity for ≥50% of follow-up (n = 359 assessed)	
	OR (95% CI)	*P*	OR (95% CI)	*P*
SLEDAI-2K score of <10	1.852 (1.009–3.398)	0.047	3.169 (1.710–5.874)	<0.001
SDI score of 0	3.158 (1.738–5.740)	<0.001	1.971 (1.092–3.560)	0.024
Number of flares in the 3 years preceding belimumab initiation	0.776 (0.649–0.928)	0.005	0.884 (0.768–1.018)	0.086
Prednisone intake of ≤7.5 mg each day	2.170 (1.220–3.857)	0.008	–	–
Kidney involvement	0.456 (0.221–0.941)	0.034	0.847 (0.410–1.751)	0.654

* Variables included in the multivariate analysis for remission were a baseline SDI score of 0, a SLEDAI-2K score of <10, kidney involvement, skin involvement, number of previous organs affected by SLE, prednisone intake of ≤7.5 mg per day, and number of flares in the 3 years preceding belimumab initiation. Variables included in multivariate analysis for low disease activity were a baseline SDI score of 0, SLEDAI-2K score of <10, kidney involvement, musculoskeletal involvement, skin involvement, and number of flares in the 3 years preceding belimumab initiation. Variables that were not considered statistically significant according to univariate analysis ($P < 0.2$) were not included in the multivariate analysis. OR = odds ratio; 95% CI = 95% confidence interval (see Table 1 for other definitions).

Using univariate analysis, concomitant antimalarial treatment was associated with lower damage accrual at the end of follow-up ($P = 0.037$), while age, disease duration of ≥10 years, and a baseline SDI score of >0 were associated with higher risk of damage accrual ($P = 0.023$, $P = 0.013$, and $P = 0.002$, respectively).

Notably, patients with an SDI score of 0 at baseline showed no significant damage increase at 1, 2, and 3 years after belimumab initiation (mean ± SD SDI score 0.02 ± 0.14 at 1 year, 0.05 ± 0.28 at 2 years, and 0.10 ± 0.38 at 3 years; $P = 0.083$, $P = 0.182$, and $P = 0.103$ versus baseline). Patients who were in remission for ≥25% of follow-up or had low disease activity for ≥50% of follow-up had lower rates of damage accrual than those who did not achieve either outcome (damage rate of 6.3% among patients in remission for ≥25% of follow-up versus 12.8% among those without remission [$P = 0.046$]; damage rate of 6.7% among patients with low disease activity for ≥50% of follow-up versus 17.0% among those without low disease activity [$P = 0.007$]).

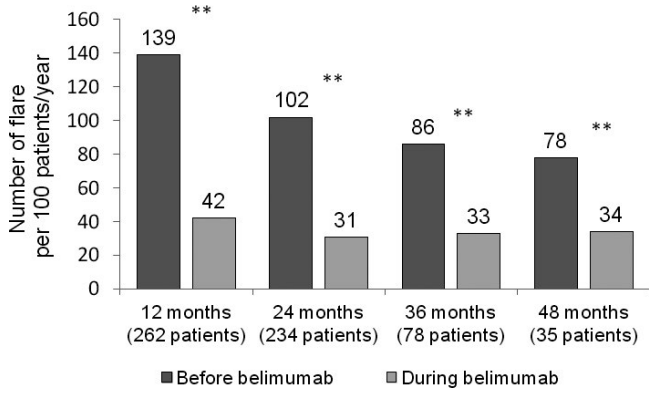


Figure 2. Incidence rate of flares occurring at 12, 24, 36, and 48 months after belimumab initiation compared to the corresponding period before belimumab initiation. ** = $P < 0.001$ by paired sample *t*-test.

Accordingly, in the multivariate model, achievement of low disease activity for ≥50% of the follow-up period was found to be protective against damage (OR 0.442 [95% CI 0.199–0.983]) ($P = 0.045$), while increased SDI score at baseline was confirmed as an independent predictor of further damage accrual (OR 3.22 [95% CI 1.25–8.33]) ($P = 0.016$). No other variables were found to be statistically significant in the multivariate model.

Safety and drug discontinuation. Among 10,104 IV belimumab infusions, no deaths or severe infusion reactions were observed. Among 866 AEs in 271 patients, 67.2% were infectious reactions, 19.7% noninfectious reactions, 12.1% hypersensitivity reactions, and 0.9% infusion reactions (Supplementary Table 3, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41253/abstract). Patients who received mycophenolate mofetil showed a higher rate of AEs (54.1% versus 42.6%; $P = 0.016$) and the number of infective AEs was also higher in patients who received mycophenolate mofetil compared to patients who received other immunosuppressants (mean ± SD 1.58 ± 2.41 versus 1.11 ± 1.89; $P = 0.026$). A higher rate of noninfectious AEs was observed in patients with other concomitant rheumatic diseases ($P = 0.046$) or hypertension ($P = 0.040$).

Drug discontinuation was observed in 165 patients after a median follow-up time of 12 months (range 1–54 months) (Figure 3) due to AEs (35.2%), inadequate response (34.5%), loss to follow-up (18.8%), pregnancy (6.7%), and remission (4.8%). Inadequate response was observed in 57 patients and was attributable to renal involvement in 19 patients, musculoskeletal involvement in 14 patients, cutaneous involvement in 13 patients, hematologic involvement in 4 patients, serosal involvement in 3 patients, neurologic involvement in 2 patients, and constitutional involvement in 2 patients.

When SRI-4 response at 6 months was used to distinguish primary inefficacy (determined as no response at 6 months) from

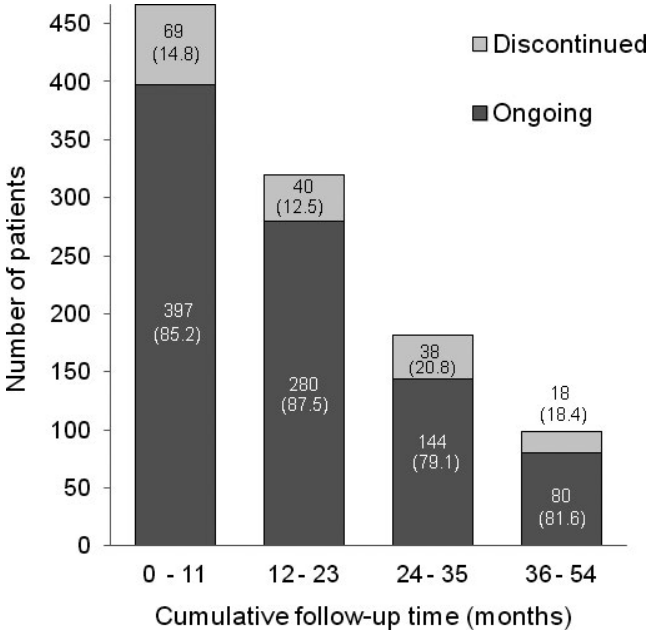


Figure 3. Number (%) of patients who discontinued belimumab treatment compared to patients who continued belimumab treatment at different follow-up time points in the Belimumab in Real Life Setting Study.

secondary inefficacy (determined as response at 6 months and subsequent worsening), 24 (42.1%) of 57 patients who were classified as inadequate responders discontinued belimumab due to secondary inefficacy. Interestingly, patients with "rhupus" (n = 12), a condition defined as a rheumatoid-like, erosive arthritis in patients who were seropositive for anticitrullinated peptide antibodies and/or rheumatoid factor (26), had a higher rate of discontinuation due to inefficacy compared to other patients with musculoskeletal involvement (36.3% versus 11.1%) (P = 0.030) as result of the failure to achieve remission of articular disease (DAS28 score of <2.6) at 6, 12, and 18 months (P < 0.01 for trend).

Multivariate analysis indicated that a higher rate of flares before belimumab initiation was found to have a negative association with predicted discontinuation due to inefficacy (OR 0.138 [95% CI 0.31–0.606]) (P = 0.009).

DISCUSSION

In our study, we evaluated belimumab effectiveness, safety, and rate of achievement of novel therapeutic targets (i.e., remission and low disease activity) in the largest European nationwide cohort of SLE patients followed-up in a prospective manner in a real-life setting. Notably, we showed a considerable rate of attainment of remission and low disease activity as well as a consistent proportion of follow-up time spent in either status, which was shown to be protective against damage accrual (11,12,23,24,27). Moreover, an overall stable rate of SRI-4 response was also observed.

Patients with higher disease activity at baseline (SLEDAI-2K score of ≥10) were more likely to achieve SRI-4 response at different time points but were less likely to achieve a cumulative remission for ≥25% of the follow-up period or low disease activity for ≥50% of the follow-up period. This may be explained by the fact that an initial drop of 4 points on the SLEDAI-2K may be more promptly achieved in patients with higher baseline disease activity, thereby leading to a faster SRI-4 response, while also requiring a longer time for a high clinical SLEDAI score to flatten to ≤2 or 0 (i.e., low disease activity or remission). Additionally, higher baseline disease activity could trigger a slower tapering of glucocorticoids, thereby also impacting the fulfillment of remission/low disease activity definitions, which include a glucocorticoid intake threshold.

Importantly, the use of belimumab in patients with early SLE demonstrated a higher chance of SRI-4 response compared to patients who had a longer disease duration at baseline. The difference between SRI-4 response rates was statistically significant at 6 and 24 months, whereas statistically significant differences in the SRI-4 response rate were not seen at 12 months despite the fact that clinically relevant effects were observed (69.9% in patients with early SLE versus 59.9% response in patients with long-term SLE). This suggests that patients with early SLE treated with belimumab have an earlier response to treatment and continue to respond better in the long term, while patients with long-standing disease at baseline either have a delayed response (around 1 year, when the SRI-4 response difference between the groups is not significant) or, in the case of no response at 1 year, they are significantly less likely to respond to belimumab therapy in the long term.

Interestingly, the greatest achievement of remission, low disease activity, and SRI-4 response rates was seen within the first 12 months of treatment (Figure 1). Thus, compared to the 6-month time point, evaluation of these outcomes within the first 12 months of treatment initiation may be considered a more suitable time window.

Absence of baseline damage had a positive association with prediction of an SRI-4 response at 12 months and achievement of remission/low disease activity, which is consistent with recent observations (28,29). Moreover, we showed that the lower the damage at baseline, the probability of achieving remission at 12 months was higher. In fact, while absence of damage was the strongest predictor of remission, the chance of achieving remission decreased as SDI score increased, suggesting that, for optimal outcomes, patients should be treated before damage is established, although the possibility of belimumab administration in patients who have already experienced some damage should not be precluded, as suggested by previous observations on pooled data from randomized controlled trials (30).

Absence of baseline damage not only supports the achievement of remission/low disease activity, but also suggests that attainment of both outcomes may be protective against damage, as patients who spent ≥50% of the follow-up period with low disease activity or ≥25% of follow-up in remission did not accrue

damage throughout the follow-up both in our cohort and in a large cohort of patients from the Hopkins Lupus Cohort (27). Moreover, damage accrual with belimumab treatment did not significantly increase in patients with a baseline SDI score of 0 at 12, 24, and 36 months. This is a relevant finding, as damage was shown to accumulate early (<1 year) and to show further progression during the disease course even among patients without preexisting damage (12,31), further supporting the need for treatment in the early stages of disease.

It should also be noted that use of belimumab versus standard of care demonstrated decreased damage accrual in Study of Belimumab in Subjects with SLE (BLISS) trials. In the present study, no control group was available as our investigations took place in real-life settings. Interestingly, however, the mean increase in SDI score in our cohort was 0.54 per 10 persons per year (i.e., about 0.27 per 5 persons per year, which is close to the mean increase in SDI score of 0.34 shown per 5 persons per year in the BLISS trials, and as such, was lower than the mean increase in SDI score recently reported in a Toronto cohort of patients who received only a standard of care regimen (0.78 per 5 persons per year) (32). Despite the fact that single damage items are not available for comparison before and after belimumab initiation in this cohort, glucocorticoid-related damage (as defined by Gladman and colleagues in their study [33]) appears to slow down following belimumab initiation (15 of 36 events overall in our cohort compared to 28 of 33 events with standard of care treatment alone [33]), which may be due to the glucocorticoid-sparing potential of belimumab (Supplementary Table 2, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41253/abstract).

Organ manifestations that respond better to belimumab include arthritis and skin rashes, especially in the acute stage of disease (3,34). Conversely, patients with "rhupus" syndrome were less likely to respond to belimumab, which led to a higher rate of discontinuation due to inefficacy. The refractory response to belimumab of a rheumatoid-like arthritis compared to a classic lupus arthritis was already demonstrated in a previous study (4) and may be related to a more aggressive phenotype likely sustained by different mechanisms taking place in the joint, against which the immunomodulatory effects of belimumab appear to be less effective.

Overall, DAS28 scores and CLASI activity was significantly improved in our cohort. However, only musculoskeletal involvement emerged as a predictor of SRI-4 response at 12 months, whereas baseline skin involvement reduced the response rate at 6 months, which is in line with data from other studies that showed skin involvement as a predictor of delayed response (35). Conversely, skin involvement was positively associated with low disease activity, suggesting that skin manifestations require a longer time to resolve and occur during a window of time during which the CLASI and SLEDAI-2k indices may fail to capture clinically relevant changes occurring before, or instead of, a complete resolution.

Remarkably, among patients who discontinued belimumab due to inadequate response, 42.1% experienced a loss of response, suggesting that more information is needed to better stratify patients at treatment initiation. In this regard, current smoker status emerged as a negative predictor of long-term response in our cohort as well as in other cohorts (29), as it likely leads to a loss of treatment efficacy and therefore should be strongly discouraged.

We observed a significant decrease in rate of flares after belimumab initiation compared to the period before belimumab treatment, consistent with randomized controlled trial findings and observations from real-life cohorts (2–4), suggesting that belimumab may restrain the effects of a relapsing–remitting disease phenotype, thereby exerting a further protective effect against organ damage. Reasons for flare reduction upon belimumab initiation need to be investigated in detail; thus far, it may be argued that stable control of disease activity with belimumab treatment, together with a tight follow-up window, may help to capture even minor signs of disease reactivation.

Our study has both strengths and limitations. Among the latter, the main limitation is the lack of a control group, which prevents further inference. However, where possible, published observations on large and known cohorts were used as comparison. It should be also mentioned that patients for whom data were not available at any given time point were excluded from the analysis of response at that particular time point; this applies either to responders, nonresponders, and patients who discontinued due to loss of efficacy before the analyzed time point (n = 24 throughout the study). This limitation is, in our view, connected to the retrospective nature of the study which poses some objective restrictions to the amount of data that can be inferred. As we aimed at being adherent to truly available data, we included in our analysis of response at different time points only patients who had complete records and who actually reached the given time point.

The greatest strength of the present study is the systematic collection of homogeneous measurements among the largest nationwide cohort of non-selected SLE patients in Europe. Thus, the findings from our cohort could offer insights into the management of patients with SLE in a real-life setting.

In summary, our study provided novel evidence showing remarkable achievement of remission or low disease activity during belimumab treatment initiated in early disease, both of which were also likely to persist over time, and also confirmed previous results on the real-life use of belimumab in terms of the decrease in global- and organ-specific disease activity, daily dose of prednisone, rate of flares, and damage progression. At the present time, belimumab is frequently used as the last option in the treatment of SLE. Based on our data, we suggest that earlier use of belimumab in patients with active SLE may maximize its efficacy since it improves patient prognosis with regard to better response, achievement of remission/low disease activity, and hindrance of damage accrual.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Doria had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Gatto, Saccon, Zen, Doria.

Acquisition of data. Gatto, Saccon, Zen, Regola, Fredi, Andreoli, Tincani, Urban, Emmi, Ceccarelli, Conti, Bortoluzzi, Govoni, Tani, Mosca, Ubiali, Gerosa, Bozzolo, Canti, Cardinaletti, Gabrielli, Tanti, Gremese, De Marchi, De Vita, Fasano, Ciccia, Pazzola, Salvarani, Negrini, Puppo, Di Matteo, De Angelis, Orsolini, Rossini, Faggioli, Laria, Piga, Mathieu, Scarpato, Rossi, de Paulis, Brunetta, Ceribelli, Selmi, Prete, Racanelli, Vacca, Bartoloni, Gerli, Larosa, Iaccarino, Doria.

Analysis and interpretation of data. Gatto, Saccon, Zen, Iaccarino, Doria.

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