DR. LAURA ANDREOLI (Orcid ID : 0000-0002-9107-3218)
DR. ALESSANDRA BORTOLUZZI (Orcid ID : 0000-0003-2416-8134)
DR. ELISA GREMESE (Orcid ID : 0000-0002-2248-1058)
PROF. FRANCESCO CICCIA (Orcid ID : 0000-0002-9352-1264)
DR. ANDREA DI MATTEO (Orcid ID : 0000-0003-0867-7051)
DR. MATTEO PIGA (Orcid ID : 0000-0002-1126-8315)
PROF. ANDREA DORIA (Orcid ID : 0000-0003-0548-4983)

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EARLY DISEASE AND LOW BASELINE DAMAGE PREDICT RESPONSE TO BELIMUMAB IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

Results of Belimumab in Real Life Setting Study (BeRLiSS)

Running title: predictors of belimumab response in clinical practice

Mariele Gatto[1]*, MD, PhD, Francesca Saccon[1]*,MD, Margherita Zen[1], MD, PhD, Francesca Regola[2], MD, Micaela Fredi[2], MD, Laura Andreoli[2], MD, PhD, Angela Tincani[2], MD, Maria Letizia Urban[3], MD, Giacomo Emmi[3], MD, PhD, Fulvia Ceccarelli[4], MD, Fabrizio Conti[4], MD, Alessandra Bortoluzzi[5], MD, PhD, Marcello Govoni[5], MD, Chiara Tani[6], MD, PhD, Marta Mosca[6], MD, PhD, Tania Ubiali[7], MD, Maria Gerosa[7], MD, Enrica Bozzolo[8], MD, Valentina Canti[8], MD, Paolo Cardinaletti[9], MD, Armando Gabrielli[9], MD, Giacomo Tanti[10], MD, Elisa Gremese[10,11], MD, Ginevra De Marchi[12], MD, Salvatore De Vita[12], MD, Serena Fasano[13], MD, PhD, Francesco Ciccia[13], MD, PhD, Giulia Pazzola[14], MD, Carlo Salvarani[14,15], MD, Simone Negrini[16], MD, PhD, Francesco Puppo[16], MD, Andrea Di Matteo[17], MD, Rossella De Angelis[17], MD, PhD, Giovanni Orsolini[18], MD, Maurizio Rossini[18], MD, Paola Faggioli[19], MD, Antonella Laria[19], MD, Matteo Piga[20], MD, Alessandro Mathieu[20], MD, Salvatore Scarpato[21], MD, Francesca W. Rossi[22], MD, PhD, Amato de Paulis[22], MD, Enrico Brunetta[23,24], MD, Angela Ceribelli[25], MD, PhD, Carlo Selmi[24,25], MD, PhD, Marcella Prete[26], MD, Vito Racanelli[26], MD, Angelo Vacca[26], Elena

Bartoloni[27], MD, Roberto Gerli[27], MD, Maddalena Larosa[1], MD, Luca Iaccarino[1], MD, PhD, Andrea Doria[1],MD

*The authors contributed equally

[1]Rheumatology Unit, Department of Medicine-DIMED, University of Padova, Padova, Italy
[2]ASST Spedali Civili di Brescia, Department of clinical and experimental sciences, Rheumatology and Clinical Immunology, Brescia, Italy
[3]University of Florence, Department of Experimental and Clinical Medicine, Firenze, Toscana, IT
[4]Dipartimento Universitario di Scienze Cliniche, Internistiche, Anestesiologiche e Cardiovascolari (SCIAC) 'Sapienza' University, Rome, Italy
[5] Section of Rheumatology Department of Medical Sciences University of Ferrara and Azienda Ospedaliera-Universitaria di Ferrara, Cona (FE), Italy
[6]Rheumatology, University of Pisa, Pisa, Italy
[7]ASST Gaetano Pini, Department of Clinical Sciences and Community Health, Clinical Rheumatology Unit Milano, Lombardia, IT
[8]Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS Ospedale San Raffaele, Milan, Italy
[9]Università Politecnica delle Marche, Dipartimento di Scienze Cliniche e Molecolari, Ancona, Italy
[10] Division of Rheumatology, Università Cattolica del Sacro Cuore Sede di Roma, Rome, Italy
[11]Division of Rheumatology, Fondazione Policlinico Universitario A. Gemelli-IRCCS, Rome, Italy
[12]University of Udine, Medical Area, Rheumatology Unit, Udine, Italy
[13]Università degli Studi della Campania Luigi Vanvitelli, Rheumatology Unit, Department of Precision Medicine Napoli, Italy
[14]Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy
[15]Università degli Studi di Modena e Reggio Emilia, Reggio Emilia, Italy
[16]Department of Internal Medicine, Internal Medicine Unit, Università degli Studi di Genova, Genoa, Italy

[17]Università Politecnica delle Marche, Deparment of Clinical and Experimental Sciences, Rheumatology Clinic, Ancona, Italy
[18]University of di Verona, Unit of Rheumatology, Verona, Italy
[19] Rheumatology and Internal Medicine Unit ASST Ovest Milanese Legnano - Magenta (Milan) Italy
[20]Rheumatology Unit, AOU University Clinic, University of Cagliari, Cagliari, Italy
[21]Rheumatology, Ospedale M. Scarlato, Scafati, Salerno, Italy
[22]Dipartimento di Scienze Mediche Traslazionali e Centro di Ricerca Immunologia Base e Clinica (CISI), University of Napoli Federico II, Napoli, Italy
[23] Istituto clinico Humanitas, Milan, Italy
[24] Dipartimento BIOMETRA, Università degli Studi di Milano, Milan, Italy
[25] Reumatologia ed Immunologia Clinica, IRCCS Istituto Clinico Humanitas, Milan, Italy
[26]Department of Biomedical Sciences and Human Oncology, Unit of Internal Medicine, University of Bari, Bari, Italy
[27]Rheumatology Unit, Department of Medicine, University of Perugia, Perugia, Italy

CORRESPONDING AUTHOR:
Prof. Andrea Doria
Division of Rheumatology
University of Padova
Via Giustiniani, 2
35128 PADOVA, Italy
Telephone: +39-049-8212190
Fax +39-049-8212191
adoria@unipd.it

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ABSTRACT

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

Methods. We retrospectively analysed data of a multicentre cohort of SLE patients receiving intravenous belimumab. Proportion of patients achieving remission, LDA and SLE Responder Index-4 (SRI-4) were evaluated. SLICC damage index (SDI) was calculated yearly. Predictors of outcomes were investigated by multivariate logistic regression.

Results. We included 466 active SLE patients from 24 Italian centres: median (range) follow-up 18 (1-60) months. SRI-4 was achieved by 49.2%, 61.3%, 69.7%, 69.6% and 66.7% patients at 6, 12, 24, 36 and 48 months. Baseline predictors of response at 6 months were SLEDAI-2K≥10 (OR 3.14, 95%CI 2.033-4.860) and disease duration≤2 years (OR 1.94, 95%CI 1.078-3.473); at 12 months SLEDAI-2K≥10 (OR 3.48, 95%CI 2.004-6.025), SDI=0 (OR 1.74, 95%CI 1.036-2.923); at 24 months SLEDAI-2K ⩾ 10 (OR 4.25, 95%CI 2.018-8.940), disease duration ≤2 years (OR 3.79, 95%CI 1.039-13.52); at 36 months SLEDAI-2K≥10 (OR 14.59, 95%CI 3.54-59.79) and baseline smoking (OR 0.19, 95%CI 0.039-0.69). Patients spending ⩾ 25% follow-up in remission (42.9%) or ⩾ 50% in LDA (66.0%) accrued significantly less damage (p=0.046 and p=0.007). Baseline SDI=0 independently predicted LDA ≥50% and remission ≥25%; the lower the baseline damage, the higher the probability of remission ⩾ 25%. Number of previous flares negatively predicted belimumab discontinuation due to inefficacy (p= 0.009)

Conclusions. The early use of belimumab in patients with active SLE and low baseline damage predicts favourable outcomes in a real-life setting.

KEYWORDS: SLE; belimumab; remission; LDA; damage.

INTRODUCTION

Since its approval for the treatment of systemic lupus erythematosus (SLE) in 2011, belimumab has progressively entered the drug armamentarium in clinical practice, despite some variable indications across countries (1).

Since then, a long way elapsed throughout real-life settings showing overall consistent results in terms of efficacy and safety (2-6). Better clinical responses were shown in patients displaying higher disease activity, while a long-standing disease, chronic manifestations and former use of immunosuppressants negatively impacted the response (2-4). Importantly, belimumab was shown to decrease disease activity, glucocorticoid (GC) intake and flare rates, thereby hindering damage progression (2-4).

Belimumab has been included in the 2019 updated European League Against Rheumatism (EULAR)-endorsed recommendations on SLE management as an approved biological drug to be used in patients refractory to standard of care (SoC), which means GC and hydroxychloroquine with or without a previously failed immunosuppressant (7).

Remission and low disease activity (LDA) 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 fall among the ultimate goals of any therapeutic strategy.

In our former study, we evaluated predictors of response to belimumab in a multicenter cohort of SLE patients (3), which was empowered in the present study becoming the largest European nationwide cohort aimed at investigating belimumab effects on disease activity, damage progression, remission and LDA.

PATIENTS AND METHODS

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

Inclusion criteria

Inclusion criteria were all the following: 1) fulfilment of the 1982 American College of Rheumatology (ACR) revised criteria or SLICC classification criteria for SLE (13,14); 2) active disease defined as clinical (c)SLEDAI>0, refractory to SoC (7); 3) IV belimumab (10 mg/Kg on day 1, 14, 28, and then every 28 days) as add-on therapy; 4) monthly follow-up due to infusion

schedule. SoC was defined according to the 2019 EULAR recommendations for the management of SLE (7) as GC and antimalarials (if not absolutely contraindicated), with or without immunosuppressive agents. Patients were considered to have early lupus in case of disease duration at baseline $\leqslant$2 years. We included SLE patients treated between January the 1st, 2013 and March the 31st, 2019. Inclusion and follow-up of patients in this study did not interfere with clinical practice.

Data collection and management

Patients were prospectively followed 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 six months included SLEDAI-2K, fatigue (Visual Analogue Scale 0-10), daily prednisone intake, complete blood count, 24-h proteinuria, anti-dsDNA antibodies, C3, C4 and concomitant medications (3). All compiled data were systematically and regularly evaluated. In case of inconsistencies or missing information, centres were required to amend the data. Patients' data not fulfilling inclusion and qualitative control criteria were excluded.

The study was approved by the University of Padova Ethics Committee (3806/AO/16) and carried out according to Helsinki Declaration. Informed consent regarding personal data treatment was obtained from patients.

Outcome measures

All centres were requested to provide the SLE responder index (SRI)-4 response (17) for each patient at 6, 12, 24, 36 and 48 months.

Organ-specific activity measures included Disease Activity Score (DAS)-28 in patients with musculoskeletal involvement and CLASI (Cutaneous LE Disease Area and Severity Index) (18) in patients with skin involvement (3).

Damage was assessed at baseline and annually by Systemic Lupus International Collaborating Clinics (SLICC)-Damage Index (SDI) and disease flares by SELENA-SLEDAI flare index (SFI). All centres were requested to provide flare number up to five years before belimumab initiation, when available.

Remission was defined as cSLEDAI=0 and prednisone $\leq$5 mg/day with immunosuppressants and antimalarials at a stable dose according to Zen et al. (19,20), while LDA was defined as

cSLEDAI≤2 regardless of treatment according to Tselios et al. (21) Moreover, we evaluated the cumulative time spent either in remission or LDA after belimumab initiation: patients were classified in 4 subgroups according to the proportion of follow-up time spent in remission or LDA (0-24%, 25-49%, 50-74% and 75-100%).

Safety and discontinuation

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

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

Statistical analysis

Data were expressed as mean±standard deviation (SD), except for CLASI and anti-dsDNA, which were expressed as median (interquartile range (IQR) 25°-75°) due to non-parametric distribution. Continuous data with a parametric distribution were compared with t-test, t-test for paired data and one-way analysis of variance (ANOVA) with Bonferroni's post hoc analysis. CLASI and anti-dsDNA were analysed by the Wilcoxon's rank sum test, Wilcoxon's test for paired data and ANOVA for ranks (Friedman's test). We investigated predictors of SRI-4, remission, LDA, damage and discontinuation for inefficacy (tested variables are reported in **Supplementary Table 1**). Backward stepwise multiple logistic regression analyses were performed, including variables with a $p<0.2$ at univariate analysis. SPSS software (version 25.0, Chicago, IL) was used for statistics; statistical significance was considered for $p<0.05$.

RESULTS

Baseline patient characteristics

Twenty-four Italian centres joined the BeRLiSS project, enrolling overall 466 SLE patients, with a median follow-up of 18 months, range 1-60. Demographic, clinical and serological features and concomitant treatments are summarized in **Table 1.**

Manifestations requiring belimumab as add-on therapy were musculoskeletal in 200 patients (42.9%), mucocutaneous in 110 (23.6%), glomerulonephritis in 56 (12.0%), haematological in 50 (10.7%), constitutional in 27 (5.8%), serosal in 23 (4.9%). Renal involvement at the time of belimumab initiation defined patients with proteinuria persistently over 0.5g/day following induction treatment for lupus nephritis or in whom a high prednisone threshold was required to

control proteinuria (≥7.5 mg/day). Belimumab was never used as induction treatment for lupus glomerulonephritis.

Seventy-seven patients (16.5%) had a baseline SLE duration ≤2 years. As expected, in comparison with patients with longer disease duration, early patients showed younger age at baseline (38.18±10.78 vs. 41.96±11.2, p=0.007), lower number of previous SLE organ involvement (2.86±1.28 vs. 3.2±1.18, p=0.023), and lower baseline SDI (0.8±1.1 vs. 1.2±1.6, p=0.044). They displayed also lower prevalence of anti-phospholipid antibody syndrome (7.9% vs. 17.2%, p=0.026) and higher prevalence of positive anti-Sm antibody (42.1% vs. 23.8%, p=0.001). No differences were observed in terms of current organ involvement, SLEDAI-2K and concomitant treatment at baseline.

Activity indices

SLEDAI-2K, fatigue, anti-dsDNA, DAS28, CLASI activity, 24h proteinuria and prednisone daily dosage significantly decreased, while C3 and C4 serum level increased during treatment (**Supplementary Table 2**).

Concerning patients with positive anti-dsDNA at baseline, data on anti-dsDNA value were available in 261 patients at 12 months and in 138 at 24 months. Among those, 142/261 (54.4%) became seronegative at 12 months and 46/138 (33.3%) at 24 months.

Response indices

Rates and timing of achievement of therapeutic targets are reported in **Figure 1**.

SRI-4

Once achieved, SRI-4 response was steadily maintained over time in most patients. Notably, 60/157 (38.2%) non-responders at 6 months became responders at 12 months, suggesting that 6 months could be a too short time to evaluate the response to belimumab. Among non-responders at 6 months, 81.8% of early vs. 44.7% of non-early lupus (p=0.022) became responders at 24 months. Independent predictors of SRI-4 response are listed in **Table 2.** By multivariate logistic regression analysis, baseline SLEDAI-2K≥10 predicted SRI-4 response at 6,12, 24 and 36 months (p<0.001 for all); SLE duration ≤2 years predicted SRI-4 at 6 and 24 months (p=0.027 and p=0.044, respectively), and SDI=0 at 12 months (p=0.036). Musculoskeletal involvement predicted SRI-4 at 12 months (p=0.014), while skin involvement was a negative predictor of SRI-4 at 6 months (p=0.001).

Interestingly, smoking emerged as a negative independent predictor of late response (p=0.014).

Remission and LDA

Proportions of patients achieving remission and LDA at 6, 12, 24, 36 and 48 months of follow-up are shown in Figure 1. Notably, ≥90% of patients achieving LDA at any time point were on prednisone≤7.5 mg/day after 6 months on belimumab.

A remarkable proportion of patients spent ≥50% follow-up time in LDA (66.1%) or ≥25% in remission (44.3%) (Supplementary Figure 1**).** One third (49/158) of patients who achieved remission ≥25% completely stopped GC treatment, achieving remission off-GC.

Independent predictors of remission and LDA are listed in **Table 3.**

By multivariate logistic regression analysis, baseline SLEDAI-2K<10 and SDI=0 predicted remission ≥25% (p=0.047 and p<0.001, respectively) and LDA ≥50% (p<0.001 and p=0.024, respectively).

High flare number before belimumab initiation decreased the likelihood of remission ≥25% (p=0.005), showing a negative trend also for LDA ≥50% (p=0.086).

Except for baseline renal involvement that negatively predicted remission (p=0.034), no other organ involvement influenced the achievement of remission or LDA.

We performed a second multivariate analysis to evaluate the effect of different levels of baseline damage on remission. We found that the OR decreased as the amount of damage increased (SDI=0 OR 12.641, 95% CI 3.739-42.557, p<0.001; SDI=1 OR 5.720, 95% CI 1.662-19.678, p=0.006; SDI=2 OR 3.976, 95% CI 1.023-15.460, p=0.046; SDI≥3 as reference), meaning that the lower the baseline damage, the higher the probability to achieve remission≥25% of follow-up.

Disease Flares

Among 466 patients, 164 experienced at least one flare (35.2%) after belimumab initiation. Overall 260 flares were observed: 92 (35.4%) musculoskeletal, 84 (32.3%) mucocutaneous, 27 (10.4%) haematological, 23 (8.9%) renal, 18 (6.9%) serosal, 9 (3.5%) constitutional and 7 (2.7%) neurological. Seven severe flares were observed in 7 patients: three haematological (haemolytic anaemia, severe lymphopenia and severe neutropenia), two renal (nephrotic flare and nephritic flare with acute kidney injury), one neurological (polyradiculopathy), one inflammatory myopathy and one severe skin vasculitis.

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

Damage accrual

Data on damage accrual after belimumab initiation were available in 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.

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

Notably, patients with baseline SDI=0 showed no significant damage increase at 1, 2 and 3 years after belimumab initiation (mean SDI 0.02±0.14, p=0.083; 0.05±0.28, p=0.182 and 0.10±0.38, p=0.103). Patients who experienced remission ≥25% or LDA≥50% follow-up had lower rates of damage accrual than those who did not (6.3% vs. 12.8% of patients, p=0.046, and 6.7% vs. 17.0%, p=0.007, respectively).

Accordingly, in the multivariate model achievement of at least 50% LDA during follow-up resulted protective against damage (OR 0.442, 95%CI 0.199-0.983, p=0.045) while increased baseline SDI confirmed as independent predictor of further damage accrual (OR 3.22, 95%CI 1.25-8.33, p=0.016). No other variables were found 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 AE in 271 patients, 67.2% were infectious, 19.7% non-infectious, 12.1% hypersensitivity reactions and 0.9% infusion reactions (**Supplementary Table 3)**. Patients on mycophenolate mofetil showed higher rate and number of infective AE compared with patients on other immunosuppressants (54.1% vs. 42.6%, p=0.016 and 1.58±2.41 vs. 1.11±1.89, p=0.026). A higher rate of non-infective AE was observed in patients affected with other concomitant rheumatic diseases (p=0.046) or with hypertension (p=0.040).

Drug discontinuation was observed in 165 patients after a median follow-up of 12 months (range 1-54) (**Figure 3**) due to AE (35.2%), inadequate response (34.5%), lost to follow-up (18.8%), pregnancy (6.7%), remission (4.8%). Inadequate response was observed in 57 patients and was due to renal activity in 19 patients, musculoskeletal in 14, cutaneous in 13, haematological in 4, serosal in 3, neurological in 2 and constitutional in 2.

When SRI-4 at 6 months was used to distinguish primary inefficacy (no response at 6 months) from secondary inefficacy (response at 6 months and subsequent worsening), 24/57 (42.1%) patients classified as inadequate responders discontinued due to secondary inefficacy. Interestingly, patients with rhupus (n=12), defined as a rheumatoid-like, erosive arthritis in

patients with serum positive anti-citrullinated peptides antibodies and/or rheumatoid factor (22) showed a higher discontinuation rate due to inefficacy vs. other patients with musculoskeletal involvement (36.3% vs. 11.1%, p=0.030), because of failure in achieving articular remission (DAS28<2.6) at 6, 12 and 18 months (p<0.01).

At multivariate analysis, a higher flare rate before belimumab initiation negatively predicted discontinuation due to inefficacy (OR 0.138, 95% CI 0.31-0.606, p=0.009).

DISCUSSION

In this study we evaluated belimumab effectiveness, safety and rate of achievement of novel therapeutic targets, i.e. remission and LDA in the largest European nationwide cohort of SLE patients prospectively followed in a real-life setting. Notably, we showed a considerable attainment of remission and LDA as well as a consistent proportion of follow-up time spent in either status, which was shown to protect against damage accrual (11,12,19,20,23). Moreover, an overall stable rate of SRI-4 response was observed.

Patients with higher disease activity (SLEDAI-2K≥10) at baseline were more likely to achieve SRI-4 response at different timepoints, but were less likely to achieve a cumulative remission ≥25% or LDA ≥50% of follow-up. This may be explained considering that an initial drop of 4 SLEDAI-2K points may be more promptly achieved in patients with higher baseline disease activity, thereby leading to a faster SRI-4 achievement, while requiring a longer time for a high cSLEDAI to flatten to ≤2 or to zero i.e. to reach LDA or remission. Additionally, a higher baseline disease activity could trigger a slower tapering of GC, thereby also impacting on achievement of remission/LDA definitions, which include a GC threshold.

Importantly, the use of belimumab in patients with early SLE provided a higher chance of response compared to patients who had a longer disease duration at baseline. The difference between response rates was statistically significant at 6 and 24 months, while temporarily losing statistical power at 12 months, despite maintaining a clinical relevance (69.9% vs. 59.9% response in early vs. non early patients). This suggests that early patients treated with belimumab respond earlier and continue to respond better in the long run, while patients with a long-standing disease at baseline either respond later (around 1 year, when the SRI-4 difference between the groups is not significant) or, in case of non-response at one year, they are significantly less likely to respond in the long term.

Interestingly, the greatest achievement of remission, LDA and SRI-4 rates was seen within the first 12 months of treatment (**Figure 1**), which may be considered as a more convenient window to evaluate response to belimumab in respect to 6 months.

Absence of baseline damage positively predicted SRI-4 response at 12 months and achievement of remission/LDA, in keeping with recent observations (24,25). Moreover, we showed that the lower the damage at baseline, the higher the probability to achieve remission. In fact, while absence of damage was the strongest predictor of remission, the chance of achieving remission decreased as SDI increased, suggesting that patients should be optimally treated before damage is established, yet not precluding belimumab administration in patients who already bear some damage, as suggested by previous observations on pooled RCT data (26).

Not only absence of baseline damage supports the achievement of remission/LDA, but those statuses are themselves protective against damage, as patients spending ≥50% of follow-up in LDA or ≥25% in remission did not accrue damage throughout the follow-up in our cohort as well as in a large study at the Hopkins Lupus Cohort (23). Moreover, damage accrual under belimumab treatment did not significantly increase in patients with a baseline SDI=0 at 12, 24 and 36 months. This is a relevant finding, as damage was shown to accumulate early (<1 year) and progressively during disease course even among patients without preexisting damage (12,27), further supporting the need of treatment in the early disease stage.

It should be also noted that use of belimumab versus standard of care decreased damage accrual in BLISS studies; herein no control group is available as we are dealing with real-world experience. Interestingly enough, however, mean SDI increase in our cohort was 0.54 per 10-person/year, i.e. about 0.27 per 5-person/year, which is close to the 0.34 retrieved in the BLISS trials and as such it is lower than the mean increase recently reported in the Toronto cohort under sole standard of care (0.78 per 5-person/year) (28). Despite single damage items are not available for comparison before and after belimumab initiation in this cohort, GC-related damage (as defined in (29)) appears to slow down following belimumab initiation (15 out of 36 events overall in our cohort vs. 28 out of 33 events under SoC alone (29)), which may be due to the GC-sparing potential of belimumab (**Supplementary Table 2**).

Organ manifestations responding better to belimumab include arthritis and skin rashes, especially when acute (3,30); conversely, rhupus syndrome was less likely to respond and led to a higher rate of discontinuation due to inefficacy. The refractoriness to belimumab of a rheumatoid-like arthritis compared with a classical lupus arthritis was already shown in a previous paper (4) and may be

related to a more aggressive phenotype likely sustained by different mechanisms taking place in the joint, on which the immunomodulation exerted by belimumab is less effective.

Overall, DAS-28 and CLASIa significantly improved in our cohort. However, only musculoskeletal involvement emerged as a predictor of SRI-4 response at 12 months, whereas baseline skin involvement hampered a response at 6 months, in line with data from others depicting skin as a predictor of delayed response (31). On the other hand, skin involvement was positively associated with LDA, suggesting that skin manifestations require a longer time to resolve, while paying the price of indexes (CLASIa and SLEDAI-2K) not capturing clinically relevant changes occurring before or instead of a complete resolution.

Remarkably, among patients who discontinued due to inadequate response, 42.1% underwent a loss of response, suggesting that more information is needed to better stratify patients at treatment initiation. In this regard, smoke emerged as a negative predictor of long term response in ours as well as in other cohorts (25), as it likely favors loss of efficacy and should be therefore strongly discouraged.

We observed a significant decrease of flare rate after belimumab initiation compared to the period before belimumab consistent with RCT findings and observations from real-life cohorts (2-4), suggesting that belimumab may tame 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; so far, it may be argued that a stable control of disease activity together with a tight follow-up connected to belimumab treatment may help to capture even minor signs of disease reactivation.

Our study has both strengths and limitations. Among the latter, the main is the lack of a control group, which prevents further inference; however, where possible, published observations on large and known cohorts were taken as comparison. It should be also mentioned that patients not reaching any given timepoint were excluded from the analysis of response at the timepoint where the information was lacking, and this applies either to responders, non-responders and patients who had discontinued due to loss of efficacy before the analyzed timepoint (n=24 throughout the study). This pitfall 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 timepoint analysis of response only patients with complete records and who really reached the given timepoint.

The greatest strength is in our view the systematic collection of homogenous measurements among the largest nationwide cohort of non-selected SLE patients in Europe, which could offer insights on the real management of our patients.

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

Author contribution: MG, FS, MZ drafted the paper and AD provided most revisions for important intellectual content. All authors were involved in the final revisions of the paper and all approved the final version. Prof. 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: AD, FS, MG, MZ, LI.

Acquisition of data: all authors listed.

Analysis and interpretation of data: AD, FS, MG, MZ, LI

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Figure legends

Figure 1. Rates and timing of achievement the therapeutic targets.

A: Proportion of patients achieving SRI-4, remission and LDA at different time points. Number of patients in brackets refers to patients analyzed at each timepoints. B: Number of patients not included in the analysis at a given timepoint according to the reason.

Footnotes: SRI-4: SLE responder index 4, Remission: cSLEDAI=0 and prednisone ≤5 mg/day according to Zen et al. (20); LDA: low disease activity, defined as clinical SLEDAI-2K≤2 according to Tselios et al. (21).

Figure 2. Incidence rate of flare before and after belimumab initiation.

Data refer to flares occurring only within the 12, 24, 36, 48 months before vs. after belimumab initiation. T-test for paired samples; **p<0.001.

Figure 3. Number of patients (%) undergoing discontinuation in the BeRLisSS cohort. Patients (%) at different time points according to the persistence or discontinuation of belimumab treatment.

Supplementary Figure 1. Proportion of patients spending different percentages of follow-up time in low disease activity (LDA) and remission since belimumab initiation.

Table 1. Demographic, clinical and serological features in 466 SLE patients treated with belimumab.

Total patients; n (%)	466 (100)
- Female; n (%)	427 (91.6)
- Male; n (%)	39 (8.4)
Caucasian ethnicity	450 (96.6)
Age at baseline; mean±SD; years	41.4±11.2
Antiphospholipid syndrome; n (%)	70 (15.0)
Concomitant rheumatic disease; n (%)	71 (15.2)
Age at diagnosis; mean±SD; years	29.8±11.9
Disease duration; mean±SD; years	11.6±8.8
Follow-up duration in months; median (25°-75°)*	18 (1-60)
SLEDAI-2K score; mean±SD (range)	9.3 ±3.3 (2-42)
SLEDAI-2K≥10; n (%)	183 (39.4)
CLASI activity score; median (25°-75°)*	1 (0-4)
CLASI damage score; median (25°-75°)*	0 (0-0)
DAS-28 score; mean±SD	3.8±1.3
Fatigue (VAS 0-10); mean±SD (range)	5.1±2.7
SDI score; median (25°-75°)	1 (0-2)
Clinical SLE manifestations at baseline	
- Musculoskeletal; n (%)	330 (70.8)
- Constitutional; n (%)	209 (44.8)
- Cutaneous; n (%)	211 (45.3)
- Haematological; n (%)	162 (34.8)
- Renal; n (%)	102 (21.9)
- Serosal; n (%)	46 (9.9)
- Neurological; n (%)	11 (2.4)
- More than 1 involvement; n (%)	338 (72.5)
- More than 2 involvements; n (%)	184 (39.5)
- More than 3 involvements; n (%)	68 (14.6)
- More than 4 involvements; n (%)	15 (3.2)

Serology at baseline	
- ANA >1:80; n (%)	466 (100)
- Anti-dsDNA; n (%)	378 (81.1)
- Anti-Sm; n (%)	125 (26.8)
- Anti-SSA; n (%)	203 (43.6)
- Anti-SSB; n (%)	82 (17.6)
- Anti-U1RNP; n (%)	139 (29.8)
- Antiphospholipid; n (%)	165 (35.4)
- Low C3 and/or C4; n (%)	395 (84.8)
Concomitant treatment	
- Oral glucocorticoids; n (%)	443 (95.1)
o Daily PDN intake; mean±SD; mg (min-max)	10.6±8.6 (0-60)
o Daily PDN intake > 5 mg; n (%)	293 (64.4)
o Daily PDN intake > 7.5 mg; n (%)	233 (51.2)
- Antimalarials; n (%)	327 (70.2)
- Immunosuppressants; n (%)	312 (66.9)
o Mycophenolate mofetil; n (%)	136 (29.2)
o Methotrexate; n (%)	66 (14.2)
o Azathioprine; n (%)	70 (15.0)
o Cyclosporine A; n (%)	37 (7.9)
o Others (i.e. leflunomide, tacrolimus); n (%)	3 (0.01)

*Variables reported as median (IQR) due to non-parametric distribution of data.

SLE: systemic lupus erythematosus; ANA: anti-nuclear antibody; dsDNA: double stranded DNA; PDN: prednisone equivalent; SD: standard deviation; SLEDAI-2K: SLE Disease Activity Index-2000; CLASI: Cutaneous Lupus Erythematosus Disease Area and Severity Index.

Table 2. Independent predictors of SRI-4 response

Variables	SRI-4 response at 6 months			SRI-4 response at 12 months			SRI-4 response at 24 months			SRI-4 response at 36 months		
	OR	95%CI	*p*	OR	95%CI	*p*	OR	95%CI	*p*	OR	95%CI	*p*
No.*		192			193			122			55	
Baseline SLEDAI-2K≥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 ≤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*
Baseline SDI=0	-	-	-	1.74	1.036-2.923	*0.036*	-	-	-	-	-	-
Baseline musculo-skeletal	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*
Baseline skin	0.42	0.250-0.689	*0.001*	-	-	-	-	-	-	-	-	-
Smoke at baseline	-	-	-	-	-	-	-	-	-	0.19	0.039-0.69	*0.014*

*number of patients on whom the analysis was carried out

- : not tested i.e. variables that were not associated with the outcomes at univariate analysis (p≥0.2) were not included in the multivariate analysis.

SDI, SLICC damage index; SLEDAI-2K, SLE disease activity index 2000; OR, odds ratio; CI confidence interval.

Variables included in multivariate analysis at 6 months: SLEDAI-2K≥10, SLE ≤2 years, musculoskeletal involvement, skin involvement, kidney involvement, age at baseline; at 12 months: SLEDAI-2K ≥10, SLE ≤2 years, musculoskeletal involvement, kidney involvement, baseline SDI =0, immunosuppressant use; at 24 months: SLE≤2 years, musculoskeletal involvement, SLEDAI-2K ≥10, antimalarial use; at 36 months: SLEDAI-2K ≥10, SLE ≤2 years, musculoskeletal involvement, smoke.

Table 3. Independent predictors of remission and LDA

Variables	Remission ≥25% of follow-up			LDA ≥50% of follow-up		
	OR	95%CI	*p*	OR	95%CI	*p*
No.*		368			359	
Baseline SLEDAI-2K <10	1.852	1.009-3.398	*0.047*	3.169	1.710-5.874	*<0.001*
Baseline SDI =0	3.158	1.738-5.740	*<0.001*	1.971	1.092-3.560	*0.024*
Flare number in the 3 years preceding belimumab initiation	0.776	0.649-0.928	*0.005*	0.884	0.768-1.018	*0.086*
PDN intake ≤7.5mg/day	2.170	1.220-3.857	*0.008*	-	-	-
Baseline kidney involvement	0.456	0.221-0.941	*0.034*	0.847	0.410-1.751	*0.654*

*number of patients on whom the analysis was carried out

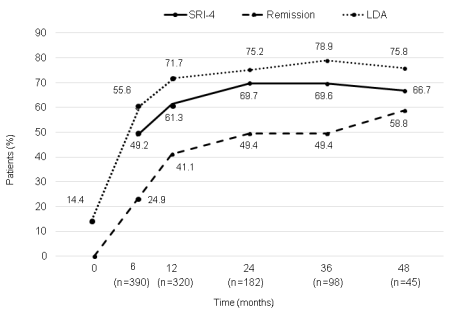
- : not tested i.e. variables that were not associated with the outcomes at univariate analysis (p≥0.2) were not included in the multivariate analysis.

SDI, SLICC damage index; LDA, low disease activity; SLEDAI-2K, SLE disease activity index 2000; PDN, prednisone; OR, odds ratio; CI confidence interval.

Variables included in multivariate analysis for Remission were: baseline SDI=0, SLEDAI-2K<10, kidney involvement, skin involvement, number of previous SLE involvements, prednisone ≤7.5mg/day, flare number in the 3 years preceding belimumab initiation.

Variables included in multivariate analysis for LDA were: baseline SDI=0, SLEDAI-2K<10, kidney involvement, musculoskeletal involvement, skin involvement, flare number in the 3 years preceding belimumab initiation.

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

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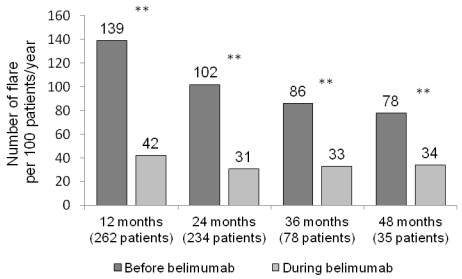

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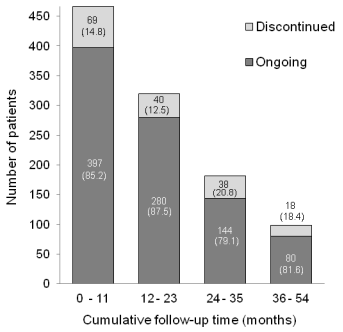

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