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Durable renal response and safety with add-on belimumab in patients with lupus nephritis in real-life setting (BeRLiSS-LN). Results from a large, nationwide, multicentric cohort

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ABSTRACT

Background: Belimumab was recently approved for treatment of lupus glomerulonephritis (LN).
Aim: To evaluate renal response and its predictors in LN patients receiving belimumab in real-life.
Patients and methods: We considered all patients fulfilling the SLEDAI-2K renal items and/or having estimated glomerular filtration rate (eGFR)≤60 ml/min/1.73 m^2, with positive anti-dsDNA and/or low C3/C4 enrolled in

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the multicentre Italian lupus cohort BeRLiSS (BElimumab in Real LIfe Setting Study), treated with monthly IV Belimumab 10 mg/kg over standard treatment. Primary efficacy renal response (PERR), defined as proteinuria ≤0.7 g/24 h, eGFR≥60 ml/min/1.73 m^2 without rescue therapy, was considered as primary outcome. Complete renal response (CRR; proteinuria <0.5 g/24 h, eGFR≥90 ml/min/1.73 m^2) was considered as secondary outcome. Prevalence and predictors of PERR were evaluated at 6, 12, 24 months by multivariate logistic regression.

Results: Among the 466 SLE patients of BeRLiSS, 91 fulfilled the inclusion criteria, 79 females, median age 41.0 (33.0–47.0) years, median follow-up 22.0 (12.0–36.0) months. Sixty-four (70.3%) achieved PERR, of whom 38.4% reached CRR. Among patients achieving PERR at 6 months, 86.7% maintained response throughout the follow-up. At multivariable analysis, hypertension (OR [95%CI]: 0.28 [0.09–0.89], p = 0.032), high baseline serum creatinine (0.97 [0.95–0.99], p = 0.01) and high baseline proteinuria (0.37, [0.19–0.74], p = 0.005) negatively predicted PERR. Positive predictors of PERR at 12 and 24 months were baseline anti-Sm positivity (OR [95%CI]: 6.2 [1.21–31.7], p = 0.029; 19.8 [2.01–186.7], p = 0.009, respectively) and having achieved PERR at 6 months (14.4 [3.28–63.6]; 11.7 [2.7–48.7], p = 0.001 for both).

Conclusions: Add-on therapy with belimumab led to durable renal response in patients with LN in a real-life setting.

1. Introduction

Lupus glomerulonephritis (LN) is one of the most serious complication of Systemic Lupus Erythematosus (SLE), occurring in up to 60% of patients during the disease course [1,2]. LN treatment encompasses multiple targets, yet still entailing a modest rate of durable renal response in the long term [3,4]. Active LN was excluded from the first belimumab randomized clinical trials (RCTs); hence, the effect of Belimumab on renal abnormalities was not investigated as a prespecified endpoint. Previous real-life studies and the pooled analysis on BLISS trials [5] showed a decrease in proteinuria levels in patients with LN treated with belimumab. In addition, a lower renal flare rate was observed in patients treated with belimumab 10 mg/kg compared with Belimumab 1 mg/kg or placebo. Recently, the phase III RCT BLISS-LN [6] on efficacy and safety of belimumab in patients with active renal involvement showed a significantly higher rate of renal response in belimumab compared to placebo arm. However, little data is available on the efficacy of belimumab in patients with LN treated in daily clinical practice and no clear prognostic factors for renal response have been pinpointed so far. Here, we performed a subanalysis on patients with renal involvement enrolled in the BeRLiSS (Belimumab in Real Life Setting Study) cohort [7]. The aim of BeRLiSS-LN is to investigate the efficacy and safety of belimumab in patients with LN and to identify predictive factors of renal response in a clinical practice setting.

2. Patients and methods

2.1. Inclusion criteria

Patients were included in the study if they fulfilled BeRLiSS criteria [7], namely active SLE with a clinical SLE Disease Activity Index (cSLEDAI) score >0 despite standard of care; positive anti-dsDNA and/or low C3/C4; adjunct therapy with intravenous belimumab (10 mg/kg on days 1, 14, and 28, and then every 28 days); at least 6 months of follow-up. In addition, they would show concomitant signs of renal activity at the time of belimumab initiation, defined as the fulfillment of SLEDAI-2K renal items [8] and/or estimated glomerular filtration rate (eGFR)≤60 ml/min/1.73 m^2.

2.2. Data collection and management

Prospectively collected data from anonymized patient records since the time of belimumab initiation were retrospectively analysed. Clinical and laboratory variables collected at baseline and every six months included SLEDAI-2K, fatigue (by Visual Analogue Scale, VAS, 0–10), physician global assessment (PGA), daily prednisone dosage, complete blood count, creatinine, eGFR, 24-h proteinuria, urinary sediment, anti-dsDNA antibodies, C3, C4, and concomitant medications). All data were systematically evaluated to find inconsistencies or missing information leading to a request of data amendment by the Centres. The enrolment into this study did not interfere with current clinical practice.

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

2.3. Study outcomes

The primary outcome was the achievement of Primary efficacy renal response (PERR) evaluated at 6, 12 and 24 months. PERR was defined as proteinuria ≤0.7 g/24 h, eGFR ≥60 ml/min/1.73 m^2 and no rescue therapy [6].

The secondary outcome was complete renal response (CRR) at the same timepoints, defined as proteinuria <0.5 g/24 h, eGFR ≥90 ml/min/1.73 m^2 and no rescue therapy [6]. We also evaluated the frequency of renal flares, defined according to SELENA-SLEDAI flare index (SFI) [9]. This means that all the episodes of increase in proteinuria >0.5 g/24 h from the previous evaluation or increase in creatinine were considered as potential LN flares.

2.4. Further evaluation of disease activity

Changes in the following variables were evaluated at 6,12, and 24 months: SLEDAI-2K, anti-dsDNA C3, C4, prednisone daily dose, PGA, as previously reported [7].

2.5. Safety and discontinuation

Discontinuation of belimumab was defined as a drug interruption for more than 6 months. Among reasons for discontinuation, inadequate response was defined according to the presence of flare and/or the persistence of increased proteinuria.

At each visit adverse events (AE) and severe AE (SAE) were recorded. AE was defined as “any untoward medical occurrence in a patient treated with a pharmaceutical product which does not necessarily have a causal relationship with this treatment”. An AE was defined SAE when hospitalization was required and/or death and/or life-threatening manifestations occurred.

2.6. Statistical analysis

For univariable analysis, non parametric tests were used as appropriate. After checking for multicollinearity, clinically significant variables were tested through multivariable logistic regression analysis with backward stepwise comparison at 6, 12 and 24 months after Belimumab initiation to define independent predictors of renal response.

Statistical significance was defined as $p < 0.05$. Analyses were performed with SPSS software version 26.

3. Results

Ninety-one patients fulfilled the inclusion criteria of this study. Demographic, clinical and serological characteristics at a baseline are shown in Table 1.

Table 1
Baseline demographic, clinical and serological features in 91 SLE patients with lupus glomerulonephritis treated with Belimumab.

Total patients; n (%)	91 (100)
-Female; n (%)	79 (86.8)
Caucasian ethnicity	87 (95.6)
Age at diagnosis; median (IQR); years	28.0 (23.0–34.0)
Age at baseline; median (IQR); years	41.0 (33.0–47.0)
Disease duration; median (IQR); years	12.0 (6.0–17.0)
Antiphospholipid syndrome; n (%)	12 (13.2)
Follow-up; median (IQR); months	22.0 (12.0–36.0)
SLEDAI-2K score; median (IQR); (range)	10.0 (8.0–14.0)
SLEDAI-2K ≥ 10; n (%)	52 (57.1)
Fatigue (VAS 0–10); median (IQR); (range)	5.0 (2.0–7.0)
Clinical SLE manifestations at baseline	
-Musculoskeletal; n (%)	49 (53.8)
-Constitutional; n (%)	42 (46.2)
-Cutaneous; n (%)	33 (36.3)
-Haematological; n (%)	34 (37.4)
-Renal; n (%)	91 (100)
-Serosal; n (%)	11 (12.1)
-Neurological; n (%)	3 (3.3)
-More than 1 involvement; n (%)	74 (81.3)
-More than 2 involvements; n (%)	55 (60.4)
-More than 3 involvements; n (%)	31 (34.1)
-More than 4 involvements; n (%)	10 (11.0)
Serology	
-ANA >1:80; n (%)	91 (100)
-Anti-dsDNA; n (%)	73 (80.2)
-Anti-Sm; n (%)	25 (27.5)
-Anti-SSA; n (%)	39 (42.9)
-Anti-SSB; n (%)	12 (13.2)
-Anti-U1RNP; n (%)	29 (31.9)
-Antiphospholipid; n (%)	32 (35.2)
-Low C3 and/or C4; n (%)	72 (79.1)
Concomitant treatment	
-Oral glucocorticoids; n (%)	87 (95.6)
o Daily PDN intake; median (IQR); mg	8.9 (5.0–16.9)
o Daily PDN intake >5 mg; n (%)	80 (87.9)
oDaily PDN intake >7.5 mg; n (%)	52 (57.1)
-Antimalarials; n (%)	60 (65.9)
-Immunosuppressants; n (%)	70 (76.9)
oMycophenolate mofetil; n (%)	47 (51.6)
oAzathioprine; n (%)	15 (16.5)
oCyclosporine A; n (%)	5 (5.5)
oMethotrexate; n (%)	4 (4.4)
Renal profile	
-Baseline 24-h proteinuria, median (IQR); grams	0.8 (0.5–1.6)
-Baseline 24-h proteinuria ≥1 g; n (%)	37 (40.7)
-Baseline 24-h proteinuria >2 g; n (%)	13 (14.3)
-Baseline creatinine, median (IQR); μmol/L (range)	72.0 (64.0–96.0)
-eGFR, median (IQR); ml/min/1.73m2 (range)	91.9 (72.1–109.9)
-eGFR<60 ml/min/1.73 m,2 n (%)	15 (16.5)
-Hypertension, n (%)	25 (28.4)
-Active Urinary sediment	46 (50.5)
-Renal biopsy	75 (82.4)
oclass I	1 (1.3)
oclass II	4 (5.3)
oclass III	14 (18.7)
oclass IV	47 (62.7)
oclass V	9 (12.0)

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; eGFR: Estimated Glomerular Filtration Rate; LN: lupus nephritis.

3.1. Achievement and maintenance of renal response

PERR was achieved by 64 (70.3%) patients during follow-up after a median time (IQR) of 6 (6–12) months. Among these patients, 35 (38.4%) also achieved CRR.

Among patients who achieved PERR at 6 months and completed the follow-up (n = 30), 26 (86.7%) maintained the response at 24 months.

Rates of achievement of renal response are reported in Table 2 and differences among patients achieving or not achieving PERR are summarized in Table S1. It is worth noting that hypertension and smoking habit were both significantly more frequent at baseline among patients who did not achieve PERR.

Overall, 9 patients (9.8%) had a renal relapse during the follow-up. Among relapsing patients, five had previously achieved PERR (5/64, 7.8%).

3.2. Clinical and serological parameters

SLEDAI-2K, PGA, 24-h proteinuria, C3, C4, prednisone daily dosage, anti-dsDNA level, significantly improved during treatment with belimumab (Table S2).

3.3. Predictors of renal response

At univariable analysis, increased baseline serum creatinine, proteinuria, smoke habit and hypertension were inversely associated with PERR, while the presence of anti-Sm antibodies showed a trend for a direct association.

At multivariable analysis, arterial hypertension (OR 0.28, 95%CI 0.09–0.89, p = 0.032), serum creatinine (OR 0.97, 95%CI 0.95–0.99, p = 0.01) and proteinuria at baseline resulted independent negative predictors of PERR during the follow-up (OR 0.37, 95%CI 0.19–0.74, p = 0.005) (Table 3).

We then analysed predictors of PERR at the definite timepoints of 6, 12, and 24 months, as shown in Table 4. Interestingly, arterial hypertension persisted as independent negative predictor of PERR at 6 months (OR 0.26, 95%CI 0.076–0.81, p = 0.021), but not at further timepoints; on the other hand, PERR at 6 months was itself an independent predictor of PERR at 12 and 24 months (p = 0.001 for both). In line with the definition of PERR, a high baseline proteinuria persisted as a negative predictor of renal response at 6 and 12 months (p = 0.001 and p = 0.003, respectively). Among patients with baseline proteinuria ≥1gr/day (n = 37), PERR was achieved by 20 (54%) and CRR by 7 (18.9%) patients at 24 months. Interestingly, presence of anti-Sm showed a trend for PERR at 12 months and was a predictor at 24 months (p = 0.009). Because SLE duration before belimumab was significantly shorter among patients displaying anti-Sm positivity (anti-Sm + vs. anti-Sm- (mean ± SD), years: 8.4 ± 7.9 vs. 13.6 ± 7.8, p = 0.006), this result is given after adjustment for disease duration.

Variables employed at uni- and multivariable analysis are listed in Table S3.

Given the low number of renal flares among patients who had

Table 2
Achievement of complete renal response and primary efficacy renal response: N (%).

	6 months	12 months	24 months
	N = 91	N = 81	N = 59
Primary Efficacy Renal Response	**44 (48.4)**	**50 (61.7)**	**39 (66.1)**
Complete Renal Response	**22 (24.2)**	**28 (34.5)**	**22 (37.3)**
Proteinuria <0.5 g/24 h	43 (47.2)	46 (56.7)	28 (47.4)
Proteinuria <0.7 g/24 h	493 (53.8)	51 (62.9)	31 (52.4)
Inactive sediment	57 (62.6)	49 (60.5)	51 (86.4)
eGFR ≥90 ml/min/1.73m2	44 (48.4)	45 (55.6)	32 (54.2)
eGFR ≥60 ml/min/1.73m2	74 (81.3)	73 (90.1)	55 (93.2)

N, number; eGFR, estimated glomerular filtration rate; h, hour.

Table 3
Baseline predictors of primary efficacy renal response (PERR) ever.

Variable	Univariable analysis			Multivariable analysis		
	OR	95% CI	p	OR	95% CI	P
Serum creatinine mg/dl	*0.97*	*0.96–0.99*	*0.004*	**0.97**	**0.95–0.99**	**0.01**
eGFR ml/min/ 1.73m^2	1.07	0.99–1.03	0.06	–	–	–
Proteinuria g/day	*0.42*	*0.24–0.72*	*0.002*	**0.37**	**0.19–0.74**	**0.005**
Arterial hypertension	*0.28*	*0.1–0.76*	*0.012*	**0.28**	**0.09–0.89**	**0.032**
Anti-dsDNA antibodies	21	0.7–6.3	0.19	–	–	–
Anti-Sm antibodies	*2.8*	*0.86–9.17*	*0.08*	2.2	0.45–10.4	0.33
C3	0.9	0.97–1.01	0.9	-	-	-
C4	0.95	0.9–1.01	0.08	0.96	0.9–1.04	0.32
Smoke	*0.22*	*0.06–0.78*	*0.019*	0.27	0.05–1.3	0.1

Variables included in the multivariable model: arterial hypertension, baseline proteinuria, baseline creatinine, smoke; anti-Sm antibodies; C4 levels.
PERR, primary efficacy renal response; eGFR, estimated glomerular filtration rate.

Table 4
Baseline predictors of PERR at different timepoints.

	6 months	12 months	24 months
	N = 91	N = 81	N = 59
Proteinuria levels at baseline	**OR 0.21 CI95% 0.09–0.53 *p* = *0.001***	**OR 0.19 CI95% 0.069–0.57 *p* = *0.003***	*OR 0.89 CI95% 0.44-1.8* p = 0.77
Baseline creatinine	**OR 0.97 CI95% 0.94–0.99 *p* = *0.008***	OR 0.99 CI95% 0.99–1.01 p = 0.46	OR 0.98 CI95% 0.95–1.02 p = 0.19
Hypertension	**OR 0.26 CI95% 0.076–0.81 *p* = *0.021***	OR 0.27 CI95% 0.06–1.18 p = 0.08	OR 0.57 CI95% 0.09–3.39 p = 0.54
Smoke	OR 0.25 CI95% 0.06–1.7 p = 0.19	–	–
PERR at 6 months	–	**OR 14.4 CI95% 3.28–63.6 *p* = *0.001***	**OR 11.7 CI95% 2.7–48.7 *p* = *0.001***
Anti-Sm positivity	–	**OR 5.52** CI95%0.98–30.9 *p = 0.05*	**OR 19.8 CI95% 2.01–186.7 *p* = *0.009***

PERR, primary efficacy renal response; N, number.
Variables for PERR at 6 months: hypertension, baseline proteinuria, baseline creatinine, smoke.
Variables for PERR at 12 months: hypertension, baseline proteinuria, baseline creatinine, PERR at 6 months, positive anti-Sm antibodies.
Variables for PERR at 24 months: hypertension, baseline proteinuria, baseline creatinine, PERR at 6 months, positive anti-Sm antibodies.
Multivariable model was adjusted for baseline confounders including age, gender, SLEDAI-2K, SDI, disease duration and corticosteroid dosage.

achieved PERR (five patients) no multivariable analysis for flare predictors was performed. At univariable analysis, a longer LN history before belimumab showed a trend toward a positive association with the risk of renal relapse (OR 1.23, 95% 0.9–1.5, p = 0.07).

3.4. Safety and drug discontinuation

Among 2280 IV Belimumab infusions, no deaths or severe infusion reactions were observed. There was a total of 217 AE in 63 patients, of them 73.3% were infectious, 16.1% non-infectious and 10.6% hypersensitivity reactions/infusion reactions (Table S4). Thirteen SAE were observed in 12 patients (19.0%).

Drug discontinuation was observed in 33 (36.3%) patients after a median follow-up of 18.9 (6–54) months. Reasons for discontinuation were inadequate response in 14 (42.4%), AE in 9 (27.3%), pregnancy in 6 (18.2%), lost to follow-up in 2 (6.1%) and not known in 2 cases (6.1%). Overall, baseline proteinuria higher than 2 g/day was associated with a greater risk of discontinuation due to any reason (OR 5.06, 95%CI 1.4–18.1, p = 0.012), while class IV LN was associated with lower probability of discontinuation due to inadequate response (OR 0.13, 95%CI 0.02–0.72; p = 0.022).

4. Discussion

Belimumab effectiveness and safety has been proven in SLE; however, few data are available in patients with LN in real-life [9,10,11]. This study analysed predictors of renal response in patients with persistent renal disease activity enrolled in the BeRLiSS cohort, which evaluates the use of Belimumab in daily clinical practice.

In our study, we found better results in terms of PERR and to some extent of CRR in comparison to BLISS-LN RCT: at 24 months PERR was achieved by 66.1% and CRR by 37.3% of our patients compared with PERR in 43% and CRR in 30% of patients enrolled in belimumab arm in BLISS-LN study [6]. In addition, in our cohort the mean time to reach PERR was shorter than 12 months, which is often regarded a useful timepoint for response [1,12]. These results suggest that Belimumab could be effective as an add-on therapy in patients with LN also in real life setting.

However, some difference between BLISS-LN and our study should be considered. First, in BLISS-LN belimumab was started as add-on treatment during the initial therapy for LN which encompassed use of high glucocorticoid dosages and of cyclophosphamide or mycophenolate mofetil for all patients. By contrast, in our study belimumab was started after LN initial treatment due to persistent yet no acute renal activity, and 23% of our patients had no ongoing immunosuppression beyond glucocorticoids or antimalarials at the time of belimumab initiation (Table 1). In addition, in the BLISS-LN study the patients had to have proteinuria ≥1 gr/day at baseline and mean baseline proteinuria, assessed as urinary protein-creatinine ratio, was 3.4 ± 3.2 g/g, which corresponds to a similar value of 24 h-proteinuria and as such is higher than the baseline proteinuria displayed in our cohort. In this regard, when analysing only patients with baseline proteinuria ≥1gr/day in our cohort, PERR was achieved by 54% and CRR by 19% of patients at 24 months, which is indeed closer to the BLISS-LN results. Finally, in our cohort belimumab was often discontinued in patients not responding after one year of treatment; therefore, patients on belimumab in the second year are those with better results.

Besides baseline creatinine, which is a known negative independent predictor of renal response [12,13], we found that high baseline proteinuria was a negative independent predictor of PERR overall and at 6 and 12 months. While this is on the one hand expected, as the definition of PERR entails low proteinuria, it also supports the utility of belimumab in case of even slightly yet persistently elevated proteinuria in order to achieve a timely response, similarly to what was demonstrated in patients with extra-renal manifestations [7]. In line with the prognostic importance of an early renal response [1,12], we established that PERR at 6 months is a strong predictive factor for further renal response at 12 and 24 months.

Interestingly, anti-Sm antibodies were independent predictors of PERR at 24 months in our cohort. The prognostic value of anti-Sm antibodies is still debated, although their presence was associated with renal involvement in SLE [14]. In our study the presence of anti-Sm antibodies was associated with a shorter SLE duration before belimumab initiation, possibly due to an earlier recognition of the disease, and a consequently prompter treatment, which might have positively influenced patient outcome. Nevertheless, anti-Sm antibodies maintained their predictive value even after adjustment for disease duration,

suggesting that anti-Sm is part of an antibody setting which delineates patients with a higher B cell-mediated activation, who are more likely to respond to belimumab [15].

It is worth noting that smoking habit and arterial hypertension at baseline were significantly associated with the lack of PERR during the follow-up (Tables 2 and 3) and that arterial hypertension persisted as an independent negative predictor of PERR thereafter (Table 4). These findings bring together a classical risk factor for deterioration of renal function i.e. arterial hypertension [1,12,13] and a recently appointed risk factor for poor belimumab response, i.e. cigarette smoke [7,16] as concomitant contributors to poor renal response among patients receiving belimumab, suggesting that their combination might be detrimental in clinical practice.

Notably, the rate of renal flares after belimumab initiation was quite low in our study. We found that among patients who achieved PERR, 5 (7.8%) had a renal flare after a mean observation period of 22 months. This is a remarkably lower prevalence of relapse than what is usually observed in clinical practice with standard of care, where 27–66% of LN patients in remission have subsequent flares [2]. While it is known that belimumab reduced the incidence of renal flares at 52-weeks in the BLISS studies [5], we confirm this effect also in a two-year- follow-up. On the other hand, it should be mentioned that challenging data have been reported regarding the possibility of new-onset LN upon belimumab treatment [17–19]. Although those observations were not connected with specific immunological perturbations induced by belimumab [15,20,21], they support the need for a continuously improved stratification of baseline immunological features, beside the clinical profiling of patients.

Finally, the overall evaluation of disease course confirmed the glucocorticoid-sparing effect of belimumab, the significant decrease in serological activity (Table S2) and the good safety profile of the drug in this subgroup of patients [7,22].

This study has several strengths and inevitable limitations. The main limitation is the lack of a control group, which prevents inference on belimumab efficacy in respect to standard of care; in addition, most patients were Caucasian and patients with very active and severe LN were not included. The main strength is the analysis of a large, nationwide, cohort of patients treated with belimumab in real-life, in whom predictors of renal response upon belimumab could be identified, thereby contributing to the identification of patients with LN who could better benefit from belimumab in clinical practice.

In summary, belimumab is an effective and safe therapeutic option for patients with LN in daily practice.

Author statement

Conceptualization, methodology, investigation, resources, data curation, visualization: MG, FS, AD, LI. Original draft: MG, FS. Formal analysis. MG, AG, MZ. Project administration and supervision: AD, LI, MG. Resources, data curation, review and editing, final approval: all contributing authors.

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Declaration of competing interest

Prof. Doria has received honoraria from GSK. The other authors have no disclosures to declare for this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jaut.2021.102729.

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