

Comparative analysis of long-term organ damage in patients with systemic lupus erythematosus using belimumab versus standard therapy: a post hoc longitudinal study

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To cite: Urowitz MB, Ohsfeldt RL, Wielage RC, *et al.* Comparative analysis of long-term organ damage in patients with systemic lupus erythematosus using belimumab versus standard therapy: a post hoc longitudinal study. *Lupus Science & Medicine* 2020;7:e000412. doi:10.1136/lupus-2020-000412

Received 1 May 2020
Revised 7 August 2020
Accepted 3 September 2020



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ABSTRACT

Objective Long-term extension (LTE) studies of belimumab in SLE do not include a comparator arm, preventing comparisons between belimumab plus standard therapy and standard therapy alone for organ damage accrual. Propensity score matching can be used to match belimumab-treated patients from LTE studies with standard therapy-treated patients from observational cohort studies. This analysis was designed to compare organ damage progression between treatment groups (belimumab plus standard therapy vs standard therapy alone) in patients with SLE with ≥5 years of follow-up, reproducing our previous study with more generalisable data.

Methods This exploratory post hoc analysis used a heterogeneous population of US and non-US patients receiving monthly intravenous belimumab from pooled BLISS LTE trials (BEL112234/NCT00712933) and standard therapy-treated patients from the Toronto Lupus Cohort. Sixteen clinical variables were selected to calculate the propensity score.

Results The 592 LTE and 381 Toronto Lupus Cohort patients were highly dissimilar across the 16 variables; an adequately balanced sample of 181 LTE and 181 matched Toronto Lupus Cohort patients (mean bias=3.7%) was created using propensity score matching. Belimumab treatment was associated with a smaller increase in Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) over 5 years than standard therapy alone (mean treatment difference=−0.453 (95% CI −0.646 to −0.260); $p<0.001$). Patients treated with belimumab were 60% less likely to progress to a higher SDI score over any given year of follow-up, compared with standard therapy alone (HR (95% CI) 0.397 (0.275 to 0.572); $p<0.001$).

Conclusion Using propensity score matching, this highly heterogeneous sample was sufficiently matched to the Toronto Lupus Cohort, suggesting that patients treated with intravenous belimumab may have reduced organ damage progression versus standard therapy alone. This analysis of a large and diverse pooled SLE population was consistent with our previously published US-focused study.

INTRODUCTION

Long-term extensions (LTEs) of the Belimumab International Systemic Lupus Erythematosus (SLE) Study (BLISS)–52

(BEL110752/NCT00424476) and BLISS-76 (BEL110751/NCT00410384) phase III trials have demonstrated that intravenous belimumab is well tolerated and efficacious for over 5 years, for the treatment of SLE.^{1–3} These LTE studies did not include a comparator arm, meaning that comparisons between belimumab plus standard therapy (referenced as belimumab throughout) and standard therapy alone were not possible.

Our recently published post hoc study used propensity score matching to match belimumab-treated patients from the US-only BLISS LTE study (BEL112233/NCT00724867)⁴ with standard therapy-treated patients from the Toronto Lupus Cohort.⁵ This analysis revealed that patients from the USA who received belimumab had significantly reduced SLE-related organ damage over 5 years compared with matched patients who received only standard therapy.

METHODS

To improve the generalisability of this analysis to other populations, we have conducted a further equivalent post hoc exploratory analysis using a more heterogeneous population of patients from the pooled BLISS LTE trials (US and non-US (BEL112234/NCT00712933)). Patients in BEL112234 received either belimumab 1 mg/kg intravenously or belimumab 10 mg/kg intravenously every 4 weeks. The propensity score is a widely adopted and used composite value that allows clinically similar patients to be compared. Propensity score matching was conducted as previously described.⁵ Briefly, the propensity score value for matching was defined as the estimated log-odds from the logistic regression. Sixteen clinical variables were selected to

calculate the propensity score. These variables were the same as those used in the US-focused analysis, aside from current smoking status, which was excluded due to unexpectedly large differences between the LTE (2%) and Toronto Lupus Cohort (24%) datasets. Based on similar propensity score value (within a calliper value defined as 20% of the SD for the distribution of the propensity score variable in the full sample), patients from the BLISS LTE trials were matched 1:1 to Toronto Lupus Cohort patients. Unmatched patients were excluded from the analysis of the propensity score-matched patient sample.

The primary objective of this analysis was to compare organ damage progression, assessed using the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI), between treatment groups for patients with ≥ 5 years of follow-up. Secondary objectives of this analysis were (1) to compare rates of organ damage progression between treatment groups, and (2) to identify the magnitude of year-to-year organ damage progression within the larger cohort, as 5-year follow-up data were not available for all patients.

RESULTS

The 592 LTE and 381 Toronto Lupus Cohort patients were highly dissimilar across the 16 variables prior to matching. Propensity score matching resulted in an adequately

balanced sample of 181 LTE and 181 matched Toronto Lupus Cohort patients with ≥ 5 years of follow-up (mean bias=3.7%) (table 1). Baseline characteristics were similar between cohorts following propensity score matching, although there was a higher rate of antimalarial use in the belimumab cohort (belimumab: 66.9%; standard therapy: 59.7%). Belimumab treatment was associated with a smaller SDI increase over 5 years than standard therapy alone (mean treatment difference=-0.453 (95% CI -0.646 to -0.260); $p<0.001$) (table 2).

For the secondary objectives, propensity score matching resulted in a sample of 323 LTE patients with ≥ 1 year of follow-up and 323 adequately matched Toronto Lupus Cohort patients, with a mean bias of 3.7% (table 3). Baseline characteristics were similar between cohorts following propensity score matching. Patients treated with belimumab were 60% less likely to progress to a higher SDI score over any given year of follow-up, compared with standard therapy alone (HR (95% CI) 0.397 (0.275 to 0.572); $p<0.001$) (table 2).

A patient receiving belimumab had a 3.1% annual probability of organ damage progression compared with 7.5% with standard therapy alone (table 2). SDI increases of ≥ 1 point were experienced by 12.7% and 26.9% of patients receiving belimumab and standard therapy, respectively. For SDI increases of ≥ 2 points, these values were 0.6% and 8.0%, respectively (table 2). Among patients with

Table 1 Variables at baseline, pre-propensity and post-propensity score matching for patients with ≥ 5 years of follow-up from pooled LTE and Toronto Lupus Cohort datasets

Variable	Pre-propensity score matching (n=973)			Post-propensity score matching (n=362)		
	Mean			Mean		
Age	39.674	37.336	19.3	39.337	39.105	1.9
Age squared	1693.9	1565.8	12.8	1691.8	1685.5	0.6
Female	0.927	0.895	11.4	0.895	0.906	-3.7
Race						
Black	0.091	0.150	-18.0	0.116	0.133	-5.0
Asian/other	0.471	0.234	51.3	0.315	0.331	-3.5
SLE duration	6.683	5.738	13.9	7.044	6.946	1.3
Hypertension	0.426	0.370	11.4	0.403	0.409	-1.1
Dyslipidaemia	0.132	0.570	-103.1	0.326	0.309	3.6
Proteinuria	0.167	0.312	-34.4	0.210	0.204	1.4
ACR criteria	5.932	5.646	20.8	5.856	5.823	2.5
Baseline SLEDAI	8.027	10.016	-42.5	9.094	8.912	4.4
Corticosteroid use	0.843	0.606	54.9	0.707	0.713	-1.2
Antimalarial use	0.698	0.522	36.5	0.669	0.597	14.9
Immunosuppressive use	0.458	0.310	30.8	0.431	0.392	7.8
Baseline SDI=1	0.233	0.150	21.3	0.204	0.193	2.8
Baseline SDI ≥ 2	0.181	0.105	21.8	0.177	0.160	4.4

ACR, American College of Rheumatology; LTE, long-term extension; SDI, SLICC/ACR Damage Index; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SLICC, Systemic Lupus International Collaborating Clinics.

Table 2 Summary of outcome data for the pooled population

	Belimumab plus standard therapy	Standard therapy	P-value
5-year SDI score change (95% CI) (n=181)*	0.265 (0.180 to 0.350)	0.718 (0.548 to 0.889)	
Difference (95% CI)	-0.453 (-0.646 to 0.260)		<0.001
Rate of organ damage progression (n=323)*			
HR vs standard therapy (95% CI)	0.397 (0.275 to 0.572)	-	<0.001
Intercept hazard rate (95% CI)	-	0.078 (0.064 to 0.096)	<0.001
Annual probability of progression [†]	3.1%	7.5%	-
Magnitude of year-on-year organ damage progression (n=323)*			
≥1-point SDI increase events, n (%)	41 (12.7)	87 (26.9)	-
≥2-point SDI increase events, n (%)	2 (0.6)	26 (8.0)	-
Proportion of ≥2-point SDI increase events/≥1-point SDI increase events, n/n (%)	2/41 (4.9)	26/87 (29.9)	-

*n values presented are equal for each cohort.

[†]The annual probability of SDI progression was derived using the hazard rate estimates from the proportional-hazards exponential regression model. CI, confidence interval; HR, hazard ratio; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index.

SDI increases, the likelihood of experiencing a ≥2-point increase in SDI was six times greater (p=0.002) if a patient was treated with standard therapy alone, compared with belimumab plus standard therapy.

DISCUSSION

Propensity score matching was able to sufficiently match this highly heterogeneous sample of BLISS belimumab-treated patients to standard therapy-treated patients (US and non-US) from the Toronto Lupus Cohort. Accrual

of long-term organ damage in SLE is multifactorial, with long-term corticosteroid use in standard therapy-treated patients playing a key role. Reduction in corticosteroid dose is an important goal in SLE management. "It has been shown that belimumab may be more protective of long-term organ damage in patients with SLE with longer periods of remission or low disease activity."⁶ This exploratory analysis suggested that belimumab plus standard therapy may slow the rate and magnitude of organ damage accrual compared with standard therapy alone.

Table 3 Variables at baseline, pre-propensity and post-propensity score matching for patients with ≥1 year of follow-up from pooled LTE and Toronto Lupus Cohort datasets

Variable	Pre-propensity score matching (n=1541)			Post-propensity score matching (n=646)		
	Mean		% Bias	Mean		% Bias
Age	38.782	36.735	16.2	38.108	37.416	5.4
Age squared	1634.0	1538.5	9.0	1611.1	1566.9	4.2
Female	0.942	0.885	20.4	0.926	0.913	4.5
Race						
Black	0.075	0.150	-24.1	0.115	0.108	2.0
Asian/other	0.457	0.301	32.7	0.337	0.362	-5.2
SLE duration	6.737	6.358	5.5	7.061	6.803	3.6
Hypertension	0.400	0.383	3.3	0.412	0.402	1.9
Dyslipidaemia	0.128	0.471	-80.7	0.279	0.282	-0.7
Proteinuria	0.169	0.346	-41.3	0.245	0.263	-4.3
ACR criteria	5.971	5.674	21.6	5.901	5.892	0.7
Baseline SLEDAI	8.273	10.100	-39.8	9.105	9.046	1.4
Corticosteroid use	0.859	0.639	52.5	0.715	0.743	-6.3
Antimalarial use	0.669	0.593	15.8	0.656	0.628	5.8
Immunosuppressive use	0.472	0.372	20.4	0.399	0.409	-1.9
Baseline SDI=1	0.241	0.150	22.9	0.235	0.195	9.8
Baseline SDI≥2	0.177	0.103	21.3	0.133	0.139	-1.8

ACR, American College of Rheumatology; LTE, long-term extension; SDI, SLICC/ACR Damage Index; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SLICC, Systemic Lupus International Collaborating Clinics.

This analysis of a larger and more diverse US and non-US pooled population was consistent with our previously published US-focused study.⁵ As discussed in our previously published study, the main limitation of this exploratory analysis was the inability to balance the time period of the LTE and Toronto Lupus Cohort groups.

CONCLUSION

These data add to the body of evidence that patients treated with belimumab have reduced organ damage progression compared with those treated with standard therapy alone.

Acknowledgements Medical writing support was provided by Liam Campbell, PhD, of Fishawack Indicia Ltd, UK, and was funded by GSK.

Contributors MBU, RLO, RCW, JJD, MZ, YA, SR and AVJ were involved in the concept or design of the study and the analysis of the data. MBU, YA, SR and AVJ were involved in the acquisition of data. MBU, RLO, RCW, JJD, MZ, YA, SR and AVJ approved the final manuscript.

Funding This study was funded by GlaxoSmithKline (GSK 206347).

Competing interests MBU has received research grants from GSK. YA, SR and AVJ are employees of GSK and hold stocks and shares in GSK; RCW, JJD and MZ are employees at Medical Decision Modeling Inc., contracted by GSK for this analysis. RLO is a non-employee consultant for Medical Decision Modeling Inc.

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

Patient consent for publication Not required.

Ethics approval The original parent studies (BEL110751 and BEL110752) and the BLISS LTE studies (BEL112233 and BEL112234) were conducted in accordance with the ethical principles of the Declaration of Helsinki, the International Council for Harmonisation on Good Clinical Practice, and the applicable country-specific regulatory requirements.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement GSK makes available anonymised individual participant data and associated documents from interventional clinical studies which evaluate medicines, upon approval of proposals submitted to www.clinicalstudydatarequest.com. To access data for other types of GSK sponsored research, for study documents without patient-level data and for clinical studies not listed, please submit an enquiry via the website.

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