## Original article

# Efficacy and safety of belimumab during maintenance therapy in patients with systemic lupus erythematosus

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## Abstract

**Objectives.** The efficacy of belimumab (BEL) during maintenance therapy in patients with SLE remains unclear in the real-life clinical setting. This study investigated the efficacy and safety of BEL in patients with SLE during maintenance therapy.

**Methods.** In this retrospective observational study, maintenance therapy was defined as low-dose glucocorticoid (GC) therapy (prednisolone equivalent dose of $\leq$0.2 mg/kg/day) in patients with a Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index (SELENA-SLEDAI) score <10. Participants comprised patients with SLE on HCQ or MMF [standard-of-care (SoC) group: $n = 103$] and those on BEL plus SoC (BEL+SoC group: $n = 100$). Selection bias was minimized using propensity score-based inverse probability of treatment weighting (IPTW). GC dose trajectories were modelled using growth mixture modelling (GMM). The primary end point was GC dose at 52 weeks.

**Results.** No significant difference was observed in patient characteristics between the two groups after IPTW adjustment. The BEL+SoC group exhibited a significant decrease in GC dose. GC dose at 52 weeks and relapse rate were significantly lower in the BEL+SoC group than in the SoC group. The proportion of patients in one of four groups defined by GMM for which GC dose was tapered to 0 mg within 52 weeks (GC tapering-discontinuation group) was significantly higher in the BEL+SoC group than in the SoC group. In the BEL+SoC group, low SELENA-SLEDAI score and low GC dose at baseline were associated with being GC dose-tapering discontinuation.

**Conclusion.** The present study suggests that BEL is suitable for patients with SLE during maintenance therapy.

**Key words:** systemic lupus erythematosus, belimumab, standard of care, glucocorticoid

**CLINICAL SCIENCE**

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### Rheumatology key messages

- Belimumab reduced glucocorticoid dose and prevented relapse in patients with SLE during maintenance therapy.
- Belimumab contributed to glucocorticoid discontinuation in patients with low SELENA-SLEDAI score on low-dose glucocorticoid.
- Belimumab is suitable for patients with SLE during maintenance therapy.

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## Introduction

SLE is a multi-organ systemic autoimmune disease that predominantly affects women of childbearing age [1]. SLE treatment involves glucocorticoid (GC) therapy with various immunosuppressive drugs. The initial GC dose and selection of immunosuppressive drugs are based on several factors, including SLE disease activity, presence or absence of major organ involvement, and complications such as infections and cardiovascular diseases [2]. However, these drugs are nonspecific, and their long-term use can increase the

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risk of organ damage and adversely affect the quality of life and prognosis of patients [3]. Accordingly, there is an urgent need to develop specific molecular targeted therapies for systemic lupus erythematosus (SLE).

Belimumab (BEL) is a fully human monoclonal antibody against B-cell activating factor, which is a member of the tumour necrosis factor family (BAFF). BEL was the first biologic approved for SLE treatment, but it may result in its own clinical effects given that BEL inhibits autoreactive B-cell survival. Based on studies examining the efficacy of BEL [4–14] in patients with SLE with moderate disease activity [mean SLE Disease Activity Index (SLEDAI) score of ~10], BEL is recommended for patients with SLE with moderate disease activity on standard therapy according to the 2019 update of the EULAR recommendations for SLE management [15]. However, the efficacy and safety of BEL in patients with SLE during maintenance therapy remain unclear.

According to the treat-to-target [16] strategy for SLE, 'lupus maintenance treatment should aim for the lowest GC dosage needed to control disease, and if possible, GCs should be withdrawn completely'. In real-world clinical practice, reducing or discontinuing drugs in patients with SLE with mild to moderate disease activity during maintenance therapy can be challenging [17].

This study aimed to investigate the efficacy of BEL compared with standard therapy for reducing GC dose, preventing relapse, and preventing organ damage progression using real-world data from patients with SLE after adjusting for confounding factors in patient background minimizing selection bias by propensity score (PS)-based inverse probability of treatment weighting (IPTW) [18]. Unlike in clinical trials, direct comparison of two groups in studies using real-world data is not valid owing to potential heterogeneity in backgrounds. In this study, we used IPTW to adjust for between-group baseline differences. Furthermore, we analysed disease activity and GC dose trajectories using growth mixture modelling (GMM) and evaluated the clinical characteristics of patients who benefited from BEL.

## Participants and methods

### Patients and study design

This was a retrospective observational study. Patients who met the 1997 ACR SLE classification criteria [19], the 2012 SLICC SLE classification criteria [20] or the 2019 EULAR/ACR classification criteria for SLE [21] were recruited from the LOOPS registry, a registry of patients with SLE treated in our hospital and affiliated hospitals. Participants comprised patients with SLE on maintenance therapy with low-dose GC (prednisolone equivalent dose ≤0.2 mg/kg/day) and a Safety of Estrogens in Lupus Erythematosus National Assessment-SLEDAI (SELENA-SLEDAI) score <10. In Japan, HCQ, MMF and BEL became available in September 2015, July 2016 and December 2017, respectively. Patients who met the aforementioned criteria of maintenance therapy with HCQ and/or MMF at the time of December 2016 (when both HCQ and MMF were available) were assigned to the standard-of-care (SoC) group. Patients who met the aforementioned criteria of maintenance therapy after December 2017 and received BEL plus SoC during the study period up to February 2020 were assigned to the BEL+SoC group. Efficacy and safety were evaluated at 52 weeks. This study was approved by the ethics review board of the University of Occupational and Environmental Health, Japan (approval number #04–23). All participants of the LOOPS registry gave written informed consent. The study was performed according to the Declaration of Helsinki.

### Clinical efficacy and outcomes

The primary end point was GC dose at 52 weeks after treatment initiation using propensity score-based IPTW. The secondary endpoints were relapse rate and adverse events at 52 weeks after treatment initiation, SELENA-SLEDAI score [22], total haemolytic complement activity (CH50), anti-dsDNA antibody titre, SLICC damage index [23] and glucocorticoid toxicity index (GTI) [24] at 52 weeks after treatment initiation. Patients with a GC dose of 0 mg at baseline were excluded from the GTI analysis. Details about the definition of the relapse are shown in the Supplementary Methods, available at *Rheumatology* online.

### Safety

Clinical laboratory tests and other safety assessments were performed at hospital visits. The incidence and severity of all adverse events were recorded. The National Institutes of Health Common Terminology Criteria for Adverse Events (CTCAE) (version 5.0) were used to describe adverse events and laboratory abnormalities.

### Statistical analyses

Patient characteristics are expressed as mean (s.d.), median [interquartile range (IQR)] or number (%) of patients. Retention rates were assessed using the Kaplan–Meier method. Student's *t test* and Mann–Whitney's *U* test were used for between-group comparisons, and the Fisher's exact test was used to compare categorical variables. The contribution degree and contribution ratio were calculated using the bootstrap forest method. The optimal cut-off value for prognostic factors was calculated using receiver operator characteristic curve analysis.

To adjust for baseline patient characteristics between the two groups, the calculated PS were weighted using the 'ratio of patients receiving BEL to all patients/propensity score' in the BEL+SoC group and the 'ratio of patients in the SoC group to all patients/1-propensity score' in the SoC group as the weighting coefficient on stability.

To understand change patterns of disease activity and GC dose in the BEL+SoC and SoC group, growth mixture modelling was applied to classify patients into

TABLE 1 Patient characteristics in the SoC and BEL+SoC groups before and after IPTW

| Variables | Before IPTW | | | After IPTW | | |
|---|---|---|---|---|---|---|
| | SoC $n = 103$ | BEL + SoC $n = 100$ | *P*-value | SoC $n = 95^a$ | BEL + SoC $n = 110^a$ | *P*-value |
| Age (years) | 42.3 (14.2) | 42.3 (14.8) | 0.977 | 44.3 (16.8) | 42.7 (14.5) | 0.477 |
| Gender, *n* (% female) | 93 (90.3%) | 91 (91.0%) | 0.862 | 113 (91.1%) | 152 (92.1%) | 0.76 |
| Disease duration (month) | 157.0 (118.4) | 161.2 (128.2) | 0.810 | 170.2 (130.2) | 150.1 (118.3) | 0.250 |
| Maintenance therapy duration (month) | 66.1 (54.7) | 56.6 (57.3) | 0.908 | 62.7 (57.7) | 51.6 (47.9) | 0.136 |
| Concomitant GC dose, mg/d, PSL equivalent | 4.7 (3.3) | 5.0 (3.2) | 0.435 | 4.6 (3.4) | 4.4 (2.9) | 0.534 |
| Number of concomitant immuno suppressant use | 1.6 (0.6) | 1.4 (0.8) | 0.090 | 1.6 (0.6) | 1.5 (0.7) | 0.513 |
| HCQ, *n* (%) | 88 (85.4%) | 92 (92.0%) | 0.260 | 80 (84.2%) | 90 (82.6%) | 0.704 |
| MMF, *n* (%) | 24 (23.3%) | 22 (22.0%) | 0.825 | 25 (26.3%) | 33 (30.0%) | 0.641 |
| AZA, *n* (%) | 20 (19.4%) | 17 (17.0%) | 0.656 | 17 (17.9%) | 15 (13.6%) | 0.444 |
| TAC, *n* (%) | 21 (20.4%) | 15 (15.0%) | 0.315 | 15 (15.8%) | 11 (10.0%) | 0.293 |
| CSA, *n* (%) | 6 (5.8%) | 3 (3.0%) | 0.328 | 4 (4.2%) | 3 (2.7%) | 0.706 |
| MTX, *n* (%) | 10 (9.7%) | 8 (8.0%) | 0.669 | 8 (8.4%) | 7 (6.4%) | 0.601 |
| MZR, *n* (%) | 6 (5.8%) | 3 (3.0%) | 0.328 | 4 (4.2%) | 2 (1.8%) | 0.419 |
| NPSLE, *n* (%) | 38 (36.9%) | 30 (30.0%) | 0.372 | 33 (34.7%) | 29 (26.4%) | 0.223 |
| LN, *n* (%) | 51 (49.5%) | 47 (47.0%) | 0.720 | 45 (48.1%) | 52 (47.1%) | 0.885 |
| LN class I/II/III/IV/V, *n* | 3/8/9/21/12 | 2/11/12/17/11 | 0.895 | 3/8/9/15/9 | 2/8/9/14/17 | 0.800 |
| SELENA-SLEDAI score | 2.7 (2.7) | 3.2 (2.4) | 0.172 | 2.9 (2.5) | 2.5 (2.2) | 0.282 |
| BILAG at least A1 or B2, *n* (%) | 3 (2.9%) | 9 (9.0%) | 0.079 | 2 (2.1%) | 3 (2.7%) | 0.565 |
| SLICC Damage Index | 0 (0–1) | 1 (0–2) | 0.018 | 0 (0–1) | 1 (0–1) | 0.853 |
| CH50 | 46.3 (14.8) | 46.6 (13.7) | 0.985 | 48.7 (13.9) | 49.7 (11.8) | 0.594 |
| Anti-ds DNA antibody | 5.0 (2.2–11.0) | 4.0 (2.0–9.8) | 0.377 | 4.0 (2.0–15.0) | 3.6 (2.0–7.8) | 0.676 |

Data are mean (S.D.), median (IQR) or number (%) of patients. BEL: belimumab; BILAG: British Isles Lupus Assessment Group Index; CH50: 50% haemolytic unit of complement; CSA: ciclosporin A; DNA: deoxyribonucleic acid; GC: glucocorticoid; IPTW: inverse probability of treatment weighting; MZR: mizoribine; SELENA-SLEDAI: Safety of Estrogens in Lupus Erythematosus National Assessment Systemic Lupus Erythematosus Disease Activity Index; SoC: standard of care; TAC: tacrolimus; PSL: prednisolone. $^a$The number of subjects changed after IPTW in the calculation; however, the actual number of subjects did not change.

different subgroups based on SELENA-SLEDAI and GC dose trajectories. GMM was performed with STATA version 16.0 (StataCorp LLC, College Station, TX, USA) [25].

Details of the procedure of calculating propensity score and GMM are shown in the Supplementary Methods, available at *Rheumatology* online.

All reported *P*-values are two-sided and were not adjusted for multiple testing. The level of statistical significance was set at $P < 0.05$. The last observation carried forward was used for patients who discontinued medication before week 52. All analyses were conducted using JMP version 15.0 (SAS Institute Inc., Cary, NC, USA) and SPSS software version 25.0 (SPSS Inc., Chicago, IL, USA).

## Results

### Comparison of treatment efficacy and safety

Participants were recruited from the LOOPS registry for patients with SLE. Treatment efficacy and safety were compared between the SoC ($n = 103$) and BEL+SoC ($n = 100$) groups. Only one patient discontinued BEL within

52 weeks after BEL introduction. The continuation rate of BEL treatment was 99%. Adverse events are presented in Supplementary Table S1 (available at *Rheumatology* online). The incidence of grade 1 or 2 infections, as defined by the CTCAE (version 5.0), was significantly lower in the BEL+SoC group than in the SoC group, whereas the incidence of CTCAE grade 3 or higher adverse events was not significantly different between the two groups.

The characteristics of the two groups are presented in Table 1 and Supplementary Table S2 (available at *Rheumatology* online). No significant between-group differences were observed with respect to GC dose, disease duration, incidence of NPSLE, incidence of LN, SELENA-SLEDAI score, CH50 or anti-dsDNA antibody titre. SLICC damage index (SDI) was lower in the SoC group than in the BEL+SoC group. Mucocutaneous abnormalities, haematology abnormalities and hypocomplementemia were more frequent in the BEL+SoC group than in the SoC group.

Comparison of treatment efficacy at 52 weeks after treatment initiation revealed no significant between-group difference in the SELENA-SLEDAI score [SoC *vs* BEL+SoC: 2.2 (3.0) *vs* 2.2 (2.5), $P = 0.928$] (Supplementary

Fig. S1A, available at *Rheumatology* online). No significant between-group difference was observed in CH50 [SoC *vs* BEL+SoC: 47.2 (15.2) U/ml *vs* 47.2 (12.5) U/ml, $P = 0.999$] (Supplementary Fig. S1B, available at *Rheumatology* online). The rate of relapse (flare) with an increase in SELENA-SLEDAI score $\geq 4$ was significantly lower in the BEL+SoC group (10.0%) than in the SoC group (22.3%) ($P = 0.017$). No significant between-group differences were observed in the rate of relapse (severe flare) with an increase in SELENA-SLEDAI score $\geq 12$ (SoC *vs* BEL+SoC: 3.9% *vs* 1.0%, $P = 0.369$) or the rate of relapse defined as at least one new BILAG A or two new BILAG B scores (SoC *vs* BEL+SoC: 9.8% *vs* 2.0%, $P = 0.101$) (Supplementary Fig. S1C, available at *Rheumatology* online). Regarding relapse type, exacerbation of LN was significantly more frequent in the SoC group (13.6%) than in the BEL+SoC group (4.0%) ($P = 0.024$) (Supplementary Table S3, left; available at *Rheumatology* online). GC dose at 52 weeks was significantly lower in the BEL+SoC group [2.8 (2.8) mg/day] than in the SoC group [4.4 (3.9) mg/day] ($P = 0.001$) (Supplementary Fig. S1D, available at *Rheumatology* online). The proportions of patients with a reduced GC dose relative to baseline and GC discontinuation during the study period were significantly higher in the BEL+SoC group than in the SoC group (GC dose reduction, SoC *vs* BEL+SoC: 59.2% *vs* 78.0%, $P < 0.001$; GC discontinuation, SoC *vs* BEL+SoC: 2.9% *vs* 25.0%, $P < 0.001$) (Supplementary Fig. S1E, available at *Rheumatology* online). The SDI at 26 and 52 weeks after treatment initiation was significantly lower in the BEL+SoC group than in the SoC group [at 26 weeks, SoC *vs* BEL+SoC: 1 (0–2) *vs* 0 (0–1), $P < 0.001$; at 52 weeks, SoC *vs* BEL+SoC: 1 (0–2) *vs* 0 (0–1), $P < 0.001$] (Supplementary Fig. S1F, available at *Rheumatology* online). The GTI at 52 weeks was significantly lower in the BEL+ SoC group [0 (0–8)] than in the SoC group [0 (0–29)] ($P < 0.001$) (Supplementary Fig. S1G, available at *Rheumatology* online).

## Comparison of efficacy after adjustment using PS-based IPTW

Patient characteristics after minimizing selection bias and adjusting for confounding factors in patient background using PS-based IPTW are presented in Table 1 and Supplementary Table S2, available at *Rheumatology* online. No significant between-group differences were observed in any of the patient background factors. The standardized difference score was below 0.1 for all factors, indicating an adequate balance of variables.

Treatment efficacy in the SoC and BEL+SoC groups after adjustment using PS-based IPTW is shown in Fig. 1 and Supplementary Fig. S2, available at *Rheumatology* online. No significant between-group differences were observed in the SELENA-SLEDAI score at 52 weeks after treatment initiation [SoC *vs* BEL+SoC: 2.0 (2.8) *vs* 1.5 (2.2), $P = 0.149$] (Fig. 1A), CH50 at 52 weeks [SoC *vs* BEL+SoC: 50.0 (15.0) *vs* 48.3 (10.0), $P = 0.353$] (Supplementary Fig. S2A, available at *Rheumatology* online), or anti-dsDNA antibody titre [SoC *vs* BEL+SoC: 4.8 (2.2–8.1) *vs* 3.0

(1.7–8.7), $P = 0.491$] (Supplementary Fig. S2B, available at *Rheumatology* online). Adverse events are shown in Fig. 1B and Supplementary Table S1, available at *Rheumatology* online.

Relapse rate was significantly lower in the BEL+SoC group than in the SoC group (SELENA-SLEDAI-defined flare, SoC *vs* BEL+SoC: 16.8% *vs* 6.4%, $P = 0.001$; BILAG-defined flare, SoC *vs* BEL+SoC: 6.3% *vs* 0.9%, $P = 0.031$) (Fig. 1B). Regarding relapse type, exacerbation of LN was significantly more frequent in the SoC group (10.5%) than in the BEL+SoC group (2.5%) ($P = 0.014$) (Supplementary Table S3, right; available at *Rheumatology* online). The SDI at 26 and 52 weeks after treatment initiation was significantly lower in the BEL+SoC group than in the SoC group [at 26 weeks, SoC *vs* BEL+SoC: 1 (0–2) *vs* 0 (0–1), $P < 0.001$; at 52 weeks, SoC *vs* BEL+SoC: 1 (0–2) *vs* 0 (0–1), $P < 0.001$] (Fig. 1C).

## Comparison of GC dose after adjustment using propensity score-based IPTW

The changes in GC dose in the SoC and BEL+SoC groups after adjustment using PS-based IPTW are shown in Fig. 2A and Supplementary Fig. S3, available at *Rheumatology* online. GC dose at 12 weeks after treatment initiation was significantly lower in the BEL+SoC group [3.5 (2.8)] than in the SoC group [5.0 (5.3)] ($P = 0.011$), and the difference became more prominent at 52 weeks [SoC *vs* BEL+SoC: 4.4 (3.9) *vs* 2.2 (2.7), $P < 0.001$]. The SoC group did not exhibit a significant decrease in GC dose at 52 weeks (Supplementary Fig. S3A, available at *Rheumatology* online), while the BEL+SoC group exhibited a significant decrease in GC dose at 52 weeks (Supplementary Fig. S3B, available at *Rheumatology* online). The proportions of patients with a reduced GC dose relative to baseline and GC discontinuation during the study period were significantly higher in the BEL+SoC group than in the SoC group (GC dose reduction, SoC *vs* BEL+SoC: 56.8% *vs* 85.7%, $P < 0.001$; GC discontinuation, SoC *vs* BEL+SoC: 3.3% *vs* 29.9%, $P < 0.001$) (Fig. 2B).

## Comparison of treatment safety after adjustment using PS-based IPTW

The GTI at 52 weeks was significantly lower in the BEL+SoC group [0 (0–19)] than in the SoC group [1 (0–29)] ($P = 0.047$) (Fig. 2C). The incidence of CTCAE (version 5.0) grade 2 or higher adverse events was significantly lower in the BEL+SoC group (6.4%) than in the SoC group (17.0%) ($P = 0.005$) (Fig. 1B). The incidence of grade 2 or higher infections was significantly lower in the BEL+SoC group (3.6%) than in the SoC group (15.8%) ($P = 0.003$) (Fig. 2D). No significant between-group difference was observed in the incidence of severe adverse events (CTCAE grade 3 or higher adverse events) (Supplementary Table S1, right, available at *Rheumatology* online).
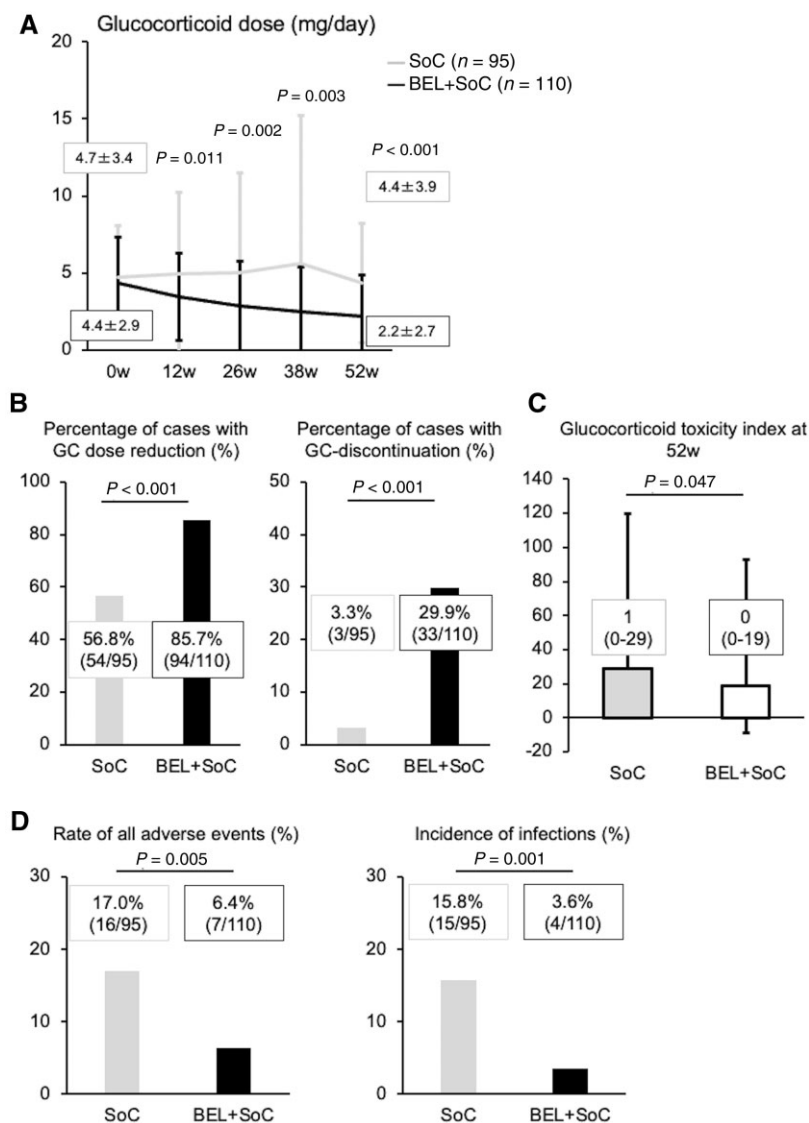
Fig. 1 Efficacy and safety of SoC *vs* BEL+SoC in SLE patients adjusted by IPTW
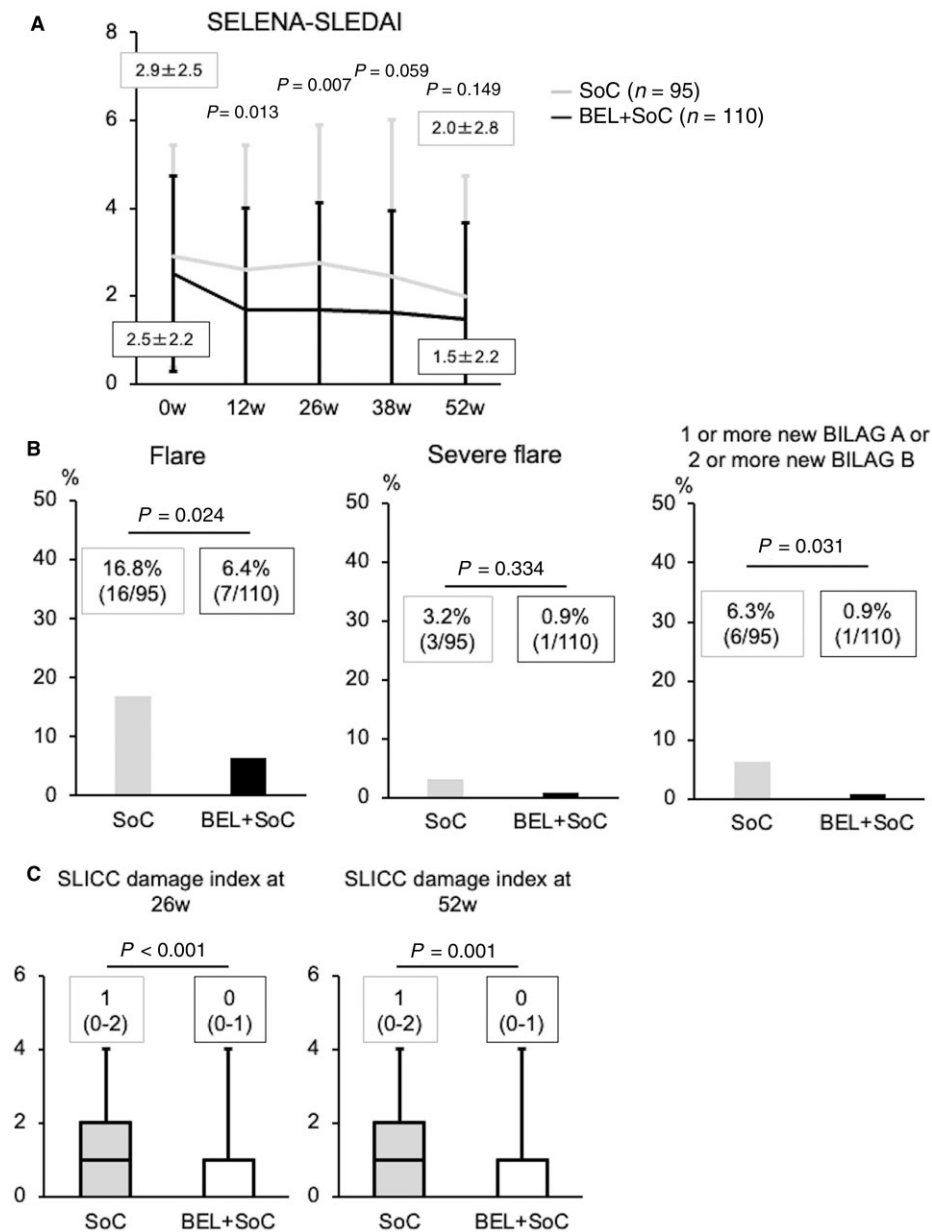


Selection bias was adjusted using propensity score-based IPTW in patients with SLE treated with standard of care (SoC) or belimumab (BEL) combined with SoC (BEL+SoC). (**A**) Changes in SELENA-SLEDAI over 52 weeks: comparison of the SoC and BEL+SoC groups. Data are presented as mean (s.d.). *P*-values were derived using the Student's t-test. (**B**) Comparison of relapse rates between the two groups using Pearson's chi-square test. Numbers represent percentages of all patients (%). Flare: An increase in score by 4 or more. Severe flare: An increase in score of 12 or more. BILAG definition of relapse states: Appearance of one new BILAG A item or two new B items. (**C**) Comparison of SLICC damage index between the two groups using Pearson's chi-square test. Numbers represent percentages of all patients (%).

## Analysis of SELENA-SLEDAI score and GC dose trajectories using GMM

The trajectories of changes in SELENA-SLEDAI score were assessed using GMM. A quadratic model was identified as the best fit (Supplementary Table S4, available at *Rheumatology* online) and the optimal number of groups was four (Supplementary Table S5, available at *Rheumatology* online) for both SELENA-SLEDAI score and GC dose.

Fɪɢ. 2 IPTW-adjusted dose and toxicity of glucocorticoid in SLE patients treated with SoC *vs* BEL+SoC



Selection bias was adjusted using propensity score-based IPTW in patients with SLE treated with standard of care (SoC) or belimumab (BEL) combined with SoC (BEL+SoC). (**A**) Changes in glucocorticoid (GC) dose over 52 weeks: comparison of the SoC and BEL+SoC groups. Data are presented as mean (ꜱ.ᴅ.). *P*-values were derived using a Student's t-test. (**B**) Comparison of percentage of cases with GC dose reduction and GC-discontinuation status between the two groups using Pearson's chi-square test. Numbers represent percentages of all patients (%). (**C**) Comparison of glucocorticoid toxicity index between the two groups using Pearson's chi-square test. Numbers represent percentages of all patients (%). (**D**) Comparison of the rates of all adverse events (left) and incidence of ≥grade 2 infections as specified by the Common Terminology Criteria for Adverse Events (right) between the two groups using Pearson's chi-square test. Numbers represent percentages of all patients (%).

SELENA-SLEDAI trajectories were classified into four trajectory groups (Supplementary Fig. S4A, available at *Rheumatology* online). No significant differences were observed in the proportion of patients in any of the trajectory groups between the SoC and BEL+SoC groups (Supplementary Figs S4B and S6, Supplementary Table S6; available at *Rheumatology* online).

GC dose trajectories were classified into four trajectory groups: group 1, the GC dose was 0 mg/day at 0 weeks and was maintained; group 2, the mean GC dose was 3.6 mg/day at 0 weeks, decreased to 0 mg/day within 26 weeks and was maintained until 52 weeks; group 3, the GC dose was ∼5 mg/day at 0 weeks and slowly decreased over 52 weeks; and

**Fɪɢ. 3** Glucocorticoid dose trajectory group modelling for patients with SLE receiving SoC and BEL+SoC
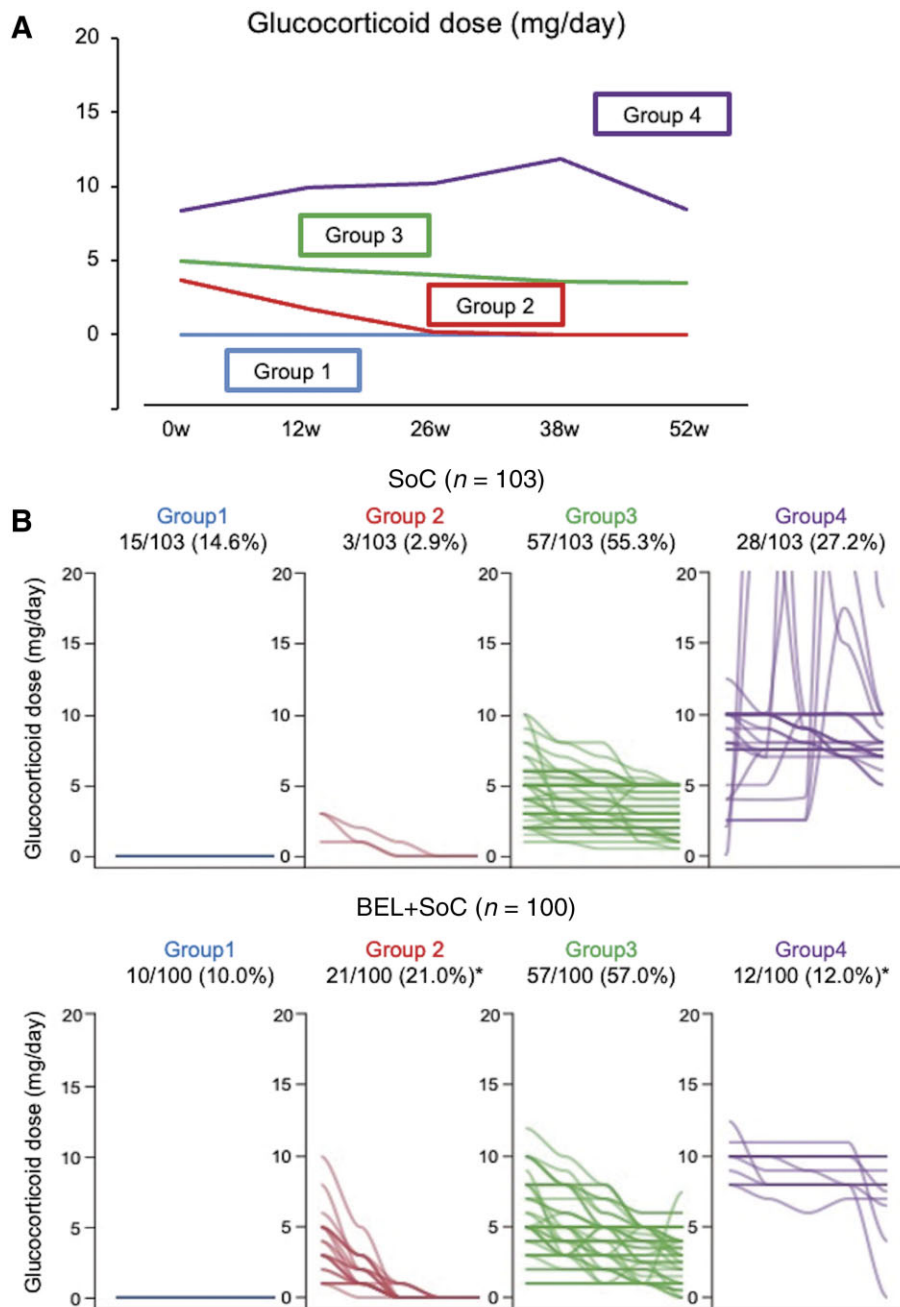


(A) Changes in glucocorticoid (GC) dose for the four patient trajectory groups. (B) Changes in GC dose for patients receiving SoC (upper) and BEL+SoC (lower) and the proportions of patients in each trajectory group. Groups 1, 2, 3 and 4 are indicated by the blue, red, green and purple lines, respectively. *$P<0.001$ *vs* SoC group according to Pearson's chi-square test.

group 4, the GC dose was ~8 mg/day at 0 weeks and increased after a relapse (Fig. 3A; Supplementary Table S7, available at *Rheumatology* online). The proportion of patients in group 2 (GC dose-tapering-discontinuation group) was significantly higher in the BEL+SoC group (21.0%) than in the SoC group (2.9%) ($P < 0.001$) (Fig. 3B; Supplementary Fig. S6, available at *Rheumatology* online). None of the patients in the GC dose-tapering-discontinuation group experienced relapse within 52 weeks. The proportion of patients in group 4 was significantly lower in the BEL+SoC group (12.0%) than in the SoC group (27.2%) ($P = 0.007$) (Fig. 3B, Supplementary Fig. S6, available at *Rheumatology* online).

TABLE 2 Factors for belonging to GC tapering-discontinuation group identified by univariable and multivariable logistic regression analyses in all patients and BEL+SoC group

| | All patients (n = 203) | | | | BEL+SoC (n = 100) | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariate analysis | | Multivariate analysis | | Univariate analysis | | Multivariate analysis | |
| | Odds ratio (95% CI) | P-value | Odds ratio (95% CI) | P-value | Odds ratio (95% CI) | P-value | Odds ratio (95% CI) | P-value |
| Age (years) | 0.98 (0.95, 1.01) | 0.267 | | | 0.98 (0.95, 1.02) | 0.258 | | |
| Gender, n (% female) | 0.69 (0.18, 2.56) | 0.576 | | | 0.49 (0.11, 2.16) | 0.366 | | |
| Disease duration (month) | 1.00 (0.99, 1.00) | 0.857 | | | 1.00 (0.99, 1.00) | 0.794 | | |
| Belimumab use | 8.86 (2.55, 30.78) | <0.001 | 12.41 (3.33, 46.26) | <0.001 | | | | |
| NPSLE | 2.20 (0.93, 5.19) | 0.073 | | | 0.48 (0.18, 1.31) | 0.154 | | |
| LN | 1.58 (0.67, 3.75) | 0.297 | | | 0.60 (0.23, 1.58) | 0.303 | | |
| Maintenance therapy duration (month) | 1.00 (0.99, 1.01) | 0.548 | 1.00 (0.99, 1.01) | 0.926 | 1.00 (0.99, 1.01) | 0.537 | 1.00 (0.99, 1.01) | 0.899 |
| Concomitant GC dose, mg/d, PSL equivalent | 0.87 (0.75, 1.00) | 0.050 | 0.81 (0.68, 0.97) | 0.007 | 0.85 (0.72, 0.99) | 0.046 | 0.81 (0.67, 0.99) | 0.027 |
| Number of concomitant immunosuppressant use | 1.33 (0.73, 2.41) | 0.347 | | | 1.28 (0.71, 2.30) | 0.445 | | |
| HCQ use | 1.22 (0.39, 3.78) | 0.736 | | | 2.45 (0.54, 11.3) | 0.245 | | |
| MMF use | 0.89 (0.31, 2.52) | 0.820 | | | 1.14 (0.37, 3.56) | 0.822 | | |
| AZA use | 1.59 (0.58, 4.33) | 0.363 | | | 1.19 (0.35, 4.13) | 0.779 | | |
| TAC use | 0.92 (0.29, 2.87) | 0.884 | | | 0.93 (0.24, 3.65) | 0.918 | | |
| CSA use | 2.23 (0.44, 11.43) | 0.335 | | | 8.21 (0.71, 95.36) | 0.092 | | |
| MTX use | 0.93 (0.20, 4.30) | 0.922 | | | 1.28 (0.24, 6.86) | 0.773 | | |
| MZR use | 0.93 (0.11, 7.73) | 0.946 | | | 1.00 (0.99, 1.01) | 0.994 | | |
| SLEDAI score | 0.80 (0.66, 0.98) | 0.112 | 0.73 (0.58, 0.92) | 0.010 | 0.79 (0.63, 0.99) | 0.043 | 0.73 (0.57, 0.94) | 0.015 |
| BILAG category At least A1 or B2, n (%) | 1.00 (0.99, 1.01) | 0.990 | | | 1.00 (0.99, 1.01) | 0.991 | | |
| SLICC Damage index | 0.58 (0.29, 1.14) | 0.113 | 0.72 (0.41, 1.25) | 0.926 | 0.72 (0.36, 1.45) | 0.319 | 0.63 (0.29, 1.37) | 0.243 |
| CH50 | 0.99 (0.97, 1.03) | 0.799 | | | 0.99 (0.96, 1.03) | 0.764 | | |
| Anti-ds DNA antibody | 0.80 (0.80, 1.01) | 0.053 | | | 0.92 (0.83, 1.02) | 0.103 | | |

BEL: belimumab; BILAG: British Isles Lupus Assessment Group Index; CH50: 50% haemolytic unit of complement; CSA: ciclosporin A; DNA: deoxyribonucleic acid; GC: glucocorticoid; MZR: mizoribine; SELENA-SLEDAI: Safety of Estrogens in Lupus Erythematosus National Assessment SLE Disease Activity Index; SoC: standard of care; TAC: tacrolimus; PSL: prednisolone.

## Factors associated with GC discontinuation in patients with SLE during maintenance therapy

Multivariate logistic regression analysis was performed to identify factors contributing to belonging to GC dose-tapering-discontinuation group. Univariate analysis was performed using explanatory variables of age, female sex, disease duration, BEL use, duration of maintenance therapy, concomitant GC dose, immunosuppressive use, number of concomitant immunosuppressive drugs, SELENA-SLEDAI score, at least one new BILAG or two new BILAG scores, SDI, CH50, anti-dsDNA antibody titre, and use of HCQ, MMF, AZA, CSA, tacrolimus (TAC), MTX and/or MZR. Multivariate logistic regression analysis was performed using BEL administration, duration of maintenance therapy, GC dose, SELENA-SLEDAI score and SDI as explanatory variables to identify factors associated with GC dose reduction. In the overall cohort, factors contributing to belonging to GC dose-tapering-discontinuation group were BEL administration (OR = 12.41, 95% CI: 3.33, 46.26, $P < 0.001$), low-dose GC (OR = 0.81, 95% CI: 0.68, 0.97, $P = 0.007$) and low SELENA-SLEDAI score (OR = 0.73, 95% CI: 0.58, 0.92, $P = 0.010$). Bootstrap forest analysis revealed that among the three factors associated contributing to belonging to GC dose-tapering-discontinuation group, BEL administration had the highest contribution degree (6.3) and contribution ratio (0.45).

Because BEL administration was the largest contributing factor to belonging to GC dose-tapering-discontinuation group, multivariate logistic regression analysis was performed only in the BEL+SoC group to identify factors associated with belonging to GC dose-tapering-discontinuation group. In both the univariate and multivariate analyses, low-dose GC (OR = 0.81, 95% CI: 0.67, 0.99, $P = 0.027$ in the multivariate analysis) and low SELENA-SLEDAI score (OR = 0.73, 95% CI: 0.57, 0.94, $P = 0.015$ in the multivariate analysis) were associated with belonging to GC dose-tapering-discontinuation group (Table 2, right). The cut-off scores for identifying patients in GC dose-tapering-discontinuation group were SELENA-SLEDAI score of 4 and GC dose of 4 mg/day (sensitivity = 0.76, specificity = 0.61, area under the curve = 0.71) (Supplementary Fig. S7, available at *Rheumatology* online).

Multivariate logistic regression analysis was performed to identify factors associated with GC discontinuation (patients with a GC dose of 0 mg at baseline were excluded) (Table 3). In the overall cohort, factors associated with GC discontinuation were BEL administration (OR = 12.96, 95% CI: 3.48, 48.26, $P < 0.001$), low-dose GC (OR = 0.73, 95% CI: 0.58, 0.89, $P = 0.002$) and low SDI (OR = 0.47, 95% CI: 0.22, 0.99, $P = 0.048$). In the BEL+SoC group, low-dose GC (OR = 0.76, 95% CI: 0.61, 0.94, $P = 0.013$ in the multivariate analysis) and low SELENA-SLEDAI score (OR = 0.76, 95% CI: 0.58, 0.99, $P = 0.046$ in the multivariate analysis) were associated with GC discontinuation by both the univariate and multivariate analyses (Table 3).

## Discussion

This study compared GC dose in patients with SLE during maintenance therapy at one year after treatment initiation between patients receiving SoC and those receiving BEL plus SoC after adjustment for selection bias using propensity score-based IPTW. The analysis revealed that BEL administration contributed to GC dose reduction. HCQ, a mainstay of SLE therapy, has been reported to be effective for reducing disease activity and relapse rate but has not been reported about reducing GC dose [26]. While various clinical studies have demonstrated that BEL is effective for preventing SLE relapse and organ damage and reducing GC doses, this study showed that BEL also exerted similar effects in the real-life clinical setting [4, 27–31]. Studies have indicated that serum BAFF concentration is higher in patients with SLE (even those with low disease activity) than in healthy controls [32, 33]. Accordingly, the present study demonstrated that BEL treatment significantly reduced GC dose by controlling disease activity in patients with SLE during maintenance therapy.

GMM analysis of GC dose trajectories revealed that GC dose decreased to 0 mg in the period from baseline to 26 weeks in a subset of patients (GC dose-tapering-discontinuation group). The proportion of patients in the GC dose-tapering-discontinuation group was higher in the BEL+SoC group than in the SoC group. Multivariate analysis and contribution analysis revealed that BEL administration was the factor most strongly associated with belonging to GC dose-tapering-discontinuation group. Similar results were obtained in the analysis of factors associated with GC discontinuation. Multivariate analysis of patients receiving BEL demonstrated that low SELENA-SLEDAI score and low GC dose at baseline were associated with belonging to GC dose-tapering-discontinuation group and GC discontinuation. In particular, patients with SLE with a SELENA-SLEDAI score ≤4 and GC dose ≤4 mg/day may be able to discontinue GC without relapse when receiving BEL during maintenance therapy. Because this study mainly included patients with SLE with very mild disease activity, tapering and discontinuation of GC might have been feasible. However, it has remained unclear whether GC can be discontinued in patients with SLE with mild disease activity. This study suggested that GC could be discontinued at a significantly higher frequency by introducing BEL to SoC than SoC alone in patients with SLE with mild disease activity. While the BeRLiSS (Belimumab in Real Life Setting Study) study suggested that BEL may be more effective particularly in patients with SLE with severe disease activity who start BEL treatment in the earlier stages or who have a low SDI score at the time of BEL introduction [8], the present study suggested that BEL might also be suitable for patients with a low SLEDAI score or patients treated with low-dose GC during maintenance therapy. Accordingly, BEL may be beneficial for treating SLE

TABLE 3 Factors for belonging to GC-discontinuation identified by univariable and multivariable logistic regression analyses in all patients and BEL+SoC group

| | All patients (*n* = 177) | | | | BEL+SoC (*n* = 90) | | | |
| | Univariate analysis | | Multivariate analysis | | Univariate analysis | | Multivariate analysis | |
| | Odds ratio (95% CI) | *P*-value | Odds ratio (95% CI) | *P*-value | Odds ratio (95% CI) | *P*-value | Odds ratio (95% CI | *P*-value |
|---|---|---|---|---|---|---|---|---|
| Age (years) | 0.98 (0.95, 1.01) | 0.116 | | | 0.97 (0.93, 1.01) | 0.054 | | |
| Gender, *n* (% female) | 0.84 (0.23, 3.09) | 0.791 | | | 0.48 (0.10, 2.32) | 0.362 | | |
| Disease duration (month) | 1.00 (0.99, 1.00) | 0.449 | | | 1.00 (0.99, 1.00) | 0.351 | | |
| Belimumab use | 11.1 (3.23, 38.18) | <0.001 | 12.96 (3.48, 48.26) | <0.001 | | | | |
| NPSLE | 1.92 (0.85, 4.33) | 0.116 | | | 1.90 (0.73, 4.94) | 0.186 | | |
| LN | 1.28 (0.57, 2.85) | 0.547 | | | 1.19 (0.47, 2.99) | 0.714 | | |
| Maintenance therapy duration (month) | 1.00 (0.99, 1.01) | 0.862 | 1.00 (0.99, 1.01) | 0.325 | 1.00 (0.99, 1.01) | 0.961 | 1.00 (0.99, 1.01) | 0.480 |
| Concomitant GC dose, mg/d, PSL equivalent | 0.79 (0.66, 0.93) | 0.006 | 0.73 (0.58, 0.89) | 0.002 | 0.80 (0.66, 0.96) | 0.020 | 0.76 (0.61, 0.94) | 0.013 |
| Number of concomitant immunosuppressant use | 1.21 (0.69, 2.12) | 0.504 | | | 1.16 (0.65, 2.07) | 0.604 | | |
| HCQ use | 1.22 (0.34, 4.43) | 0.765 | | | 0.61 (0.13, 2.77) | 0.523 | | |
| MMF use | 0.77 (0.29, 2.04) | 0.598 | | | 1.05 (0.36, 3.11) | 0.926 | | |
| AZA use | 1.58 (0.61, 4.10) | 0.350 | | | 1.23 (0.38, 3.97) | 0.733 | | |
| TAC use | 0.72 (0.23, 2.24) | 0.571 | | | 0.67 (0.17, 2.63) | 0.566 | | |
| CSA use | 1.83 (0.35, 9.58) | 0.473 | | | 5.57 (0.48, 64.32) | 0.169 | | |
| MTX use | 0.69 (0.15, 3.19) | 0.632 | | | 0.86 (0.16, 4.55) | 0.854 | | |
| MZR use | 1.83 (0.35, 9.58) | 0.473 | | | 1.31 (0.11, 15.15) | 0.828 | | |
| SLEDAI score | 0.92 (0.77, 1.09) | 0.331 | 0.85 (0.68, 1.06) | 0.147 | 0.78 (0.62, 0.99) | 0.040 | 0.76 (0.58, 0.99) | 0.046 |
| BILAG category At least A1 or B2, *n* (%) | 1.00 (0.99, 1.01) | 0.991 | | | 1.00 (0.99, 1.01) | 0.994 | | |
| SLICC Damage index | 0.44 (0.21, 0.89) | 0.023 | 0.47 (0.22, 0.99) | 0.048 | 0.54 (0.26, 1.15) | 0.109 | 0.46 (0.20, 1.05) | 0.065 |
| CH50 | 1.00 (0.97, 1.03) | 0.998 | | | 1.00 (0.97, 1.04) | 0.936 | | |
| Anti-ds DNA antibody | 0.95 (0.89, 1.02) | 0.147 | | | 0.96 (0.91, 1.02) | 0.191 | | |

BEL: belimumab; BILAG: British Isles Lupus Assessment Group Index; CH50: 50% haemolytic unit of complement; CSA: ciclosporin A; DNA: deoxyribonucleic acid; GC: glucocorticoid; MZR: mizoribine; SELENA-SLEDAI: Safety of Estrogens in Lupus Erythematosus National Assessment SLE Disease Activity Index; SoC: standard of care; TAC: tacrolimus; PSL: prednisolone.

according to the treat-to-target [16] strategy for reducing the toxicity of nonspecific drugs over the long term.

In this study, BEL was effective for reducing GC dose, and the relapse rate was lower in the BEL+SoC group than in the SoC group. Given the association between increased serum BAFF and relapse of SLE disease activity [34], BEL may be effective for preventing relapse. In addition, the relapse rate of LN was lower in the BEL+SoC group than in the SoC group, which could be underpinned by the increased BAFF expression in patients with LN [35–38]. The current findings support the potential of BEL in preventing relapse of LN in accordance with the BLISS-LN trial [39], which reported the effectiveness of BEL in remission induction of LN. Furthermore, our study demonstrated that BEL plus SoC contributed more to the prevention of organ damage compared with SoC alone. We hypothesize that BEL was effective in decreasing GTI and preventing organ damage by reducing GC dose and preventing relapse, thereby resulting in a decrease in the SDI.

This study also demonstrated that the incidence of adverse events was lower in the BEL+SoC group than in the SoC group. A significant reduction in GC dose with BEL treatment may have contributed to the decrease in the incidence of adverse events, including infections. Although the number of patients with successful tapering of immunosuppressive drug doses was larger in the BEL+SoC group than in the SoC group, no statistically significant difference was observed before and after adjustment using propensity score-based inverse probability of treatment weighting (IPTW) [before IPTW adjustment: SoC *vs* BEL+SoC: 9.7% (10/103) *vs* 13.0% (13/100), $P = 0.4595$; after IPTW adjustment: SoC *vs* BEL+SoC: 14.7% (14/94) *vs* 23.3% (26/110), $P = 0.0811$]. Only one patient discontinued BEL owing to drug eruption, and the continuation rate of BEL was 99%. Among patients ($n = 22$) in the BEL+SoC group that did not reduce GC dose, only one patient developed CTCAE grade 2 infectious enteritis, suggesting that BEL was effective in preventing adverse events via GC dose reduction, and BEL itself had a high safety profile.

This study had some limitations. First, although the selection bias was minimized by adjusting for differences in baseline characteristics using propensity score-based IPTW, unidentified confounding factors may not have been controlled for. Second, the results may have been affected by the difference in the era between the SoC and BEL+SoC groups. However, no new drugs became available for SLE treatment in Japan during the study period from December 2017 (when BEL became available for SLE treatment) to February 2020; hence, the potential effects of the different era would have been small.

The study participants comprised patients with SLE receiving GC $\leq 0.2$ mg/kg/day and with a SELENA-SLEDAI score $<10$ (mean SELENA-SLEDAI score of $\sim 3$). Our analysis indicated that BEL plus SoC was more effective than SoC alone in preventing relapse, reducing

GC dose and preventing the progression of organ damage, thus highlighting the suitability of BEL for treating patients with SLE with mild to moderate disease activity. Future randomized prospective comparative trials are warranted to confirm our findings.

In summary, our study demonstrated that BEL was effective in reducing GC, preventing relapse of disease activity and preventing the progression of organ damage in patients with SLE during maintenance therapy. Our findings suggest that BEL administration in patients with SLE with a SELENA-SLEDAI score $\leq 4$ and GC dose $\leq 4$ mg/day may enable a reduction in GC dose and GC discontinuation without relapse.

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## Data availability statement

Data cannot be shared for ethical/privacy reasons.

## Supplementary data

Supplementary data are available at *Rheumatology* online.

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