Title:

Distinct immune networks stratify organ involvement and response to B cell targeted therapies in systemic lupus erythematosus

Authors

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Background

We have recently completed the BEAT-lupus trial comparing belimumab vs placebo, both after rituximab, in systemic lupus erythematosus (SLE) (1). There is a clear unmet need for biomarkers that could guide precision targeting of advanced therapies for this heterogenous disease.

Objectives

To identify biomarkers of clinical response to belimumab after rituximab in the BEAT-lupus trial.

Methods

We constructed a model utilising a range of clinical, coupled with routine and exploratory laboratory data, from the BEAT-lupus trial to identify variables at baseline (screening) that could predict a major clinical response (MCR, defined as reduction to BILAG C in all domains, steroid dose of ≤7.5mg/day & SLEDAI≤2, without anti-dsDNA antibody component) at 52 weeks. Relevant serum autoantibodies and cytokines were assayed by ELISA/Simoa, and interferon signatures and BAFF expression measured by RT-PCR. A linear mixed model was applied to longitudinal data collected during the trial stratified by treatment and clinical response.

Results

A major clinical response (MCR) was achieved in 48% (10 responders, 11 non-responders) of patients who received belimumab after rituximab compared to 35% (8 responders, 15 non-responders) in the placebo group (i.e. rituximab alone), added to tapered standard of care, at 52 weeks. Baseline serum IgA2 anti-dsDNA antibody levels emerged as the only positive predictor of attaining MCR in belimumab treated patients (AUROC 0.8, 95% confidence interval [CI] 0.7-1.0), but negatively predicted MCR in the placebo arm (AUROC 0.2, CI 0.1-0.4). At baseline 77% and 85% of patients were positive for serum IgA2 anti-dsDNA antibodies in belimumab and placebo arms respectively, which reduced to 30% at 52 weeks in the belimumab group but remained unchanged with placebo (Fisher exact test, p=0.007). In striking contrast, the percentage of patients who remained IgG anti-dsDNA antibody positive from baseline to 52 weeks were similar between the belimumab and placebo group, despite the serum levels significantly falling in the belimumab group (1). A significant reduction in serum IgA2 anti-dsDNA antibody levels at 24 and 52 weeks from baseline was only observed in belimumab responders (Figure 1).

The number of circulating IgA2-secreting (but not total) plasmablasts (p=0.032) and T follicular helper cells (p=0.031) were significantly reduced at 52 weeks in the belimumab treated arm compared to placebo. Elevated serum IgA2 anti-dsDNA antibody levels were also associated with active renal disease (odds ratio, OR 3.2, CI 1.7-5.8, p<0.001). In contrast, serum IgA1 anti-dsDNA antibody (OR 1.3, CI 1.0-1.7, p=0.042) and interferon-alpha levels (OR 1.4, CI 1.0-2.0, p=0.041), and interferon transcriptional signature (OR 1.1, CI 1.0-1.3, p=0.027), were significantly associated with mucocutaneous disease activity but did not predict response to B cell targeted

therapy. Patients with a high baseline serum IL-6 were less likely to achieve an MCR irrespective of therapy (OR 0.4, CI 0.2-0.9, p=0.033). Serum IgA2 (p=0.001) and IgA1 (p=0.038) anti-dsDNA antibody levels were significantly higher in active renal and mucocutaneous disease respectively in an independent cross-sectional lupus cohort.

Conclusions

IgA2 anti-DNA autoantibodies are biomarkers of renal involvement and response to belimumab after rituximab in systemic lupus erythematosus. Our study reveals distinct molecular networks associated with renal and mucocutaneous involvement, and response to B cell targeted therapies, which could guide precision targeting of current therapies for this heterogenous disease.

References:

1. Shipa M, et al. Annals of Internal Medicine. 2021;174:1647-57.

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Conflict of interest statement

MRE has received grant/research support from GSK. MRE and CG have been members of the speakers' bureau for GSK and have received consultancy fees for attending GSK advisory boards. CG also reports personal fees for honoraria from consultancy work from the Center for Disease Control and Prevention, AbbVie, Amgen, Astra-Zeneca, EMD Serono, MGP, Sanofi and UCB, personal fees for speakers bureau from UCB and an educational grant from UCB to Sandwell and West Birmingham Hospitals NHS Trust that supported her research work.

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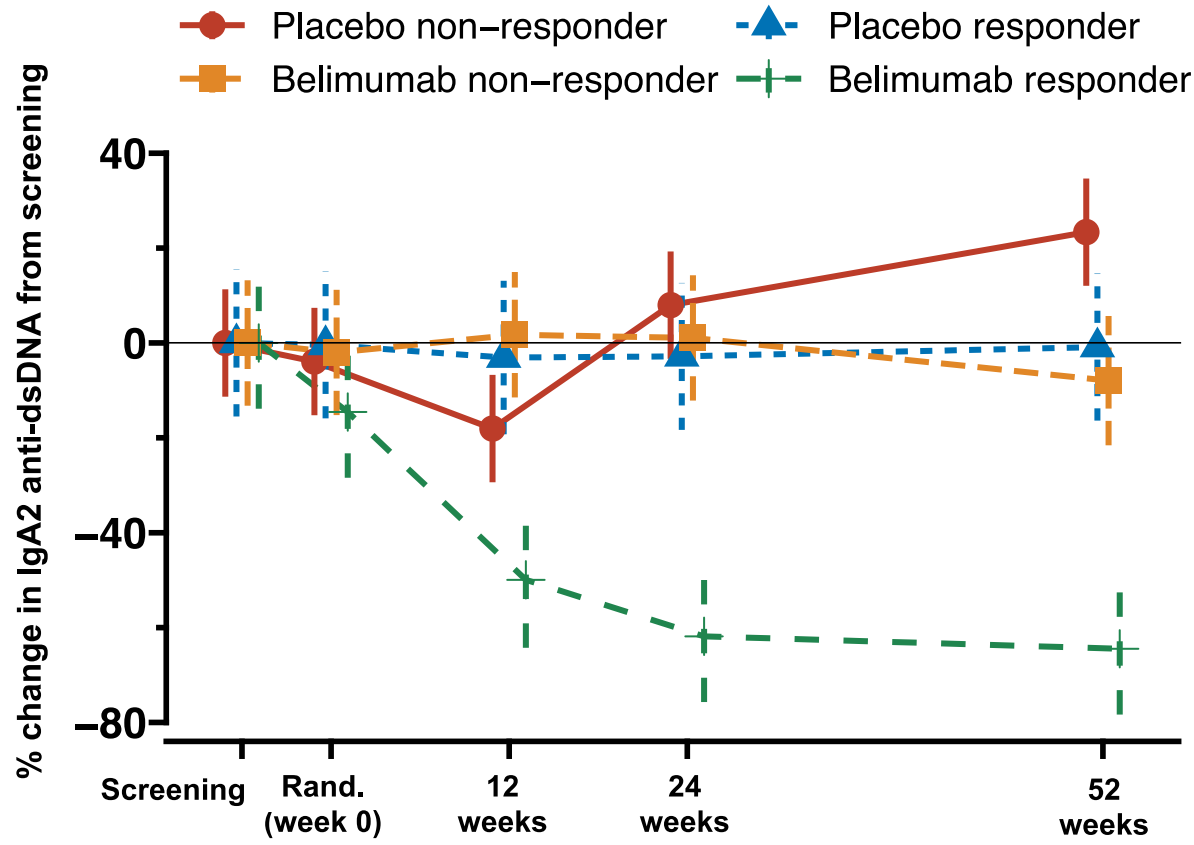

Number of patients

Placebo-NR	15	15	15	15	15
Placebo-R	8	8	8	8	8
Belimumab-NR	11	11	11	11	10
Belimumab-R	10	10	10	10	10

	Estimated difference – Mean in OD (95% CI) at 24 weeks	*Estimated difference – Mean in OD (95% CI) at 52 weeks*
Placebo responder vs non-responder	-0.09 (-0.23 to 0.05) p = 0.199	-0.19 (-0.33 to -0.05) p = 0.007
Belimumab responder vs non-responder	-0.63 (-0.90 to -0.36) p < 0.001	-0.55 (-0.84 to -0.27) p <0.001

Figure 1. Percentage change in serum IgA2 anti-dsDNA antibody levels through to 52 weeks stratified by clinical response to belimumab (after rituximab) and placebo (after rituximab) at 52 weeks.