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Smoking and pre-existing organ damage reduce the efficacy of belimumab in systemic lupus erythematosus

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ABSTRACT

Objectives: Belimumab is the first biologic drug approved for Systemic Lupus Erythematosus (SLE). Here, we aimed to investigate the effects of belimumab on clinical and serologic outcomes, and sought to identify predictors of treatment response in three Swedish real-life settings.

Methods: Fifty-eight patients were enrolled at initiation of belimumab and followed longitudinally for up to 53 months. Surveillance outcomes included the SLE Disease Activity Index 2000 (SLEDAI-2K), 100 mm Visual Analogue Scales for Physician's Global Assessment (PGA), fatigue, pain and general health, and the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI). Assessment of treatment response included the SLE responder index (SRI). B lymphocyte stimulator (BLyS) levels were determined using ELISA.

Results: SLEDAI-2K (median baseline score: 8.0; IQR: 4.0–13.8), PGA and corticosteroid use decreased during therapy, and patients reported improvements on fatigue, pain, and general health ($p < 0.0001$ for all). SDI scores remained stable ($p = 0.08$). Patients with baseline SDI scores >1 showed decreased probability and prolonged time to attain SRI response (HR: 0.449; 95% CI: 0.208–0.967), as did current smokers compared with non-smokers (HR: 0.103; 95% CI: 0.025–0.427). In contrast, baseline BLyS levels ≥ 1.2 ng/mL predicted increased probability and shorter time to attain SRI response (HR: 2.566; 95% CI: 1.222–5.387).

Conclusions: Disease activity and corticosteroid usage decreased, patient-reported outcomes improved, and no significant organ damage was accrued during follow-up. Smoking and organ damage predicted reduced treatment efficacy. These findings might contribute to a better selection of patients who are likely to benefit from belimumab.

1. Introduction

Despite pharmacological advances and increased survival rates [1–3], systemic lupus erythematosus (SLE) is still associated with premature mortality [4–9]. The development of new therapies is therefore of vital importance.

Belimumab is the first biologic agent approved for the treatment of SLE [10]. It is an IgG1-λ monoclonal antibody that specifically binds to soluble B lymphocyte stimulator (BLyS), also known as B-cell activating factor belonging to the Tumor Necrosis Factor (TNF) family (BAFF). BLyS and a proliferation-inducing ligand (APRIL), another member of the TNF ligand superfamily, are pivotal molecules for B cell homeostasis and are implicated in the pathogenesis of SLE [11–13].

The efficacy of belimumab in SLE was demonstrated in two phase III randomised clinical trials (RCTs) [14,15], with serologically active patients showing better responses [16]. Post-hoc analyses have facilitated the derivation of predictors of response [16] and evaluation of the efficacy of belimumab in organ-specific manifestations, such as lupus nephritis (LN) [17], but patient groups with severe disease phenotypes were excluded from these trials. In this real-life study, we aimed to investigate the effects of belimumab on clinical and serologic outcomes, and also sought to identify baseline predictors of treatment response.

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2. Material and methods

2.1. Patients

Fifty-eight patients with moderately active SLE despite standard of care treatment from the Karolinska ($n = 30$), Skåne ($n = 19$) and Linköping ($n = 9$) University Hospitals were enrolled in this prospective study between 2011 and 2015. The patients were followed longitudinally with visits at baseline and at months 3, 6, 12, 24, 36 and 48, or more frequently if clinically indicated. All patients fulfilled the 1982 revised criteria [18] and/or the Systemic Lupus International Collaborating Clinics criteria [19] for classification of SLE. Baseline characteristics are presented in Table 1.

Written informed consent in accordance with the ethical principles of the declaration of Helsinki was obtained from all patients. The study protocol was approved by the regional ethics review boards at Karolinska Institutet, Lund University, and Linköping University.

Table 1
Baseline characteristics.

Sex; $n = 58$	
Female; *n* (%)	53 (91.4%)
Ethnicity; $n = 58$	
Caucasian; *n* (%)	55 (94.8%)
African; *n* (%)	2 (3.4%)
African American; *n* (%)	1 (1.7%)
Age (years); M (IQR); $n = 58$	41.3 (31.2–51.0)
SLE disease duration (years); M (IQR); $n = 58$	7.8 (4.3–14.2)
SLEDAI-2K; M (IQR); $n = 58$	8.0 (4.0–14.0)
SLAM-R; M (IQR); $n = 30$	13.5 (9.8–17.5)
PGA (100 mm VAS); M (IQR); $n = 57$	50.0 (50.0–70.5)
SDI; M (IQR); $n = 58$	1.0 (0.0–2.0)
Pain (100 mm VAS); M (IQR); $n = 56$	51.5 (31.5–70.8)
Fatigue (100 mm VAS); M (IQR); $n = 56$	71.0 (35.5–83.8)
General health (100 mm VAS); M (IQR); $n = 56$	55.5 (36.0–73.0)
Stanford HAQ functional disability index; M (IQR); $n = 38$	0.50 (0.22–0.88)
EQ-5D health questionnaire; M (IQR); $n = 56$	0.69 (0.59–0.80)
Number of DMARDs tested until baseline[a]; M (IQR); $n = 58$	3 (1–4)
Number of DMARDs at baseline[a]; M (IQR); $n = 58$	1 (0–1)
Azathioprine; *n* (%)	18 (31.0%)
Mycophenolate[b]; *n* (%)	10 (17.2%)
Methotrexate; *n* (%)	8 (13.8%)
Cyclosporine; *n* (%)	2 (3.4%)
Antimalarials at baseline; *n* (%)	44 (75.9%)
Corticosteroids at baseline; *n* (%)	54 (93.1%)
Prednisone equivalent dose at baseline (mg/day); M (IQR); $n = 58$	10.0 (7.5–15.0)
Previous exposure to corticosteroids (years); M (IQR); $n = 40$	7.3 (4.4–12.0)
Previous mean prednisone equivalent (mg/day); M (IQR); $n = 40$	10.0 (7.8–12.5)
Reason for belimumab	
Arthritis; *n* (%)	27 (48.2%)
Mucocutaneous manifestations; *n* (%)	27 (48.2%)
Hematologic manifestations; *n* (%)	10 (17.5%)
Lupus nephritis; *n* (%)	7 (12.3%)
Neuropsychiatric lupus; *n* (%)	4 (7.0%)
Serositis; *n* (%)	3 (5.3%)
General manifestations[c]; *n* (%)	2 (3.5%)
Serologic activity; *n* (%)	1 (1.8%)
Respiratory[d]; *n* (%)	1 (1.8%)
Smoking status; $n = 57$	
Current smokers; *n* (%)	7 (12.3%)
Former smokers; *n* (%)	20 (35.1%)
Never smokers; *n* (%)	30 (52.6%)

SLE: systemic lupus erythematosus; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; SLAM-R: Systemic Lupus Activity Measure-Revised; PGA: Physician's Global Assessment; SDI: Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index; HAQ: Health Assessment Questionnaire; EQ-5D: EuroQol Research Foundation 5 Dimension health questionnaire; DMARDs: disease-modifying antirheumatic drugs; M: median; IQR: interquartile range.

[a] Excluding antimalarials.

[b] Mycophenolate mofetil ($n = 9$) and mycophanolate sodium ($n = 1$).

[c] Fatigue.

[d] Lung bleeding prophylaxis.

2.2. Evaluation of disease activity, organ damage and quality of life

Disease activity was assessed using the SLE Disease Activity Index (SLEDAI) 2000 (SLEDAI-2K) [20], Systemic Lupus Activity Measure-Revised (SLAM-R) [21,22], British Isles Lupus Assessment Group (BILAG) index [23,24], Physician's Global Assessment (PGA) on 100 mm visual analogue scales (VAS) [25], and the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA)-SLEDAI PGA (scored 0–3) [26]. We also used the modified SLEDAI-2K (mSLEDAI-2K), a variant of the SLEDAI-2K in which the serologic items (anti-double stranded (ds)DNA and complement levels) are excluded [27]. Organ damage was evaluated using the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) [28]. Quality of Life (QoL) was evaluated using patient reports for pain, fatigue and general health on 100 mm VAS. Global health was determined by the EuroQoL Research Foundation [29] 5 Dimension (EQ-5D) health questionnaire, scored according to the UK tariff [30]. Functional status was assessed using the Stanford Health Assessment Questionnaire (HAQ) functional disability index [31].

Urinary status was evaluated using urine test strips and urinary sediment. Proteinuria was estimated using the 24-hour urine albumin excretion (g/day). Renal biopsies were assessed using the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification system for LN [32].

2.3. Evaluation of serologic activity

Titres of anti-dsDNA were determined using the *Crithidia luciliae* substrate based immunofluorescence technique (CLIFT) [33] at each visit in the local laboratories of the three academic centres. Serum anti-dsDNA levels were also determined simultaneously from longitudinally collected samples by addressable laser bead immunoassay (ALBIA), using the Connective profile MX 117 FIDIS™ kit (Theradiag, Paris, France). Complement protein C3 (reference range 0.67–1.29 g/L) and complement protein C4 (reference range 0.13–0.32 g/L) levels were determined using nephelometry.

Quantikine enzyme-linked immunosorbent assay (ELISA; R&D Systems, Bio-Techne, Minneapolis, USA) was used for detection of BLyS. Concentrations of circulating APRIL were determined using Platinum ELISA (Affymetrix, eBioscience, Vienna, Austria).

2.4. Definitions

Response to treatment was defined in line with the SLE responder index (SRI) [34] as a reduction of ≥4 points in SLEDAI-2K, no new BILAG A or >1 new BILAG B, and no deterioration in PGA by ≥30 mm. Low disease activity was defined as a SLEDAI-2K ≤4, no activity in major organ systems, no haemolytic anaemia or gastrointestinal activity, no new SLE activity, a SELENA-SLEDAI PGA ≤1, a prednisone equivalent dose ≤7.5 mg/day, and well tolerated doses of immunosuppressive drugs and approved biologic agents, according to the Lupus Low Disease Activity State (LLDAS) [35]. Attainment of mSLEDAI-2K = 0 was also analysed as a treatment response outcome.

2.5. Statistics

For comparisons within related samples, we used the non-parametric Wilcoxon signed-rank test. For comparisons between independent samples, we used the Mann-Whitney *U* test.

Linear mixed models for repeated measurements were used to investigate treatment outcomes, which were included in the model as the dependent variable. Patient visits were included as repeated and fixed effects, and patients as a random effect. The models were adjusted for age, sex, ethnicity, and clinical practice setting. Cox regression models were used for identification of baseline predictors of treatment response.