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Impact of belimumab on the utility of serological markers for assessing systemic lupus erythematosus activity

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ABSTRACT

Objectives To evaluate the dynamics of C3, C4 and anti-dsDNA antibody levels and their association with clinical activity and flares in patients with systemic lupus erythematosus (SLE) treated with belimumab (BEL).

Methods Retrospective longitudinal cohort study from the BELILES-GEAS registry. Serological markers were assessed at the time of SLE diagnosis, at baseline, at each follow-up visit (months 3, 6, 12, 18, and 24 after treatment initiation) and during disease flares.

Results A total of 371 patients were included, with a median drug exposure of 13.2 months. At baseline, 70.1% of patients were seropositive. SLE Disease Activity Index 2000 (SLEDAI-2K) and cSLEDAI scores and prednisone doses decreased significantly over time, whereas serum C3 and C4 levels, anti-dsDNA positivity and immunosuppressant use remained stable. Among 95 (25.6%) patients who experienced 139 (14.5%) flares, longitudinal analysis adjusted by immunosuppressant use and prednisone dose revealed no association between flare occurrence and low C3 or C4, whereas anti-dsDNA antibody positivity was (C3 OR=1.31, 95% CI 0.82 to 2.09; C4 OR=1.08, 95% CI 0.62 to 1.86, and anti-dsDNA OR=1.81, 95% CI 1.09 to 3.01, respectively). When stratified by flare severity, low C3 levels showed a borderline association with moderate-to-severe flares (OR=1.82, 95% CI 0.99 to 3.31), while no significant associations were observed for C4 or for mild flares. There was no association between serum level of C3 or C4 and cSLEDAI. The flare-discriminative performance of SLEDAI-2K and cSLEDAI was similar (AUC-ROCs 0.779 vs 0.781, p=0.88).

Conclusion In SLE patients treated with BEL, the clinical utility of serological markers appears dissociated from disease activity. While C3 and C4 levels were not clearly related to disease activity or flares, low C3 levels showed a borderline association with moderate-to-severe flares, and anti-dsDNA positivity remained associated with increased flare risk, supporting a clinical assessment–driven approach with complementary use of anti-dsDNA.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Serum complement levels (C3 and C4) and anti-dsDNA antibodies are widely used biomarkers for assessing disease activity and flare risk in systemic lupus erythematosus (SLE).

⇒ Clinical trials of belimumab (BEL) have shown improvements in both clinical outcomes and serological markers; however, the clinical relevance of serological normalisation in routine clinical practice, particularly under BLyS inhibition, remains controversial.

WHAT THIS STUDY ADDS

⇒ In a large multicentre real-world cohort of SLE patients treated with BEL, serum C3 and C4 levels were not associated with clinical disease activity or overall flare occurrence.

⇒ However, low C3 levels showed a borderline association with moderate-to-severe flares, suggesting potential relevance in the context of severe immune activation and disease activity.

⇒ In contrast, anti-dsDNA antibody positivity remained independently associated with an increased risk of flares.

⇒ The inclusion of serological markers did not improve the ability of the SLE Disease Activity Index 2000 to discriminate flares compared with the serology, excluding clinical SLEDAI.

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HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings support a shift towards prioritising clinical assessment over complement levels when monitoring disease activity in SLE patients receiving BEL, although C3 hypocomplementaemia may warrant closer attention in patients presenting with moderate-to-severe flares.

⇒ Anti-dsDNA antibody status may provide complementary prognostic information, particularly in selected high-risk patient subgroups.

⇒ The results contribute to the ongoing debate on treat-to-target strategies in SLE and question the role of serological normalisation as an independent therapeutic objective in patients treated with BEL.

INTRODUCTION

Systemic lupus erythematosus (SLE) is the prototypical multisystem autoimmune disease.[1 2] Its physiopathology is extremely complex, involving nearly all components of the immune system, which accounts for the immunological and clinical heterogeneity of the disease. Despite significant advances in the understanding of its mechanisms, particularly in the era of targeted therapies and monoclonal antibodies, the follow-up, monitoring and prognosis of patients with SLE still rely primarily on clinical findings supported by classical serological and biochemical parameters.[1–5]

Among the latter, serum complement factors and anti-double-stranded DNA (anti-dsDNA) antibodies remain the only markers consistently accepted for this purpose.[1 2 5] These parameters, together with a detailed evaluation of the clinical and organ-specific involvement, are integrated into standardised assessment tools such as the SLE Disease Activity Index 2000 (SLEDAI-2K) or the British Isles Lupus Assessment Group (BILAG) index.[6–8] These scores are essential for evaluating disease activity and guiding treatment, as reflected in the lupus low disease activity state (LLDAS), the DORIS remission criteria and the European League Against Rheumatology (EULAR) recommendations for SLE management.[9 10]

Nonetheless, serum C3 and C4 factors and anti-dsDNA antibodies are not always reliable indicators of clinical disease activity. In fact, their relevance guiding therapeutic decisions, and whether they should be included in treatment targets, is currently under debate.[11 12] Consequently, some authors advocate for clinical assessment and monitoring based solely on clinical parameters, as in the clinical SLEDAI, with these biomarkers serving as supportive tools rather than as definitive indicators of disease activity.[4 9 10]

Belimumab (BEL) is a human monoclonal antibody directed to B-lymphocyte stimulator (BLyS), also known as BAFF (B-cell activating factor).[13] BLyS plays a central role in B-cell proliferation, maturation and differentiation, particularly in autoreactive B cells. By blocking the interaction between soluble human BLyS and B-lymphocyte receptors, BEL inhibits B-cell-mediated immunity, a key mechanism in the pathophysiology of SLE.[5] Since the first studies conducted in the BLISS trials, numerous reports have confirmed the short and long-term benefit of BEL in SLE including lupus nephritis.[14–17] These benefits include decreasing clinical activity, preventing flares, minimising organ damage and reducing steroid use, all with a favourable safety profile.[17–22] Consequently, the most recent EULAR recommendations positioned BEL as a pivotal treatment in the management of the disease.[10]

From an immunological point of view, BEL rapidly blocks B-cell hyperactivity, leading to a decrease in CD19+ and naive B-cells, along with an increase in switched memory B cells.[23] This modulation of humoral immunity, partly responsible for its favourable safety profile, results in reduced production of anti-dsDNA antibodies by autoreactive B-cells and, consequently, less consumption of serum C3 and C4.[13] Therefore, the reduced disease activity and flare severity observed in patients treated with BEL often parallels a decrease in serological and immunological activity.[13 17 24] Indeed, earlier studies have proved that anti-dsDNA positivity, low C3/C4 levels and higher baseline clinical activity are predictors of a greater reduction in SLE activity and flare risk in patients receiving BEL therapy.[24] However, despite their widespread use, the clinical utility of traditional serological markers for assessing disease activity and predicting flares in patients receiving BEL remains uncertain, as BLyS inhibition may directly modify their levels independently of underlying clinical disease activity through its intrinsic effects on B-cell activation and autoantibody production.[12 18 23 24]

Based on this background, we hypothesised that BEL treatment may dissociate the behaviour of serological markers from clinical disease activity, thereby limiting their utility as biomarkers for monitoring disease activity and predicting flares. Accordingly, the aim of this study is to analyse the dynamics of serum C3, C4 and anti-dsDNA antibodies in SLE patients treated with BEL and to evaluate their association with clinical activity and the flare occurrence.

MATERIALS AND METHODS

A longitudinal multicentre, retrospective cohort study was conducted using data from the BELILES-GEAS registry. This registry includes patients with SLE, classified according to the 2019 EULAR/ACR criteria,[25] in the Internal Medicine Departments of 36 Spanish hospitals belonging to the Group of Systemic Autoimmune Diseases (GEAS) of the Spanish Society of Internal Medicine. All eligibility criteria were defined at the beginning of the study population description. Specifically, both intravenous and subcutaneous formulations of BEL were included; no specific age restrictions beyond adulthood (≥18 years) were applied; and previous or concomitant therapies, including B-cell–depleting treatments, were not considered exclusion criteria. Patients could be included in the registry from 2013. Demographic, clinical, laboratory and disease activity data were collected from the initiation of BEL treatment at predefined follow-up time points (3, 6, 12, 18 and 24 months) and at the time of disease flare or treatment withdrawal. This study was approved by the Institutional Review

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Board at the Hospital Clinic, Barcelona (protocol code HCB/2020/0756, approved on 29 December 2020). In addition, all participating hospitals obtained local Ethics Committee approval.

Clinical activity, SLE flare and other endpoints

Chronic disease was defined as persistent clinical activity during the follow-up period prior to BEL initiation, whereas relapsing-remitting disease was characterised by the occurrence of flares alternating with phases of clinical remission.

An SLE flare was defined as the onset or worsening of SLE signs or symptoms in any organ or system attributed to disease activity, leading to a change in the physician's therapeutic approach or in the patient's baseline treatment. This included modification or escalation of immunosuppressive therapy, an increase in baseline prednisone dose, or the use of methylprednisolone pulses due to new disease activity rather than previously uncontrolled disease. Minor treatment adjustments, such as the use of non-steroidal anti-inflammatory drugs alone, were not considered flares. No predefined threshold for prednisone increase was applied; instead, treatment changes were based on the treating physician's clinical judgement.

Clinical activity at each visit or flare was evaluated by the SLEDAI-2K.[6] Mild activity or flare was defined as a SLEDAI-2K<6, while moderate-to-severe activity or flare was defined as a score ≥6. We constructed a variable termed clinical SLEDAI (cSLEDAI), which includes only the clinical domains of the SLEDAI-2K, excluding serum C3/C4 levels and anti-dsDNA antibodies. Organ involvement at disease onset, baseline, during follow-up and at the time of flares was categorised according to the 2019 EULAR/ACR classification criteria.[25]

The Systemic Lupus International Collaborating Clinics/American College (SLICC/ACR) Damage Index for SLE was recorded at baseline, along with the presence of related conditions such as Sjögren's disease or antiphospholipid syndrome, based on their respective criteria.[26–28]

Serological markers

Baseline antibody status throughout the disease course—including anti-Sm, anti-Ro, anti-La, anti-RNP, anticardiolipin, anti-beta-2 glycoprotein I, lupus anticoagulant and rheumatoid factor—was determined according to each centre's cut-off values. Serum levels of C3 and C4, as well as anti–dsDNA antibody status, were assessed at the time of SLE diagnosis, at baseline and at each follow-up visit or disease flare. Laboratory measurements were performed locally at each participating centre using routine clinical assays (eg, nephelometry for complement fractions and ELISA or CLIA for anti–dsDNA antibodies), with centre-specific reference ranges and cut-offs.

To ensure comparability across centres, units for C3 and C4 were standardised, and values were reviewed and harmonised by categorising them relative to local reference ranges (ie, low/normal). Given the heterogeneity in assay methods and the lack of standardised quantitative anti-dsDNA measurements across centres, anti-dsDNA antibodies were analysed as a qualitative variable (positive vs negative/normal). Patients were considered seropositive if any of these markers were abnormal according to local reference ranges.

Statistical analysis

Descriptive statistics are presented as means and SD or medians with 25 and 75 percentiles (p25; p75) or IQR for continuous variables. Categorical variables were reported as frequencies (percentages). The contrast of hypothesis between groups was tested using the Pearson χ^2 for categorical variables or Student's t/Mann-Whitney U tests for numerical, as appropriate.

First, we analysed the dynamics of serum C3, C4 and anti-dsDNA antibodies positivity, disease activity scores, prednisone dose and immunosuppressant use over a 2-year period following BEL initiation, at fixed intervals (3-6-12-18-24 months). Random-effects regression models were used to evaluate trends during this period. The models included the corresponding baseline scores as covariates to adjust for pre-existing differences between patients and follow-up time points as a categorical factor to estimate the trajectory of changes across assessments visits. The random-effects specification was chosen to account for within-subject correlation across repeated measurements while allowing for individual-level random intercepts. Predicted marginal means at each follow-up visit were estimated, adjusting for baseline values, and were graphically displayed with 95% CIs over the course of the follow-up period.

Second, to evaluate the association between serum C3, C4 and anti-dsDNA positivity and the risk of flares during follow-up, different multilevel mixed-effects logistic regression models were fitted, with repeated observations over time at the patient level. Flares were additionally categorised as mild (SLEDAI<6) or moderate-to-severe (SLEDAI≥6). Fixed effects included the corresponding biomarker levels, immunosuppressant use and prednisone dose, while a random intercept was specified at the centre level to account for between-centre heterogeneity in baseline risk. The OR with the corresponding 95% CI were estimated as the effect sizes. For serum C3/C4, both quantitative and qualitative measures (normal vs below normal range) were performed. For anti-dsDNA antibodies, only qualitative association was evaluated (negative vs positive). Missing data were handled via complete case analysis; no data imputation was performed.

Third, the longitudinal relationship between cSLEDAI and serum C3 and C4 levels was assessed using random-effects linear regression models. The outcome variable was the cSLEDAI score at each follow-up time point, and the predictors were serum C3 and C4 levels measured at the corresponding visits. The random-effects specification was selected to account for the within-subject correlation inherent in repeated measurements over

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time, while allowing for unequally spaced time intervals across individuals.

Fourth, the ability of the SLEDAI-2K and cSLEDAI to discriminate flares was evaluated following an approach based on the area under the curve (AUC)—'receiver operating characteristic'—ROC. A value of AUC-ROC of 0.5 indicates random discrimination, and a value of 1 indicates perfect discrimination. A model with an AUC-ROC roughly above 0.7 is considered to be useful to predict the responses of individual subjects.[29] Stata's roccomp command was used to compare more than two ROC areas. This analysis was performed to assess whether the inclusion of serological markers in the SLEDAI-2K provides additional discriminative value over the clinical SLEDAI in patients receiving BEL.

Finally, subgroup analyses were performed to explore heterogeneity across groups and to identify potential effect modifiers.[30] Baseline disease severity (mild vs moderate-to-severe), patient's profile (chronic-persistent vs recurrent-flares), baseline complement consumption, elevated anti-dsDNA antibodies, seropositivity, and baseline use of immunosuppressants were considered in subsequent analyses.

For all the analyses, a significance level of 0.05 was set. Stata v18 software was used (StataCorp. 2023. Stata Statistical Software: Release 18. College Station, TX: StataCorp LLC.)

RESULTS

Study population

A total of 371 patients with SLE were included in the registry (table 1). Online supplemental appendix figure 1 illustrates the year of BEL initiation. Overall, 333 (89.8%) were female, and 315 (84.9%) were Caucasian, with a median age of 40.4 years and a disease duration of 7.8 years (2.1; 16) when BEL was initiated. The median SLICC at baseline was 0. A total of 218 patients (58.8%) exhibited a relapsing–remitting disease course characterised by recurrent flares, whereas 153 patients (41.2%) followed a chronically persistent disease course. The accumulated SLE organic involvement is shown in table 1. Regarding serological profile, 209 patients (56.3%) had low C3 or C4 levels, 288 (77.6%) tested positive for anti-dsDNA antibodies, 147 (39.6%) for anti-Ro antibodies and 106 (28.6%) for anti-Sm antibodies at some point during the disease course. Classification criteria for antiphospholipid syndrome were fulfilled in 44 patients (11.9%) and 57 (15.4%) met criteria for Sjogren's syndrome. At baseline, 326 patients (87.9%) were receiving hydroxychloroquine, 332 (89.5%) were on prednisone (median daily dose 7.5) and 300 (80.9%) were being treated with at least one conventional immunosuppressant agent. Prior to BEL initiation, 84 patients (22.6%) had received Rituximab before BEL.

BEL exposure and serological and clinical activity

Among the 371 patients treated with BEL, 42.6% received the intravenous formulation and 56.3% the subcutaneous

Table 1 Demographic and clinical characteristics, accumulated organic involvement, serological profile and baseline treatment of patients with SLE from BELILES GEAS cohort

Demographic characteristics	
Age at SLE diagnosis (years) (mean, SD)	31.7 (13.8)
Age at the time of BEL initiation (years) (mean, SD)	40.4 (16.6)
Female sex (n, %)	333 (89.8)
Disease duration (years) (median, p25-p75)	7.8 (2.1–16)
Ethnic (n, %)	
Caucasian	315 (84.9)
Mestizo	32 (8.6)
African	4 (1.1)
Asian	3 (0.8)
Others-unknown	17 (4.6)
Clinical course (N, %)	
Chronic-persistent	153 (41.2)
Remitting-relapsing	218 (58.8)
SLICC/ACR Damage Index (median, p25-p75)	**0 (0–1)**
Accumulated SLE organic involvement (n, %)	
Joints	323 (87.1)
Skin	264 (71.2)
Haematological	190 (51.2)
Systemic/constitutional	167 (45)
Kidney	158 (42.6)
Mucosa	130 (35)
Serous	121 (32.6)
Neurological	38 (10.2)
Vasculitis	37 (9.9)
Lung	21 (5.7)
Heart	19 (5.1)
Psychiatric	12 (3.2)
Others	41 (11.1)
Serological profile and associated autoimmune diseases (n, %)	
Low complement (C3 or C4)	209 (56.3)
Anti-ds-DNA antibody	288 (77.6)
Anti-Ro antibody	147 (39.6)
Anti-RNP antibody	126 (34)
Anti-Sm antibody	106 (28.6)
Anti-La antibody	48 (12.9)
Rheumatoid factor	20 (5.4)
Lupus anticoagulant	111 (29.9)
IgG aCL antibodies	70 (18.9)
IgM aCL antibodies	57 (15.4)
IgG B-2GPI antibodies	59 (15.9)

Continued

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Table 1 Continued

Demographic characteristics	
IgM B-2GPI antibodies	43 (11.6)
Sjögren disease	57 (15.4)
Antiphospholipid syndrome	44 (11.9)
Baseline treatment (n, %)	
Hydroxychloroquine	326 (87.9)
Chloroquine	0
Mepacrine	36 (9.7)
Prednisone	332 (89.5)
Dose (median, p25-p75)	7.5 (5-15)
Conventional immunosuppressant	300 (80.9)
Mycophenolate/mycophenolic acid	122 (32.9)
Methotrexate	95 (25.6)
Azathioprine	76 (20.5)
Tacrolimus	21 (5.7)
Cyclosporine	5 (1.4)
Cyclophosphamide	7 (1.9)
Previous Rituximab	84 (22.6)

aCL, anticardiolipin; anti-ds-DNA, anti-double-stranded DNA; BEL, belimumab; B-2GPI, beta-2 glycoprotein I; p25-p75, percentiles 25 and 75; RNP, ribonucleoprotein; SLE, systemic lupus erythematosus; SLICC/ACR Damage Index, Systemic Lupus International Collaborating Clinics/American College (SLICC/ACR) Damage Index for Systemic Lupus Erythematosus.

formulation (table 2). BEL was discontinued in 95 patients (25.6%) due to lack of efficacy (35.8%), adverse events (17.9%), pregnancy (14.4%), disease stabilisation (7.4%), death (4.2%) and other causes (21.1%). Therefore, the median duration of drug exposure was 13.2 months.

At baseline, 260 patients (70.1%) were seropositive for anti-dsDNA and/or hypocomplementemia. In the overall cohort, 201 patients (54.2%) showed complement consumption, with low C3 levels in 167 patients (45.0%; median 81 mg/dL) and/or low C4 levels in 133 patients (35.9%; median 14 mg/dL). Additionally, 185 patients (53.8%) had elevated anti-dsDNA antibody titers. Prior to BEL initiation, the median SLEDAI-2K and cSLEDAI scores were 8 and 7, respectively.

The values and trends of serum biomarkers, activity scores, prednisone dose and immunosuppressant use following BEL initiation were evaluated by random-effects regression models (online supplemental appendix tables 1 and 2, figure 1). After adjusting for baseline values and pre-existing differences between patients, a significant decrease in SLEDAI-2K and cSLEDAI scores and prednisone doses was confirmed over time ($p<0.05$). In contrast, serum C3 and C4 levels, anti-dsDNA positivity and immunosuppressant use did not change significantly.

Table 2 Belimumab treatment and baseline serological and clinical activity

Intravenous belimumab (n, %)	158 (42.6)
Subcutaneous belimumab (n, %)	209 (56.3)
Drug exposure (months) (median, p25-p75)	13.2 (4.1–29.4)
Withdrawal (n, %)	95 (25.6)
Lack of efficacy	34 (35.8)
Adverse events	17 (17.9)
Pregnancy	13 (14.4)
Disease stabilisation	7 (7.4)
Death	4 (4.2)
Others	20 (21.1)
Baseline serological and clinical activity	
Seropositive (n, %)	260 (70.1)
Complement consumption (n, %)	201 (54.2)
C3 levels (mg/dL) (median, p25-p75)	81 (65–99)
Low C3 levels (n, %)	167 (45)
C4 levels (mg/dL) (median, p25-p75)	14 (8.6–20)
Low C4 levels (n, %)	133 (35.9)
Elevated anti-ds-DNA antibodies (n, %)	185 (53.8)
SLEDAI-2K (median, p25-p75)	8 (6-12)
Mild activity (n, %)	72 (21.2)
Moderate-to-severe activity (n, %)	268 (78.8)
cSLEDAI (median, p25-p75)	7 (4-10)

anti-ds-DNA, anti-double-stranded DNA; cSLEDAI, clinical SLEDAI; p25-p75, percentiles 25 and 75; SLEDAI-2k, SLE Disease Activity Index 2000.

Dynamics and clinical utility of serological markers during SLE flares

During follow-up, 371 patients completed a total of 961 visits. Flares were identified in 139 visits (14.5%), affecting 95 patients (25.6%) (table 3). The most frequent organ involvement during disease flares was cutaneous, observed in 89 flares (64.0%), followed by joint involvement in 81 (58.3%) and constitutional symptoms in 51 (36.7%), respectively. The median SLEDAI-2K and cSLEDAI scores at the time of flare were 6 and 4, respectively. Accordingly, 58 (42%) were classified as mild (SLEDAI-2K<6) and 74 (53%) as moderate-to-severe (SLEDAI-2K≥6).

Among the 961 visits, serum C3 and C4 were measured in 869 (90.4%), and anti-dsDNA antibodies were assessed in 697 (72.5%). During flares, 42.5% had low C3 levels (median: 81 mg/dL), 23.0% had low C4 levels (median: 17 mg/dL), and 53.2% showed elevated anti-dsDNA antibody titers.

Multilevel mixed-effects logistic regression analyses showed that serum C3 (OR=0.99, 95% CI 0.99 to 1.01) and C4 levels (OR=1.00, 95% CI 0.99 to 1.00), adjusted by immunosuppressant use and prednisone dose, were not associated with the risk of clinical flare. Similarly,

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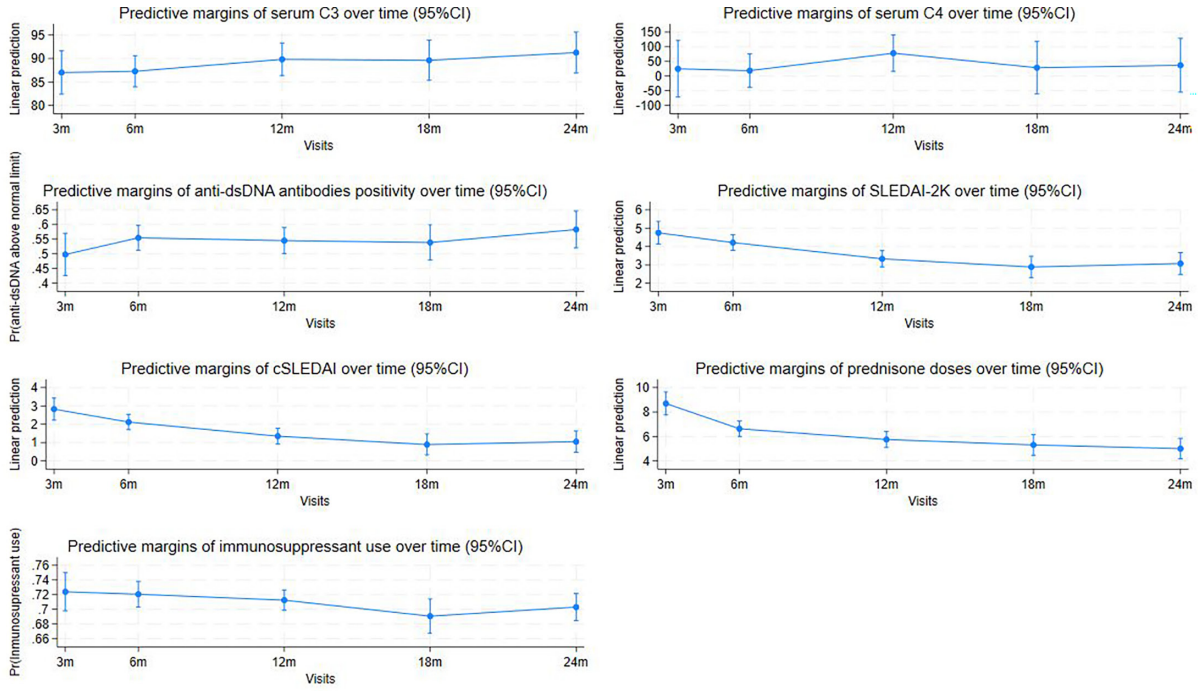


Figure 1 Adjusted predictive margins of serological markers, disease activity and treatment variables over time in SLE patients treated with belimumab. The figure shows adjusted predictive margins of serum C3, serum C4, anti-dsDNA antibody positivity, SLEDAI-2K, clinical SLEDAI (cSLEDAI), prednisone dose and immunosuppressant use across follow-up visits (3, 6, 12, 18 and 24 months) after belimumab initiation in the BELILES-GEAS cohort. Estimates were derived from random-effects regression models accounting for within-patient correlation and adjusted for baseline values. Data are presented as predicted marginal means (or probabilities for binary outcomes) with 95% CIs. For serum C4, the CIs at some timepoints extend below zero, reflecting the imprecision of the linear modelling approach applied to a right-skewed variable with low absolute values; the central predicted marginal means remain positive and biologically plausible at all timepoints. GEAS, Group of Systemic Autoimmune Diseases; SLEDAI-2K, SLE Disease Activity Index 2000.

Table 3 Organ involvement of SLE flares during follow-up

SLE flares during follow-up (n, %)	139 (14.5)
Moderate-to-severe flares* (n, %)	74 (53)
Organ involvement of SLE flares (n, %)	
Skin-mucosa	89 (64)
Joint	81 (58.3)
Systemic-constitutional	51 (36.7)
Haematological	28 (20.1)
Serous	15 (10.8)
Kidney	13 (9.4)
Neurological	8 (5.8)
Serological and clinical activity of SLE flares	
C3 levels (mg/dL) (median, p25-p75)	81 (69–104)
Low C3 levels (n, %)	59 (42.5)
C4 levels (mg/dL) (median, p25-p75)	17 (11–23)
Low C4 levels (n, %)	32 (23)
High anti-dsDNA antibody (n,%l)	65 (53.2)
SLEDAI-2K (median, p25-p75)	6 (4-9)
cSLEDAI (median, p25-p75)	4 (2-8)

*Moderate-to- severe fare was defined as a SLEDAI-2k≥6.
anti-dsDNA, anti-double-stranded DNA; cSLEDAI, clinical SLEDAI; SLEDAI-2k, SLE Disease Activity Index 2000.

no association was observed for C3 in either mild or moderate-to-severe flares (OR=1.01, 95% CI 0.99 to 1.02 and OR=1.00, 95% CI 0.99 to 1.01, respectively), nor for C4 (OR=1.00, 95% CI 0.99 to 1.01 and OR=1.00, 95% CI 0.99 to 1.01, respectively).

Qualitative analyses showed that low C3 (OR=1.31, 95% CI 0.82 to 2.09) and low C4 levels (OR=1.08, 95% CI 0.62 to 1.86) were not associated with the risk of flare. When flares were stratified by severity, no significant associations were observed for mild flares (C3, OR=0.64, 95% CI 0.30 to 1.37; C4, OR=0.40, 95% CI 0.13 to 1.20) or for moderate-to-severe flares for C4 (OR=1.54, 95% CI 0.81 to 2.93). For C3, however, the association with moderate-to-severe flares yielded an OR of 1.82 (95% CI 0.99 to 3.31), a magnitude that, while not reaching conventional statistical significance, may be clinically relevant and warrants cautious interpretation.

There was no association between serum level of C3 (coefficient: −0.001, p=0.796), neither C4 (coefficient 0.00006, p=0.809) and cSLEDAI.

Regarding anti-dsDNA antibodies, positivity was associated with an increased risk of flare (OR=1.81, 95% CI 1.09 to 3.01). This association was no longer statistically significant when stratified by severity: mild (OR=2.00, 95% CI 0.99 to 4.03) and moderate-to-severe flares (OR=1.83,

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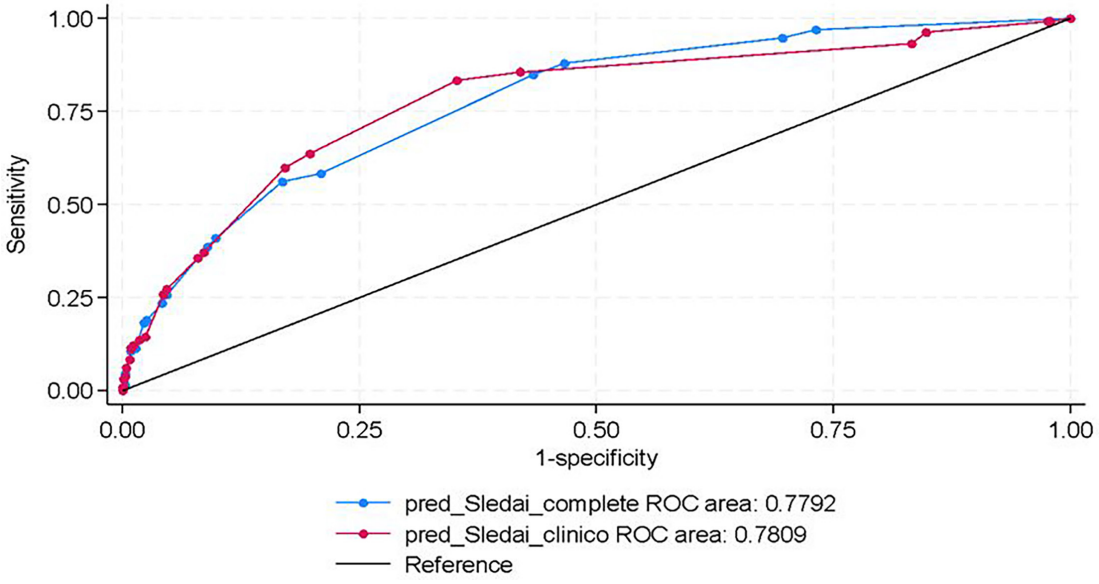


Figure 2 Discriminative ability of SLEDAI-2K and clinical SLEDAI scores for predicting clinical flares in SLE patients treated with belimumab in the BELILES-GEAS cohort over 24 months of follow-up. The figure shows the area under the receiver operating characteristic curve (AUC-ROC) for SLEDAI-2K and clinical SLEDAI, illustrating and comparing their performance in discriminating clinical flare during follow-up. GEAS, Group of Systemic Autoimmune Diseases; SLEDAI-2K, SLE Disease Activity Index 2000.

95% CI 0.95 to 3.50), likely due to limited sample size and statistical power.

Finally, we assessed the ability of SLEDAI-2K and cSLEDAI to discriminate flares (figure 2). The AUC-ROC comparison between SLEDAI-2K (0.779) and cSLEDAI (0.781) indicated no significant difference in their ability to discriminate disease flares (p=0.88).

Subgroup analyses

Subgroup analyses were performed to evaluate the impact of baseline characteristics and clinical profiles on the main findings (online supplemental appendix table 3). Variables included baseline disease severity (mild vs moderate-to-severe), clinical phenotype (chronic-persistent vs remitting-relapsing), complement consumption, elevated anti-dsDNA antibody titers, seropositivity and baseline use of immunosuppressants. Notably, clinical flares were associated with anti-dsDNA antibody positivity in patients with a remitting-relapsing disease course (OR=2.71, 95% CI 1.37 to 5.40), in those with baseline anti-dsDNA positivity (OR=9.03, 95% CI 1.91 to 42.64) and in patients receiving immunosuppressants prior to BEL initiation (OR=2.36, 95% CI 1.31 to 4.23). Similarly, correlations between C3 and C4 levels and the cSLEDAI remained weak across all subgroups, and no differences were observed in the ability of the two curves to discriminate disease flares.

DISCUSSION

This multicentre, retrospective observational study provides real-world evidence that, beyond the early clinical benefit and reduction in disease activity associated with BEL, the utility of serological markers in SLE is dissociated. Serum complement levels in SLE patients treated with BEL are not associated with clinical activity or flare occurrence overall; however, low C3 levels showed a borderline association with moderate-to-severe flares, suggesting that its utility may be most apparent in the context of more pronounced immune activation and disease activity. In contrast, positivity for anti-dsDNA antibodies is consistently associated with flare occurrence. Consequently, clinical decisions regarding disease activity in patients receiving BEL may be better guided by clinical assessment and anti-dsDNA status, as the associative value and clinical utility of serum C3 and C4 appears to be attenuated and does not meaningfully enhance the ability of the SLEDAI-2K to discriminate flares.

The majority of the available data regarding serological markers in patients treated with BEL are those from the BLISS clinical trials. The first studies by Furie *et al*, and Navarra *et al*, among others, clearly demonstrated that the benefits of BLyS inhibition on SLE activity were accompanied by a normalisation of the major SLE serological markers, including serum C3, C4 and anti-dsDNA antibodies.[16 17] In fact, van Vollenhoven and colleagues described that treatment with BEL had greater benefit in patients with complement consumption and anti-dsDNA positivity, reflecting its effect on B-cell driven autoimmunity and classical complement cascade activation.[24] Expanding on this, Stohl *et al* described in detail the dynamics and trends of autoantibodies, complement and immunoglobulins after BLyS inhibition with BEL, as well as the drug's impact on circulating B-cell subsets.[13] In addition, they also examined the correlation of these changes with clinical outcomes and activity scores, confirming that the therapeutic benefit of BEL was

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maintained regardless of normalisation of complement or anti-dsDNA antibodies.

Under the current debate regarding the importance of serological remission in SLE patients, and whether the normalisation of complement or autoantibodies should be a treatment target itself, more recent reports from the same cohorts and population have studied the association of these biomarkers with SLE activity in patients receiving BEL treatment.[4 9 11 31] For example, a recent study confirmed that, in patients with DORIS remission or LLDAS, active serology is associated with a higher risk of severe flares.[12] This effect was even more pronounced for anti-dsDNA antibodies, and for renal flares, in line with findings reported by Jägerback *et al*.[32] Accordingly, and although therapeutic decisions should likely not aim to achieve serological remission in patients who have already reached clinical remission, these reports support the clinical utility of these markers on SLE patients treated with BEL.[31 33]

Despite the strengths of these studies, it should be noted that they are derived from BEL clinical trials, which applied strict inclusion criteria, including high clinical and serological activity, such as strong anti-dsDNA antibodies positivity at baseline.[13 16 17] While this profile was common among patients treated with BEL during the early years following its approval, its use has since broadened to include a wider range of patients beyond those enrolled in the original trials.[10] Furthermore, clinical management and outcomes in clinical trials do not always reflect routine clinical practice. In this context, our multicentre retrospective study provides valuable real-world insights into the dynamics and clinical utility of SLE biomarkers in patients receiving BEL.

First, in our cohort, BEL was associated with an early and sustained reduction in clinical disease activity, as evidenced by a marked decline in SLEDAI-2K and cSLEDAI scores, as well as in mean prednisone dose from baseline. The protective effect was further supported by a low rate of flares, an infrequent incidence of kidney and neurological involvement and lower SLEDAI-2K and cSLEDAI scores during flares compared with baseline. Taken together, these findings indicate that BEL promptly reduced disease activity, with severe flares being uncommon and, when present, associated with lower SLEDAI-2K and cSLEDAI values relative to baseline, in line with previous evidence from clinical trials and real-world studies.[13 16 17 34] However, this clinical improvement was not reflected in serum C3, C4 titers and anti-dsDNA antibody positivity.

In line with the above, serum C3 and C4 levels were neither associated with nor correlated with clinical flares or cSLEDAI in the overall SLE population or in subgroup analyses. When stratified by flare severity, no associations were observed for mild flares or for C4 in moderate-to-severe flares. However, low C3 levels showed a borderline association with moderate-to-severe flares, a finding that, while not reaching conventional statistical significance, is consistent with the hypothesis that complement consumption may be more relevant in the context of severe immune activation, as suggested by previous literature.[12 32] In addition, anti-dsDNA positivity was associated with flare occurrence overall. This association was even more evident in patients who were anti-dsDNA-positive at baseline, those with a recurrent disease profile and those receiving immunosuppressive therapy, consistent with findings from the BLISS trials and related reports.[16 17]

These observations support the hypothesis that BEL exposure, through its modulation of B-cell subsets and humoral autoimmunity, results in a different serological and autoantibody profile in SLE.[13] Accordingly, certain autoantibodies may exhibit different predictive roles in patients treated with BEL compared with those receiving placebo.[32] In parallel, BLyS inhibition promotes a shift toward activation of the alternate complement pathway, which may explain why serum complement were not associated with clinical activity, and why only C3 may retain some relevance in the context of severe immune activation, as suggested by its borderline association with moderate-to-severe flares in our study and its reported correlation with glomerular involvement in others.[1 33 35] Taken together, our findings suggest that complement levels, in the setting of BLyS inhibition, B-cell immune modulation and control of specific autoreactive lymphocyte subsets, have limited utility as biomarkers of overall disease activity, although C3 may still carry signal in the context of more severe flares.[5 13 23 32] However, similarly to what has been described previously, anti-dsDNA positivity in patients receiving BEL is associated with disease activity and flares during follow-up.[12]

Third, and despite the dissociation between the utility of complement levels and anti-dsDNA positivity, the addition of these biomarkers to cSLEDAI did not improve its capacity to discriminate flares. It should be noted that these two analyses address distinct questions: the logistic regression evaluated whether serum complement and anti-dsDNA positivity are independently associated with flare, whereas the AUC-ROC comparison assessed whether the addition of serological components to the SLEDAI-2K provides incremental discriminative performance over the clinical-only score. These are conceptually different analyses and their results are not contradictory but complementary. These results contribute to and expand the ongoing debate surrounding serological normalisation as a treat-to-target objective, particularly regarding its utility in the context of clinical remission, low disease activity state or quiescent disease.[4 12 31–33] While post hoc analyses from the BLISS trials have shown that biomarker normalisation predicts fewer renal and severe flares and potentially better long-term outcomes, our findings suggest that these serological markers do not substantially enhance clinical flare detection and, therefore, may have limited value when used in isolation to guide treatment or management decisions.[12 32] However, reflecting the complexity and heterogeneity of SLE, as well as the methodological limitations of our study, these findings should be interpreted with caution, particularly

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in patients who were anti-dsDNA–positive at disease onset, those receiving immunosuppressive therapy at baseline or those with a recurrent-flare profile, as the association between anti-dsDNA and flare occurrence was particularly striking in this group. Similarly, the borderline association between low C3 and moderate-to-severe flares suggests that C3 hypocomplementemia may retain clinical relevance in the context of more severe immune activation, and this possibility warrants further prospective evaluation. Further research is warranted to clarify whether marker normalisation should be pursued as a treatment goal in its own right.[4 31]

While our study provides robust data from a multicentre, real-world SLE population, certain limitations must be acknowledged, including the retrospective nature of the study and the short-term follow-up. On the one hand, the association between serological markers and flares was assessed cross-sectionally, as both were measured at the same visit, precluding evaluation of their associate value for subsequent clinical events, although this approach reflects real-world clinical practice where biomarkers are interpreted alongside concurrent clinical assessment. Besides, inter-laboratory variability in complement and anti-dsDNA measurement techniques and reference ranges across centres may have influenced the results, particularly regarding C3 and C4 findings, given that assay methods are known to vary substantially between platforms and laboratories. Although centre-specific categorisation and longitudinal modelling were used to mitigate this effect, residual heterogeneity cannot be excluded. Furthermore, the flare definition was based on physician-driven treatment escalation, which, while reflective of real-world clinical practice, may introduce inter-centre variability in flare ascertainment. In addition, although C3, C4 and anti-dsDNA antibody are established markers and predictors of SLE activity, we did not include a matched control population of SLE patients not treated with BEL.[2 3 33] Therefore, to generalise and validate our findings, future studies should compare the dynamics, associations with clinical activity and discriminative performance of these biomarkers in patients treated with BEL versus those not receiving BEL. On the other hand, the population size did not allow us to perform subgroups analysis to assess the impact of certain immunosuppressants on the dynamics and titers of these serological markers, nor to evaluate differences across flare types, including organ-specific manifestations or SLEDAI-2k clinical domains, as reported elsewhere.[32] Additionally, this cohort predominantly comprises patients from Spain, with a high proportion of Caucasian individuals, which may limit the generalisability of our findings to more ethnically diverse populations, given the known differences in SLE epidemiology, clinical expression and outcomes across ethnic groups.

In conclusion, in patients with SLE treated with BEL, the clinical utility of serological markers appears dissociated from disease activity. While serum C3 and C4 levels were not clearly related to disease activity or flare occurrence overall, low C3 levels showed a borderline association with moderate-to-severe flares, suggesting that C3 hypocomplementemia may retain relevance in the context of severe immune activation. Notably, anti-dsDNA antibody positivity remains associated with an increased risk of flares, particularly in patients with baseline positivity, recurrent disease or concomitant immunosuppressive therapy. These findings support a clinical management approach in which disease activity assessment in patients receiving BEL should primarily rely on clinical evaluation, with anti-dsDNA status providing complementary clinical information prognostic information, rather than pursuing serological normalisation as an independent treatment target.

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