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Stratifying patients by TNFSF13B genotype revealed increased flare and renal flare risk, but a greater benefit from belimumab: a potential biomarker for personalized treatment in systemic lupus erythematosus

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ABSTRACT

Objective: To examine whether SLE patients carrying the TNFSF13B variant (BAFF-var) differ in the risk of overall and renal flares and the benefits from belimumab.
Methods: This retrospective study analyzed data from a monocentric cohort of Sardinian SLE patients between January 2006 and December 2022. We recorded demographic, clinical, serological, and treatment variables. A flare was defined as a new SLE manifestation or worsening of an existing one that required a change in therapy. Renal flares, categorized as nephritic or nephrotic, were recorded. Soluble B-cell activating factor (sBAFF) levels were evaluated in patients naïve to any treatment. We used Kaplan-Meier curves, Cox regression, and Poisson regression to investigate the association between BAFF-var and flares.
Results: Among 233 screened patients, 194 (89.2 % female, 61.3 % BAFF-var carriers) were included. The mean age was 41.1 (±14.8) years, and the mean number of follow-up visits was 17 (±8). sBAFF levels increased according to BAFF-var genotype ($p < 0.001$). BAFF-var was significantly associated with an increased risk of flares (HR 1.5 per copy variant; 95 %CI 1.2–2.0; $p = 0.002$), and the frequency of flares (IRR 1.3 per copy variant; 95 % CI 1.1–1.6; $p = 0.009$). In 38 biopsy-confirmed lupus nephritis patients, the BAFF-var was associated with a higher risk of renal flare (HR 9.3; 95 %CI 1.7–49.5; $p = 0.008$). In 35 relapsing-remitting patients, belimumab reduced both the risk and frequency of flares, with higher effectiveness in patients carrying the BAFF-var (HR 0.12; 95 %CI 0.02–0.58; $p = 0.009$).
Conclusions: Pending further validation, BAFF-var may serve as a predictive and prognostic biomarker for personalized treatment in SLE.

1. Introduction

Systemic Lupus Erythematosus (SLE) is a multisystem chronic autoimmune disease with a strong genetic background, marked by unpredictable flares [1]. Preventing disease flares can lower the risk of quality of life impairment, damage accumulation, hospitalization, and mortality [2]. A significant challenge in effectively managing SLE is the absence of prognostic biomarkers for flare, which could hamper decision-making strategies in treat-to-target approaches. Previous case-control studies comparing soluble biomarkers, including complement fractions and anti-dsDNA levels, as flare predictors have produced inconclusive results [2]. Additionally, there is a notable lack of predictive biomarkers to identify SLE patients who would benefit most from new targeted therapies. This represents a challenge for implementing treat-to-target

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strategies and precision medicine in SLE.

The B-cell activating factor (BAFF), also known as B-lymphocyte stimulator (BLyS), is a pivotal cytokine in SLE pathogenesis [3]. BAFF is primarily produced by monocytes and dendritic cells and is essential for B-cell activation and plasma-cell survival. An excess of BAFF is responsible for autoreactive B-cell survival and reduced B-cell apoptosis, favoring the differentiation in plasma cells and the autoantibodies production [3]. High serum levels of BAFF are associated with high disease activity, high anti-dsDNA levels, low C3 complement levels, positivity of anti-Sm, and renal involvement [4,5]. Targeting soluble BAFF (sBAFF) with belimumab, a specific anti-BAFF monoclonal antibody, reduces disease activity, lowers serologic activity, and decreases flare risk, including renal flares [6–8]. Recently, a functional variant in the *TNFSF13B* gene, which encodes the cytokine and drug target BAFF, was found to be associated with susceptibility to SLE [9]. This result was independently validated in other SLE cohorts [10,11]. The causal variant is an insertion-deletion (GCTGT→A), with the minor allele (A) representing the alternative allele known as "BAFF-var." This variant introduces an alternative polyadenylation motif, resulting in a truncated gene transcript that escapes miRNA inhibition. This leads to increased production of sBAFF, which subsequently upregulates humoral immunity, as evidenced by higher levels of sBAFF, B lymphocytes, and antibodies. [9]. The discovery of the BAFF overexpressing *TNFSF13B* variant raises implications for clinical research. Some relevant hypotheses would be that constitutive overexpression of BAFF in SLE patients may influence the disease phenotype and clinical course by increasing the risk of flare or determining differential responses to treatment.

The present study investigates whether BAFF-var status may influence the SLE clinical course and patients stratified according to BAFF-var status might benefit differently from anti-BAFF treatment.

2. Patients and methods

2.1. Study design

A retrospective analysis of routinely collected data from SLE patients referred to the Lupus Clinic of Cagliari (Italy) between January 1, 2006, and December 31, 2022, was performed. Inclusion criteria were: 1) fulfillment of at least one set of validated criteria for SLE classification among the revised 1997 ACR criteria, 2012 SLICC criteria, and 2019 EULAR/ACR criteria; 2) at least 3 consecutive visits (2 within 12 months) during the study interval; 3) availability of data from medical records. The local ethics committee approved the study (Comitato Etico AOU Cagliari PG/21303/2014), and all participants gave their written informed consent.

2.2. Data collection

Demographic factors, including gender, age at onset, and date of diagnosis, were collected. Previous and ongoing clinical manifestations were recorded at baseline and flare according to the BILAG-2004 definitions [12]. In patients with renal involvement, kidney biopsy and renal histology data were collected according to the 2003 ISN/RPN Lupus Nephritis Classification [13]. Antinuclear antibodies (ANA), anti-Ro/SSA, anti-La/SSB, anti-Sm, anti-RNP, lupus anticoagulant, anticardiolipin, and anti-B2-glicoprotein1 results were listed. At each visit, disease activity was assessed using the SLEDAI-2K score [14] and the Physician Global Assessment (PGA) [15]. The SLICC/ACR Damage Index (SDI) assessed damage at baseline and at the last visit [16]. Renal assessment, including 24-h proteinuria (PrU24h), urinary sediment (red and white blood cells, urinary casts), and serum creatinine, was recorded, as well as anti-dsDNA antibodies and serum complement levels. Ongoing use and new prescription of prednisone (PDN), antimalarials (i.e., hydroxychloroquine, chloroquine), immunosuppressants (i.e., azathioprine, methotrexate, mycophenolate mofetil, calcineurin inhibitors, cyclophosphamide), and biologic drugs (i.e., rituximab and belimumab) were assessed at every visit. The mean daily PDN dose (or equivalent mg/day) was recorded for each patient at every study follow-up visit. Authors who collected the data (MPP, GR, FC, EC) were blinded to *TNFSF13B* genotyping results.

2.3. TNFSF13B genotyping and serum BAFF quantification

Custom TaqMan assays were developed to genotype the minor allele (A), which we designated as BAFF-var in contrast to the BAFF wild type (BAFF-wt). $BAFF^{wt/var}$ and $BAFF^{var/var}$ individuals are referred to as BAFF-var carriers. Sera from 58 naïve to treatment, newly diagnosed, SLE patients were collected before starting any therapy, and sera from 60 age-, sex—, and genotype-matched healthy blood donors were used as controls. To understand the factors influencing the dynamics of sBAFF levels, we conducted a longitudinal evaluation starting from pre-treatment and continuing at six-month intervals for a year in a subgroup of 21 SLE patients for whom longitudinal samples were available. After being stored at −80 °C, sera were used to measure sBAFF cytokine using plates from a single batch, with a consistent lot number of the ELISA (R&D Systems). Duplicate samples from three controls and three patients were included on each ELISA plate, serving as an internal control. All samples were run in duplicate wells. A coefficient of variation (CV) ≤8 % was established as a threshold for consistency and reproducibility between assay plates.

2.4. Study outcomes

The occurrence of disease flares was the primary study endpoint. Among secondary study endpoints, the achievement of Lupus Low Disease Activity State (LLDAS) [17], DORIS Remission (DR) [18], and renal outcomes of interest were recorded. Flares were defined as the onset of a new SLE manifestation or worsening of a pre-existing clinical manifestation resulting in a therapy change [19]. Significant treatment modifications were defined as starting or increasing the dosage of glucocorticoids, antimalarials, immunosuppressants, or biologic agents. LLDAS-50 was defined as the achievement of SLEDAI-2K ≤ 4 with no activity in major organ systems and no new features of activity compared to the previous assessment, PGA≤1.0, PDN ≤7.5 mg/day, with stable background treatment with antimalarials and/or immunosuppressants, in at least 50 % of the visits. DR-50 was defined as the achievement of cSLEDAI-2K = 0, PGA≤0.5, PDN ≤5 mg/day, with stable background treatment with antimalarials and/or immunosuppressants in at least 50 % of the visits.

The renal outcomes of interest during follow-up were analyzed in a sub-analysis of patients with biopsy-confirmed lupus nephritis [20]. Renal flares were categorized as nephritic flares (i.e., an increase in glomerular haematuria by ≥ 10 RBCs/hpf with or without a decrease in eGFR by ≥ 10 %, irrespective of changes in proteinuria) or nephrotic flares (reproducible doubling of proteinuria to >1000 mg/24 h if a complete renal response (CRR) had been previously achieved or reproducible doubling of proteinuria to ≥2000 mg/24 h if a partial renal response (PRR) had been previously achieved). The other renal outcomes of interest were the achievement of the PRR (≥50 % reduction in proteinuria to sub-nephrotic levels and serum creatinine within 10 % of baseline values) or the CRR (proteinuria <500 mg/24 h and serum creatinine within 10 % of baseline values) and development of stage 3–4 chronic kidney disease (CKD: eGFR 15–60 mL/min/1.73 m2 for more than 3 months) or end-stage renal disease (ESRD: eGFR <15 mL/min/1.73 m2 or the initiation of renal replacement therapy).

2.5. Statistics

The sample size was calculated based on a 50 % flare rate over follow-up derived from a previous study conducted in our cohort [21]. According to Peduzzi et al. [22], a sample size of 160 patients was sufficient to precisely estimate a multivariate Cox proportional-hazards

model for the risk of flare development with up to 8 independent factors.

Continuous variables are presented as mean ± standard deviation (SD) or median and interquartile range (IQR). Univariate analysis, using the Chi-square test or Fisher's exact test, was performed to analyze the association between study endpoints and BAFF-var for categorical variables, and the Student t-test or Mann-Whitney test was used when appropriate for continuous variables. Analysis of Variance (ANOVA) and the Kruskal-Wallis tests were employed to assess the differences between the means and medians, respectively, of more than two groups. Time-to-event data were analyzed using the non-parametric Kaplan-Meier method and the semi-parametric Cox proportional-hazards model. Kaplan-Meier curves were compared with the log-rank test. Multivariate Cox regression models, with flare development as the dependent variable and time to flare as the time variable, were fitted with covariates with $p < 0.1$ at univariate analysis to identify baseline factors independently associated with an increased risk of flare. The Cox regression analysis results are presented as hazard ratios (HRs) with 95 % confidence intervals (CIs). Poisson regression models with the number of flares as the dependent variable were fitted with covariates with $p < 0.1$ to evaluate the flare incidence rate ratio (IRR), with 95 %CI, for every BAFF-var copy. A p-value <0.05 was considered statistically significant.

3. Results

3.1. Study cohort

In total, 194 out of 233 new patients who joined the Lupus Clinic of Cagliari (Italy) during the study interval fulfilled the criteria for enrolment. Table 1 summarizes the relevant features of this cohort. Out of the excluded patients, 3 did not meet any validated criteria for SLE classification, 25 had an inadequate number of visits or inadequate intervals between follow-up visits, 7 had incomplete data, and 4 were excluded after BAFF-var genotyping failed. All patients were Caucasian, of whom 98.5 % were from Sardinia. The mean follow-up was 8.8 (±4.6) years, and the mean number of visits per patient was 16.9 (±8.1), totaling 3274 visits. At baseline, 59 patients (30.4 %) were in LLDAS and 38 (19.6 %) in DR (see Supplementary Tables 1 and 2).

Table 1
Baseline characteristics of the lupus cohort at entry into the study.

FEATURES	VALUE
Age in years, mean (±SD)	41.1 (±14.8)
Gender, female/male	177/17
Disease duration in years, median (IQR)	8.96 (0–9.0)
Follow-up in years, mean (±SD)	8.8 (±4.6)
Number of visits, mean (SD)	16.9 (±8.1)
Cumulative manifestations [a]	
Constitutional	136 (70.0)
Mucocutaneous	147 (75.8)
Neuropsychiatric	23 (11.9)
Musculoskeletal	182 (93.8)
Cardiorespiratory	68 (35.0)
Gastrointestinal	4 (2.1)
Ophthalmic	5 (2.6)
Hematologic	86 (44.3)
Renal	53 (27.3)
SLEDAI-2k, median (IQR)	2 (0–6)
PGA, median (IQR)	0 (0–0.4)
SDI, median (range)	0 (0–5)
Medications[b]	
Prednisone	188 (96.9)
Hydroxychloroquine	165 (85.0)
Immunosuppressants	128 (66)
Biologics	3 (1.5)

[a] According to BILAG-2004 domains.
[b] Previous or ongoing at baseline. Unless otherwise expressed, numbers are absolute values (percentage). BILAG: British Isles Lupus Assessment Group. SLEDAI-2k: Systemic Lupus Erythematosus Disease Activity Index 2000. PGA: Physician Global Assessment. SDI: SLICC/ACR Damage Index.

3.2. BAFF-var frequency and serum BAFF quantification

TNFSF13B genotyping revealed the BAFF-var allele in 119 patients (61.3 %), with 20 patients (10.3 %) homozygous for BAFF-var. The allele frequency of BAFF-var was calculated at 0.35. sBAFF levels were higher ($p < 0.001$) in SLE patients naïve to treatment than in healthy blood donors, and they increased (Fig. 1A and supplementary table 3) in a genotype-dependent manner after stratifying data based on *TNFSF13B* genotyping ($p < 0.001$ by the Kruskal-Wallis test). Longitudinal evaluation of sBAFF levels included 21 SLE patients (7 BAFF-wt homozygous, 9 heterozygous, and 4 BAFF-var homozygous), 6 of whom experienced flares during the 1-year follow-up, indicating fluctuating levels throughout the follow-up period (Fig. 1B). Treatment did not differ from the entire cohort (data not shown). In the 21 patients longitudinally followed up, sBAFF levels were influenced by disease activity, as measured by SLEDAI-2K ($r = 0.462$; $p < 0.001$) and prednisone daily dose ($r = -0.282$; $p = 0.035$), while no correlation with flare or BAFFvar genotyping was found. The CV for duplicate sample measurements was consistently below 8 %, with most samples having a CV of less than 2 %. The mean CV across all plates was 1.64 (±1.48), indicating high intra-assay precision and reproducibility.

BAFF-var did not influence the clinical presentation or autoantibody profiles in SLE patients (Table 2).

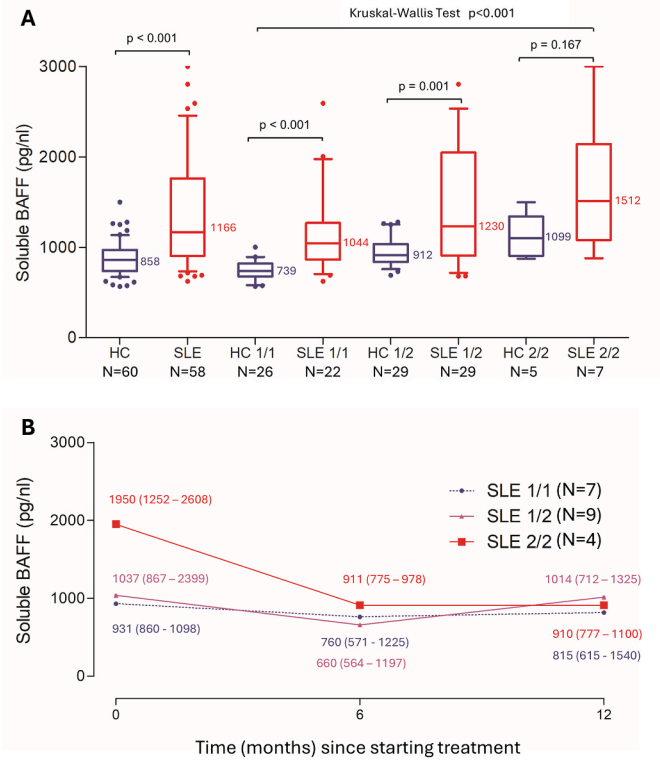

Fig. 1. (A) Comparison of median (10–90 percentile) serum BAFF levels in SLE cases naïve to treatment (red) versus controls (blue). The X-axis label indicates the number of samples per class, separating the complete set from the homozygotes wild type (1/1), heterozygotes (1/2), and homozygotes for BAFF-var (2/2). N refers to the sample size. Data between groups and across groups were compared using the Mann-Whitney and Kruskal-Wallis tests, respectively. **(B) Longitudinal comparison of median (10–90 percentile) serum BAFF levels over time in SLE cases, starting from the pre-treatment stage, according to genotyping.** The X-axis refers to time since starting treatment. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 2
Association of the BAFF-var allele with baseline features of the 194 SLE patients enrolled.

FEATURES	BAFF-WT carriers (n = 75)	BAFF-VAR carriers (n = 119)	p
Age in years, mean (±SD)	43.4 (±16.4)	39.6 (±13.6)	0.084
Gender, female/male	68/7	109/10	0.823
Disease duration in years, median (IQR)	3.7 (0–9.0)	2.3 (0–8.9)	0.409
Number of visits, mean (±SD)	16.2 (±7.8)	17.3 (±8.2)	0.381
Cumulative manifestations[a]			
Constitutional	54 (72)	82 (69.5)	0.648
Mucocutaneous	61 (81.3)	86 (72.9)	0.152
Neuropsychiatric	9 (12)	14 (11.9)	0.961
Musculoskeletal	73 (97.3)	109 (92.4)	0.107
Cardiorespiratory	25 (33.3)	43 (36.4)	0.691
Gastrointestinal	0 (0)	4 (3.4)	0.109
Ophthalmic	2 (2.7)	3 (2.5)	0.950
Hematologic	30 (40)	56 (47.5)	0.336
Renal	21 (28)	32 (27.1)	0.866
Serologic features[b]			
Anti-dsDNA	63 (84)	100 (84.7)	0.995
Anti-Sm	20 (26.7)	27 (22.9)	0.530
Anti-RNP	21 (28)	30 (25.4)	0.668
Anti-SSA	32 (42.7)	43 (36.4)	0.326
Anti SSB	6 (8.0)	14 (11.9)	0.402
LA	9 (12.0)	24 (20.3)	0.141
ACL	12 (16.0)	26 (22)	0.319
AntiB2GPI	6 (8.0)	19 (16.1)	0.108
Low C3 and/or C4	40 (53.3)	73 (61.3)	0.271
SLEDAI-2k, median (IQR)	2 (0–4)	2.2 (0–4)	0.975
PGA, median (IQR)	0 (0–0.3)	0 (0–0.4)	0.656
SDI≥1	18 (24.0)	27 (22.9)	0.834
Medications[b]			
Prednisone	72 (96.0)	113 (94.9)	0.737
Prednisone mg/day, median (IQR)	5.7 (2.8–12.5)	7.1 (5–10)	0.270
Hydroxychloroquine	67 (89.3)	97 (81.5)	0.143
Immunosuppressants	50 (66.7)	78 (65.5)	0.873
Methotrexate	21 (28.0)	31 (26.1)	0.765
Mycophenolate mofetil	14 (18.7)	20 (16.8)	0.740
Azathioprine	13 (17.3)	22 (18.5)	0.839
Calcineurin Inhibitors	2 (2.7)	6 (5.0)	0.419
Cyclophosphamide	2 (2.7)	4 (3.4)	0.786
Biologics[c]	1 (1.3)	2 (1.7)	0.849
LLDAS	24 (32.0)	35 (29.4)	0.855
DORIS remission	14 (18.7)	24 (20.2)	0.798

[a] According to BILAG-2004 domains.
[b] Previous or ongoing at baseline.
[c] All patients treated with biologics received Rituximab. Unless otherwise expressed, numbers are absolute values (percentages). BILAG: British Isles Lupus Assessment Group. SDI: SLICC/ACR Damage Index. LA: Lupus anticoagulant. ACl: Anticardiolipin antibodies IgM/IgG. aB2GPI: anti-B2-glycoprotein I IgM/IgG.

3.3. SLE outcomes

One-hundred-nine patients (56.2 %) experienced at least one flare during follow-up, with 60 patients (30.9 %) having more than one flare. Over follow-up, the median number of flares was higher (p = 0.038) in BAFF-var carriers (1; IQR 0–2) than in BAFF-wt homozygous (0; IQR 0–1). Specifically, 35/75 (46.7 %) $BAFF^{wt/wt}$, 59/99 (59.6 %) $BAFF^{wt/var}$, and 15/20 (75 %) $BAFF^{var/var}$ patients experienced at least one flare during follow-up (p = 0.013), suggesting a genotype-dependent effect. In the entire cohort, the median time to the first flare was 1.8 years (IQR 0.7–4.3). Kaplan-Meier analysis showed that BAFF-var carriers had an increased risk of flare (HR 1.52; 95 %CI 1.03–2.24; p = 0.032) (Fig. 2). The risk was higher for $BAFF^{var/var}$ (HR 1.82; 95 %CI 0.94–3.53) and $BAFF^{wt/var}$ (HR 1.49; CI95 % 0.99–2.22) when compared to $BAFF^{wt/wt}$ (p = 0.076) supporting the hypothesis of a genotype-dependent effect (Fig. 2). The results of the univariate analysis are reported in the supplementary table 4. After adjusting for age and gender, Cox regression model showed BAFF-var (HR 1.5 per copy variant; 95 %CI 1.2–2.0; p = 0.002), disease duration <1 year (HR 0.46; 95 %CI 0.30–0.71; p < 0.001), DR (HR 0.41; 95 %CI 0.24–0.71; p = 0.001), renal involvement (HR 1.7; 95 %CI 1.1–2.6; p = 0.017), and musculoskeletal involvement (HR 5.3; 95 %CI 1.3–21.5; p = 0.019) as baseline factors independently associated with the risk of flare development. Baseline treatment did not affect the risk of flare development. Poisson regression showed that BAFF-var (IRR 1.3 per copy variant; 95 %CI 1.1–1.6; p = 0.009) was independently associated with an increased flare rate over time (Table 3). Table 4 compares the characteristics of flares that occurred in BAFF-WT and BAFF-var carriers.

At the end of the follow-up, 125 participants (64.7 %) achieved LLDAS-50, including 76 BAFF-var carriers (63.9 %) and 49 BAFF-wt homozygous (65.3 %) with no significant difference (p = 0.992). Additionally, 39.3 % of participants (n = 76) achieved DR-50, comprising 37.3 % of BAFF-var carriers (n = 44) and 42.7 % of BAFF-wt carriers (n = 32), also showing no significant difference (p = 0.503). At baseline, 44 (22.7 %) patients scored SDI≥1 (median 0, range 0–5), while during follow-up, 96 patients (49.5 %) accrued organ damage, and 106 (54.6 %) patients had at least 1 item of SDI damage (median 1; range 0–10) at the end of follow-up. There were no differences in the proportion of individuals with BAFF-var (49.6 %) and BAFF-wt (49.3 %) who accumulated damage during follow-up, and the median SDI (median 1, IQR 0–2 vs. median 1, IQR 0–2; p = 0.376) at the end of follow-up was similar for both groups.

3.4. Lupus nephritis outcomes

During the study period, 38 SLE patients were diagnosed with biopsy-proven lupus nephritis. Among them, 33 (86.8 %) were female, 21 (55.3 %) were BAFF-var carriers (6 BAFF-var homozygous), 4 (10.5 %) were diagnosed with mesangial proliferative lupus nephritis class II, 24 (63.2 %) with proliferative class III or IV lupus nephritis, 4 (10.5 %) with mixed class glomerulonephritis and 6 (15.8 %) with pure membranous class V. The mean age at diagnosis was 35 years (±16.7), with a median follow-up after biopsy of 1.7 years (0–9.7). Flares occurred in 12 (33.3 %) patients, 10 (26.3 %) with BAFF-var, accounting for 22 (5 nephritic and 17 nephrotic) flares. The risk for renal flare was higher in BAFF-var carriers (HR 3.1; 95 %CI 0.93–10.1; p = 0.0648) (Fig. 2). Univariate analysis results are documented in supplementary table 5. After adjusting for age and gender, the Cox regression model showed BAFF-var (HR 9.3; 95 %CI 1.7–49.5; p = 0.009) and baseline 24-h proteinuria >3 g (HR 7.7; 95 %CI 2.1–28.2; p = 0.002) as baseline factors independently associated with the risk of flare development. At the end of follow-up, 35 (92.1 %) patients achieved PRR, 31 (81.6 %) achieved CRR, 11 (28.9 %) evolved into CKD, and only 1 (2.6 %) patient developed ESRD. None of these outcomes was associated with the BAFF-var.

3.5. Outcome of patients treated with belimumab

Of 109 SLE patients who experienced at least a flare during follow-up, 35 received belimumab intravenous or subcutaneous treatment, 32 (91.4 %) were female, and 22 (62.8 %) were BAFF-var carriers (2 BAFF-var homozygous). The mean age was 41.4 (±13.4) years, and the mean duration of SLE was 12.8 (±10.9) years. No statistically significant differences in demographic and clinical features at baseline were found in the BAFF-wt group compared to the BAFF-var group (Table 5). Out of 35 patients receiving belimumab after at least one previous flare, 11 (31.4 %) experienced at least one new flare during a mean follow-up of 40.2 (±23.3) months, resulting in a total of 13 flares. Treatment with belimumab was effective in these patients with relapsing-remitting SLE, reducing the proportion experiencing flares by 68.6 % in the whole cohort (p < 0.001), 81.8 % among BAFF-var carriers (p < 0.001), and 46.2 % among BAFF-wt carriers (p = 0.011) over 3 years of follow-up. (Fig. 3). During follow-up, only 4/22 patients carrying BAFF-var (18.2 %) experienced flares compared to 7/13 BAFF-wt carriers (53.8

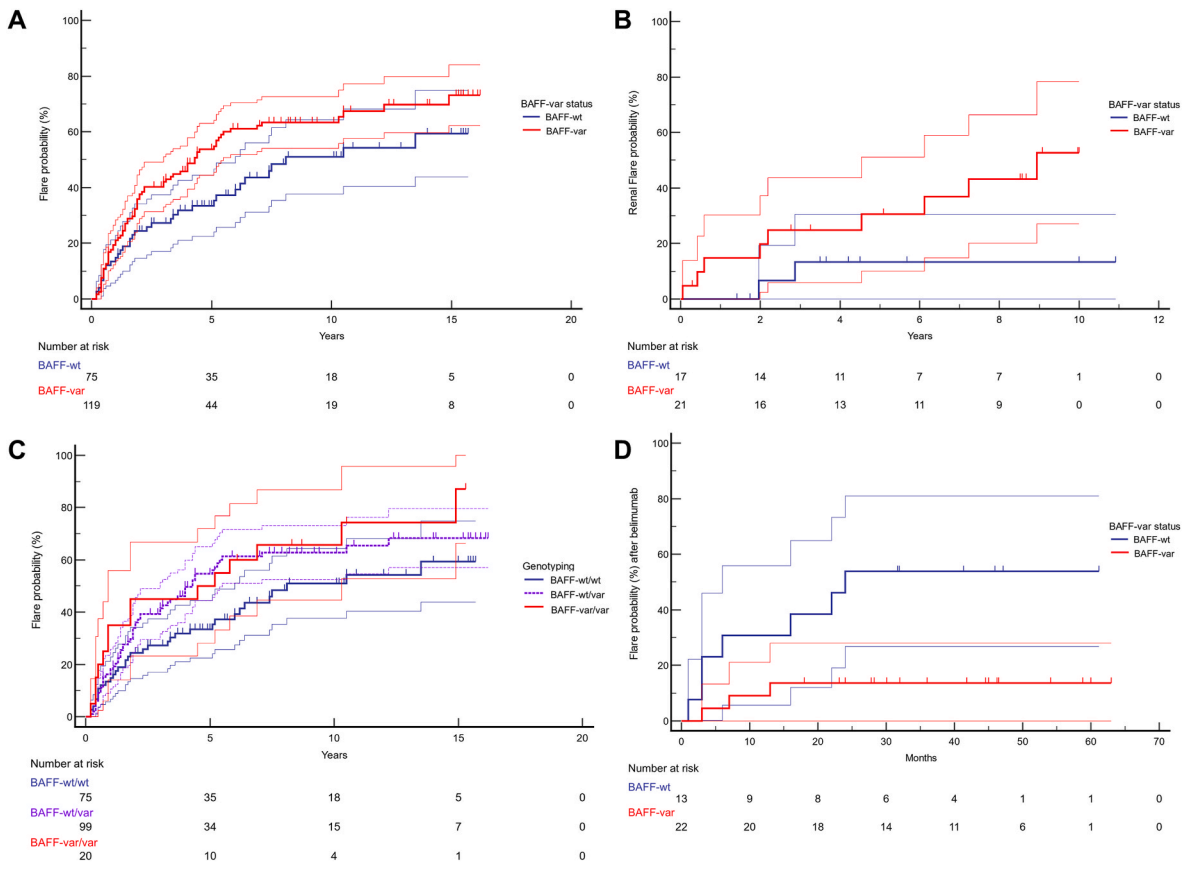

Fig. 2. Kaplan-Meier curves depicting **(A)** the probability of flare and **(B)** renal flare in SLE patients, both with and without the BAFF-var, **(C)** the probability of flare based on TNFSF13B genotype and **(D)** the impact of belimumab treatment on flare probability in SLE patients with and without the BAFF-var. The pale lines indicate the 95 % confidence interval.

Table 3
The Poisson regression analysis revealed factors associated with the number of flares during follow-up.

Variables	Coefficient	IRR	95 % CI	p-value
Constant	−3.13	0.04	0.01–0.19	<0.001
Age	−0.05	0.99	0.98–1.01	0.358
Gender	0.97	2.63	1.23–5.62	0.012
BAFF-var (per copy variant)	0.26	1.30	1.07–1.58	0.009
Mucocutaneous[a]	0.62	1.86	1.30–2.66	0.001
Musculoskeletal[a]	1.72	5.62	1.79–17.67	0.003
Renal[a]	−0.15	0.85	0.63–1.15	0.307
Immunosuppressant[b]	0.16	1.17	0.88–1.56	0.267
DORIS remission	−0.73	0.48	0.31–0.73	0.001

[a] According to BILAG-2004 domains.
[b] ongoing at baseline. BILAG: British Isles Lupus Assessment Group.

%) ($p = 0.018$). The number of flares experienced by the 35 patients dropped from 52 during the 3 years before starting belimumab to 13 during the 3 years after ($p < 0.001$), from 32 to 4 ($p < 0.001$) in the 22 BAFF-var carriers, and from 20 to 9 ($p = 0.027$) in the 13 BAFF-wt carriers. Repeated measures ANOVA showed that the mean number of flares did not differ between groups ($p = 0.738$) during the 3 years before belimumab treatment, even if it was significantly lower in BAFF-var than in BAFF-wt carriers ($p = 0.012$) during the 3 years after belimumab treatment (Fig. 3). Kaplan-Meier analysis showed that BAFF-var carriers treated with belimumab had a reduced risk of flare (HR 0.18; 95 %CI 0.05–0.68; $p = 0.011$) (Fig. 2). Univariate analysis results are documented in Supplementary Table 6. After adjusting for age and gender, the Cox regression model demonstrated the protective effect of BAFF-var (HR 0.12; 95 % CI 0.02–0.58; $p = 0.009$) and the predictive effect of anti-Sm (HR 4.0; 95 % CI 1.1–15.2; $p = 0.043$) on the risk of flare development in patients treated with Belimumab.

4. Discussion

This study demonstrates that BAFF-var is associated with an increased risk of flares, including renal flares, and assists in identifying which SLE patients are most likely to benefit from belimumab treatment. These findings can significantly impact the prognosis of SLE by addressing unmet requirements for personalized treatment, endorsing tighter control measures, and prioritizing belimumab for BAFF-var carriers.

Despite advances in treatment, SLE patients often experience flares of varying severity that can impact both short- and long-term outcomes [23]. Clinical disease flares require considerable medical resources, resulting in increased healthcare costs [24]. Preventing flares represents a distinct therapeutic target in SLE, but no flare prediction test exists, and traditional clinical or serologic markers of disease activity have low accuracy in predicting flares [25]. In a subgroup of our patients, longitudinal evaluation of sera revealed that sBAFF levels are influenced by disease activity and daily prednisone dose. The sBAFF level correlates with SLE disease activity, but prospective studies investigating the relationship between sBAFF levels and changes in SLE disease activity have yielded conflicting results, likely due to differences in assay sensitivity, disease activity score, or study population [26]. A post-hoc analysis of the phase III RCTs BLISS-52 and BLISS-76 showed that baseline sBAFF levels ≥2 ng/mL at screening were independent prognostic factors for increased risk of moderate and severe SLE flare [27]. Although sBAFF levels were inconsistent in differentiating pre-flare from pre-non-flare samples, their inclusion improved the accuracy of a

Table 4
Characteristics of flares occurring in BAFF-wt and BAFF-var over follow-up.

FEATURES	Flares in BAFF-WT (n = 64)	Flares in BAFF-VAR (n = 145)	p
Age in years, mean (±SD)	46.79 (±21.8)	41.5 (±12.3)	0.472
Patients who flared	35 (46.7)[a]	74 (62.2)[a]	0.034
Time to first flare, median (IQR)	1.78 (0.70 - 5.63)	1.83 (0.70 - 4.00)	0.411
Sex female (%)	31 (93.9)	68 (97.1)	0.432
Clinical Manifestations at the time of flare			
Constitutional	10 (6.4)	25 (17.2)	0.789
Mucocutaneous	31 (48.44)	63 (43.5)	0.478
Neuropsychiatric	4 (6.25)	4 (2.8)	0.221
Muscoloskeletal	45 (70.3)	97 (66.9)	0.581
Cardiorespiratory	3 (4.7)	7 (4.8)	0.973
Gastrointestinal	0 (0)	0 (0)	–
Ophtalmic	0 (0)	0 (0)	–
Renal	10 (15.6)	27 (18.6)	0.616
Hematologic	7 (4.5)	23 (15.9)	0.359
Clinical manifestations determining therapy changes			
Constitutional	1 (1.6)	6 (4.1)	0.344
Mucocutaneous	25 (39.1)	49 (33.8)	0.442
Neuropsychiatric	3 (4.7)	6 (4.1)	0.849
Muscoloskeletal	38 (59.4)	77 (53.1)	0.374
Cardiorespiratory	3 (4.7)	5 (3.5)	0.660
Gastrointestinal	0 (0)	0 (0)	–
Ophtalmic	0 (0)	0 (0)	–
Renal	7 (10.9)	22 (15.2)	0.424
Hematologic	4 (6.3)	12 (8.3)	0.621
Serological features			
anti-dsDNA (%)	43 (68.3)	100 (70.4)	0.810
C3	87 (±27.3)	85.8 (±24.6)	0.550
C4	13 (±7.0)	12.6 (±9.0)	0.753
Clinimetric features			
SLEDAI-2K, mean (±SD)	7.7 (±5.0)	6.6 (±3.8)	0.050
PGA, mean (±SD)	1.4 (±0.5)	1.3 (±0.5)	0.071
Treatment			
Prednisone in mg, mean (±SD)	12.0 (±9.9)	11.2 (±9.6)	0.346
Hydroxychloroquine	49 (76.6)	101 (69.7)	0.414
Methotrexate	20 (31.3)	38 (26.2)	0.471
Cyclosporine A	1 (1.6)	4 (2.8)	0.608
Cyclophosphamide	2 (3.12)	2 (1.4)	0.390
Azathioprine	18 (28.1)	47 (32.4)	0.562
Mycophenolate mofetil	4 (23.4)	33 (22.8)	0.889

BILAG: British Isles Lupus Assessment Group. SLEDAI: Systemic Lupus Erythematosus Disease Activity Index, PGA: Physician Global Assessment. Unless otherwise expressed, numbers are absolute values (percentage).
**According to BILAG2004.
[a] Percentages calculated over 75 BAFF-wt Carriers and 119 BAFF-var carriers.

Table 5
Characteristics of BAFF-wt and BAFF-var SLE carriers receiving treatment with belimumab.

FEATURES	BAFF-WT (n = 13)	BAFF-VAR carriers (n = 22)	p
Age in years, mean (±SD)	42.1 (±11.5)	41.0 (±13.5)	0.811
Sex, female (%)	12 (92.3)	20 (90.9)	0.888
Disease duration in years, median (IQR)	12 (5.7–15.2)	11.5 (5–21)	0.561
Follow-up in months, mean (±SD)	38.9 (±24.9)	40.9 (±22.9)	0.800
Active clinical manifestations according to BILAG-2004 domains			
Constitutional	9 (69.2)	14 (63.3)	0.739
Mucocutaneous	11 (84.6)	17 (77.3)	0.605
Neuropsychiatric	–	–	
Musculoskeletal	8 (61.5)	14 (63.6)	0.902
Cardiorespiratory	1 (7.7)	2 (9.1)	0.838
Gastrointestinal	–	–	
Ophthalmic	–	–	
Hematologic	2 (15.4)	5 (22.7)	0.605
Renal	4 (30.8)	6 (27.3)	0.827
Serologic features			
Anti-dsDNA	13 (100)	21 (95.4)	0.442
Anti-Sm	4 (30.8)	7 (31.8)	0.949
Anti-RNP	6 (46.1)	10 (45.4)	0.968
Anti-SSA	8 (61.5)	10 (45.4)	0.404
Anti-SSB	2 (15.4)	1 (4.5)	0.275
Antiphospholipid antibodies[b]	3 (23.1)	8 (36.3)	0.420
Low C3 and/or C4	12 (92.3)	20 (90.9)	0.888
SLEDAI-2K, mean (± SD)	10.5 (±4.6)	8.5 (±2.8)	0.177
PGA, mean (± SD)	1.3 (±0.5)	1.3 (±0.5)	0.475
SDI, median (range)	1 (0–3)	1 (0–3)	0.651
Medications[a]			
Prednisone mg/day, mean (±SD)	10.3 (±8.1)	11.8 (±9.3)	0.626
Hydroxychloroquine	10 (76.9)	17 (77.3)	0.981
Immunosuppressants	11 (84.6)	21 (95.4)	0.275
Micophenolate mofetil	4 (30.8)	10 (45.4)	0.398
Azathioprine	5 (38.5)	8 (36.3)	0.902
Methotrexate	2 (15.4)	2 (9.1)	0.577
Calcineurin Inhibitors	0 (0)	1 (4.5)	0.460
Specific manifestations of disease flare after starting Belimumab			
Number of flares	9	4	–
Number of severe flares	4	2	–
Mucocutaneous	3	0	–
Serositis	3	0	–
Musculoskeletal (i.e., synovitis)	2	2	–
Vasculitis	1	0	–
Renal	0	1	–
Neurologic (i.e., chorea)	0	1	–

[a] Ongoing at baseline.
[b] At least one of the following: Lupus anticoagulant, Anticardiolipin antibodies IgM/IgG, anti-B2-glycoprotein I IgM/IgG. Unless otherwise expressed, numbers are absolute values (percentages). BILAG: British Isles Lupus Assessment Group. SLEDAI-2k: Systemic Lupus Erythematosus Disease Activity Index 2000. PGA: Physician Global Assessment. SDI: SLICC/ACR Damage Index.

multiparametric molecular flare index when combined with other selected immune mediators [28]. Increased BAFF mRNA levels in PBMCs correlated better with SLE disease activity than sBAFF [29]. Therefore, the evidence suggests that the overexpression of *TNFSF13B* is somewhat associated with an increased risk of flare in SLE, but sBAFF cannot be used as a standalone prognostic biomarker. Indeed, sBAFF levels can fluctuate in response to various stimuli such as aging, monocyte activation, infections, or treatments [30,31]. The BAFF-var causal mutation generates a shorter 3' UTR at the transcript level that avoids inhibitory post-transcriptional regulation, leading to the constitutive overexpression of the *TNFSF13B* gene and remarkably elevated levels of sBAFF over time [32]. The higher sBAFF levels contribute to the survival and expansion of autoreactive B-cells, eventually amplifying SLE pathogenic mechanisms, including autoantibody production and dysregulation of innate and adaptive immunity [9]. Our findings confirmed that sBAFF levels are elevated in SLE patients compared to healthy controls and established that, in both cohorts, they rise based on the *TNFSF13B* genotype. The BAFF-var genotype-dependent effect is further supported by our evidence, which shows that each copy variant confers a 50 % higher risk of flares and is associated with a 30 % increase in the incidence rate of flares. These data have significant implications for research and clinical management of patients with SLE. Future studies could explore how incorporating BAFF-var into polygenic risk scores, or multiparametric indices, might help estimate the risk of flare development. Additionally, identifying individuals with this genetic variant could enhance monitoring strategies, enabling clinicians to anticipate and manage flares more effectively.

Notably, our findings support the idea that the heightened risk of flare associated with the BAFF-var can be effectively addressed by prioritizing treatment with belimumab. In randomized controlled trials and observational studies, belimumab has been shown to effectively control SLE disease activity and reduce flare rates, including renal flares [6–8,33–35]. A systematic literature review found that the use of belimumab in real-world data was associated with a 66% reduction in flares, with a mean of 1.15 flares per patient per year in the 12 months preceding belimumab administration, compared to 0.39 flares per patient per year 12 months after belimumab administration. However, it also

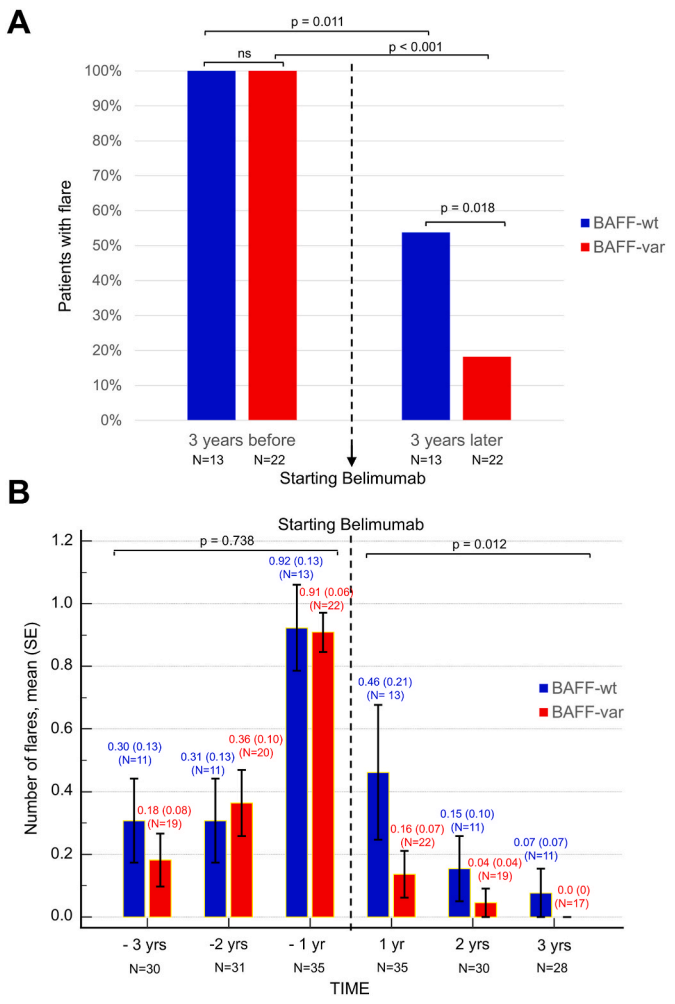

Fig. 3. Bar graphs comparing **(A)** the proportion of patients experiencing flares and **(B)** the mean number of flares between SLE patients with and without the BAFF variant during the three years before and the three years after starting treatment with belimumab. P values were obtained from (A) Fisher's exact test and (B) repeated measures ANOVA test. N indicates absolute numbers in groups and subgroups.

reported that up to 61% of SLE patients still experience a flare despite belimumab treatment [35]. Pooled meta-analysis of the phase III RCTs BLISS-52 and BLISS-76 showed a lower risk of severe flare after treatment with belimumab in SLE patients with higher BAFF mRNA and sBAFF levels [36]. Data from our cohort supported these findings, showing a lower risk of flares and a better reduction in flare incidence among patients carrying the BAFF-var allele. The most significant finding from our results is that BAFF-var may act as a clinically useful, affordable, and easy-to-assay predictive biomarker to identify individuals most likely to benefit from treatment with belimumab. Screening patients for BAFF-var may help clinicians prioritize belimumab as a treatment option, enabling personalized strategies for SLE patients.

It is important to note that the generalizability of our findings must take into account the unique distribution of the BAFF-var in different populations. BAFF-var is more commonly found in Southern Europe, with an allele frequency ranging from 5.0 % (Spain) to 26.7 % (Sardinia). In contrast, its frequency progressively decreases as we move toward Northern Europe, ranging from 1.8 % to 4.0 %. Interestingly, BAFF-var is either absent or extremely rare in Africa and Asia. In the United States, the allele frequency ranges from 1.6 % to 6.7 %, while in Latin America, it ranges from 1.2 % to 6.4 %, according to the 1000 Genomes Project [37] (Supplementary Table 7). These significant ethnic and regional genetic differences highlight the need for targeted genetic screening based on individual ancestry, prompting population-specific studies to validate our results.

This study has limitations. First, although this retrospective monocentric study offered proof of the potential role of BAFF-var as a candidate prognostic and predictive biomarker, our findings require additional validation in multicentric prospective observational studies and RCTs. Confirming our results in post-hoc analyses of pooled data from belimumab RCTs would be beneficial, especially in examining the impact of BAFF-var on other outcomes such as SRI-4 treatment response and prednisone sparing. Despite the study's monocentric design, the distinct Sardinian ethnicity of our SLE cohort, which includes a higher proportion of individuals with the BAFF-var, strengthened the statistical power. This enabled us to identify the effects of BAFF-var even with a relatively small sample size. Furthermore, this retrospective analysis did not examine endophenotype changes associated with a reduced risk of flare in BAFF-var individuals treated with belimumab. An ongoing study aims to clarify the mechanisms behind this effect (NCT05659407) [38]. Unexpectedly, despite influencing flare development, including renal flare, BAFF-var did not affect systemic and renal long-term outcomes in our cohort, which requires further investigation in clinical studies specifically designed with this aim.

In conclusion, the BAFF-var demonstrates promise as a prognostic biomarker for an increased risk of flares, including renal flares, and as a predictive biomarker indicating a better response to belimumab treatment in patients with SLE. With further validation, it will be possible to develop a personalized strategy for monitoring flares and prioritizing treatment with belimumab based on an individual's genetic profile and ethnic background.

CRediT authorship contribution statement

Marta Paola Pireddu: Writing – original draft, Investigation, Formal analysis, Data curation. **Giulia Rizzo:** Writing – review & editing, Formal analysis, Data curation. **Fabio Congiu:** Writing – original draft, Formal analysis, Data curation. **Elisabetta Chessa:** Supervision, Methodology, Investigation, Formal analysis, Data curation. **Maristella Pitzalis:** Writing – review & editing, Resources, Methodology, Investigation, Data curation. **Elena Ragusa:** Writing – review & editing, Visualization, Data curation. **Alberto Floris:** Writing – review & editing, Visualization, Validation, Supervision, Software, Methodology, Formal analysis, Conceptualization. **Francesca Deidda:** Writing – review & editing, Methodology, Investigation, Data curation. **Mattia Congia:** Writing – review & editing, Validation. **Micaela Rita Naitza:** Writing – review & editing, Methodology. **Maria Maddalena Angioni:** Writing – review & editing, Methodology, Investigation, Data curation. **Francesco Cucca:** Writing – review & editing, Resources, Conceptualization. **Alberto Cauli:** Writing – review & editing, Funding acquisition, Conceptualization. **Matteo Piga:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

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Appendix A. Supplementary data

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Data availability

Data will be made available on request.

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