Belimumab is Able to Induce a Significant Improvement of Joint Activity Status in Patients Diagnosed with Systemic Lupus Erythematosus: Results From a 12-Month Longitudinal Study

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ABSTRACT **Background:** Belimumab was the first biological drug approved for the treatment of systemic lupus erythematosus (SLE) patients. Phase II/III randomized controlled trials and real-life studies identified patients with musculoskeletal involvement as best responders.

Objectives: To evaluate the effectiveness of belimumab in SLE-related joint involvement.

Methods: The cohort comprised SLE patients receiving belimumab for musculoskeletal indications. Belimumab was intravenously administrated according to protocols; all the patients were evaluated at baseline (T0) and after 3 (T1), 6 (T2), and 12 (T3) months. The authors assessed joint activity by disease activity score 28, simple disease activity index (SDAI), clinical disease activity index (CDAI), and swollen tender ratio. Each patient underwent musculoskeletal ultrasound of 34 joints to assess synovial effusion, synovial hypertrophy, and power Doppler. A semi-quantitative scale (0–3) was administered to obtain a total inflammatory score (0–216).

Results: We evaluated 20 patients (males/females 1/19, median age 45 years [interquartile range (IQR) 12], median disease duration 144 months [IQR 144]). CDAI and SDAI significantly decreased at T1 (P = 0.02 and P = 0.01, respectively) and this improvement was maintained at the following time-points (CDAI: T2 P = 0.008, T3 P = 0.004; SDAI: T2 P = 0.006, T3 P = 0.01). A significant reduction of median ultrasound score was identified at T1 (T0 20.5 [IQR 13.5] vs. T1 7.5 [IQR 4.7], P < 0.001), and maintained at T2 (7.0 [IQR 5], P < 0.0001) and T3 (7.0 [IQR 9.0], P < 0.0001).

Conclusions: Belimumab induces a sustained improvement of ultrasound-detected inflammatory status at the articular level.

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KEY WORDS: arthritis, belimumab, joint involvement, systemic lupus erythematosus (SLE), ultrasound

Joint involvement is one of the most frequent features in systemic lupus erythematosus (SLE) patients, involving up to 90% of patients at the disease onset or during its course [1]. Together with inflammatory arthralgia, SLE patients could experience more aggressive arthritis characterized by the development of erosive damage, potentially leading to disability [1]. This phenotype, described in up to 40% of SLE patients with joint involvement, has been associated with specific biomarkers, in particular antibodies directed against citrullinated and carbamylated proteins [2,3]. Moreover, there is a possible genetic susceptibility for SLE-related erosive damage, but only little data are available regarding the association with specific genetic polymorphisms [4].

The presence of erosive damage has been widely demonstrated by different imaging techniques; in particular, ultrasound has been extensively applied to assess SLE joint involvement, contributing to the re-definition of this manifestation [5]. Ultrasound is able not only to assess erosive damage, but to evaluate the joint inflammatory status as well [6]. Data from the literature underline the need to assess joint involvement activity with specific indices, to capture the modification of joint activity status [7]. We previously evaluated the application of clinimetric indices validated for rheumatoid arthritis patients, underlining a higher sensitivity in comparison with global disease activity indices [8,9].

Belimumab, a soluble B-lymphocyte stimulator (BLyS) inhibitor, was the first biological drug approved to treat SLE patients, its efficacy and safety was assessed in the BLISS-52 and BLISS-76 phase 3 randomized controlled trials (RCTs), leading to drug approval [10,11]. The use of belimumab in a real-life setting confirmed its efficacy in the different SLE-related manifestations. Focusing on joint involvement, post-hoc analysis evaluating the pooled data of phase 2 and 3 RCTs identified patients with musculoskeletal features as best responders [12,13]. The study conducted by Iaccarino and colleagues [14] demonstrated the effectiveness of belimumab in determining the

improvement of this manifestation, when evaluated by disease activity score on 28 joints (DAS28). Moreover, the presence of polyarthritis was identified as an independent predictors of 12-month response [15]. In our 12-month longitudinal study, we evaluated the to evaluate the effectiveness of belimumab in SLE-related joint involvement by using specific joint activity indices and ultrasound assessment.

PATIENTS AND METHODS

We included all SLE patients referred to the Lupus Clinic, Sapienza University of Rome (Sapienza Lupus Cohort) who were receiving belimumab for musculoskeletal manifestations refractory to standard treatment. SLE diagnosis was made according to the 1997 American College of Rheumatology (ACR) revised criteria [16]. Belimumab was added to ongoing therapy and was intravenously administrated at 10 mg/kg on day 1, 14, 28, and then every 28 days. All the patients were evaluated at baseline (T0) and after 3 (T1), 6 (T2), and 12 (T3) months of treatment.

The study was approved by the local ethics committee (Sapienza University of Rome, Policlinico Umberto I, Rome, Italy) and was conducted according to the Declaration of Helsinki. All patients gave their informed consent.

CLINICAL AND LABORATORY EVALUATION

Clinical and laboratory data were reported in a standardized electronic form, including demographics, past medical history with date of diagnosis, co-morbidities, and previous and concomitant treatments. A complete physical examination was performed on all the SLE patients.

Laboratory evaluation included antinuclear antibodies (ANA) detected by indirect immunofluorescence (IIF) on HEp-2 and anti-double strand(ds)DNA by IIF on Crithidia Luciliae in accordance with the manufacturer's instructions (Orgentec Diagnostika, Mainz, Germany). Extractable nuclear antigens (ENAs, anti-Ro/ Sjögren's-syndrome-related antigen A [SSA], anti-La/SSB, anti-Smith (Sm), anti-ribonucleoprotein [RNP]), anticardiolipin (anti-CL, IgG, and IgM isotypes), and anti-β2-glycoprotein I (anti-β 2GPI, IgG, and IgM isotypes) antibody detection were performed by ELISA (Diamedix, Miami, FL, USA). Lupus anticoagulant (LA) was assessed according to the guidelines of the International Society on Thrombosis and Hemostasis. C3 and C4 serum levels (mg/dl) were studied by radial immunodiffusion. The erythrocyte sedimentation rate (ESR) was determined with standard methods (mm/h, Westergren), C-reactive protein (CRP) by using the immunoturbidimetric method (mg/dl). SLE disease activity was evaluated according to the SLE disease activity index 2000 (SLEDAI-2k) [17].

JOINT ASSESSMENT

A single rheumatologist conducted the joint assessment, including tender and swollen joint counts (0–28), visual analogue scale (VAS) for pain, and patients and physicians global health assessment [18].

From these parameters, we calculated the following joint activity indices: DAS28, simplified disease activity index (SDAI), clinical disease activity index (CDAI), and swollen tender ratio (STR), previously applied in SLE patients.

ULTRASONOGRAPHIC EVALUATION

Each patient underwent a musculoskeletal ultrasound assessment with the application of power Doppler (PD). The ultrasound assessment was performed by a single rheumatologist sonographer, experienced in musculoskeletal ultrasound, who was blinded to the clinical and laboratory findings. A systematic multiplanar grey-scale and PD examination of 34 joints (wrist, metacarpophalangeal, proximal interphalangeal, knee, and metatarsophalangeal joints of both sides) was performed using a MyLab 70 XVision Gold (Esaote, Firenze, Italy) machine equipped with multi-frequency linear array transducers (6–18 MHz). B-mode frequency ranged from 12 to 18MHz (12 MHz for knee assessment, 15 MHz for wrist and 18MHz for metacarpophalangeal and proximal interphalangeal); PD pulse repetition frequency was 750 Hz; Doppler frequency was 9.16 MHz; low wall filters were used, with color box positioned at the level of the assessed site. We evaluated the presence of synovial effusion, synovial hypertrophy and PD according with the outcome measures in rheumatology (OMERACT) definitions [19]. These elementary lesions were scored according to a semi-quantitative scale (0 = absent, 1 = mild, 2 = moderate, and 3 = severe). The sum of the semi-quantitative scores resulted in the total patient inflammatory score (0–216). Moreover, we evaluated the presence of erosive damage at level of metacarpophalangeal, proximal interphalangeal, and metatarsophalangeal joints according with OMERACT definitions [19].

STATISTICAL ANALYSIS

Statistical analyses were performed using Graph Pad Prism Version 5 (La Jolla, CA). Continuous data were presented as means with standard deviations (SDs) or medians with interquartile range (IQR), depending on the distribution of the data (tested with the Kolmogorov-Smirnov test). Categorical data were presented as proportions. Mann Whitney test was performed. Univariate comparisons between nominal variables were calculated using the chi-square test or Fisher's exact test where appropriate. Pearson's and Spearman's tests were used to perform the correlation analysis where appropriate.

Two-tailed P values were reported. A P value < 0.05 was considered statistically significant.

RESULTS

Our cohort comprised 20 SLE patients, male/female 1/19, median age 45 years (IQR 12), median disease duration 144 months (IQR 144). Table 1 shows the main demographics, clinical, laboratory features of enrolled patients, and data about disease treatments.

During the follow-up, two patients stopped belimumab treatment after 6 months, due to lack of response. Table 2 shows the global disease activity in terms of SLEDAI-2k and joint involvement activity, as assessed by tender and swollen joints count, DAS28, CDAI, SDAI, and STR. In agreement with previous data, median SLEDAI-2k values significantly decrease in comparison with baseline at all time-points evaluated (T1 $P = 0.004$, T2 $P = 0.01$, T3 $P = 0.001$). Concerning joint activity indices, CDAI and SDAI significantly decreased at T1 ($P = 0.02$ and $P = 0.01$, respectively). This improvement was maintained at the following time-points. CDAI: T2 $P = 0.008$, T3 $P = 0.004$, SDAI: T2 $P = 0.006$, T3 $P = 0.01$. A decrease was observed for DAS28 and for tender and swollen joints count, but this decrease became significant only after 6 months of treatment.

We evaluated joint inflammatory status by ultrasound. As shown in Figure 1, a significant reduction of median ultrasound inflammatory score was seen at T1 (T0: 20.5 [IQR 13.5] vs. T1: 7.5 [IQR 4.7], $P < 0.001$). This significant improvement was maintained at T2 (7.0 [IQR 5], $P < 0.0001$), and T3 (7.0 [IQR 9.0], $P < 0.0001$). Ultrasound detected erosive damage was observed in 7 patients (35.0%). No correlation was found between the different activity indices (DAS28, CDAI, SDAI, and STR) and the ultrasound inflammatory score at baseline.

Table 1: Demographic, clinical, laboratory features, and treatments of SLE patients (N= 20)

Clinical manifestations, n (%)	
Skin involvement	15 (75.0)
Serositis	4 (20.0)
Hematological manifestations	15 (75.0)
Neuropsychiatric involvement	5 (25.0)
Renal involvement	1 (5.0)
Laboratory manifestations, n (%)	
Anti-DNA	17 (85.0)
Anti-SSA	6 (30.0)
Anti-SSB	3 (15.0)
Anti-Smith	2 (10.0)
Anti-RNP	4 (20.0)
Anti-cardiolipin IgG/IgM	8 (40.0)
Anti-β2 glicoprotein I IgG/IgM	5 (25.0)
Lupus anticoagulant	3 (15.0)
Low C3/C4 levels	15 (75.0)
Treatments, n (%)	
Glucocorticoids	20 (100.0)
Hydroxychloroquine	18 (90.0)
Cyclosporine A	8 (40.0)
Methotrexate	14 (70.0)
Cyclophosphamide	0
Mycophenolate mofetil	11 (55.0)
Azathioprine	10 (50.0)
Rituximab	2 (10.0)

RNP = ribonucleoprotein, SLE = systemic lupus erythematos, SSA = Sjögren's-syndrome-related antigen A, SSB = Sjögren's syndrome-related antigen B

DISCUSSION

In this study we evaluated the effectiveness of belimumab in the SLE-related joint involvement. Our results demonstrated the ability of the drug to control the activity of this manifestation, as suggested by the significant reduction of ultrasound inflammatory score and clinimetric indices, in particular CDAI and SDAI.

Joint involvement represents a frequent manifestation in SLE patients, with a significant impact on health related quality of life [1]. Moreover, it has been widely demonstrated that SLE patients could develop erosive bone damage, thus requiring more aggressive treatment. Despite this evidence, only a few studies focused on SLE-related joint involvement, in particular in terms of drug efficacy. The introduction of belimumab for the treatment of SLE patients seemed to change this aspect [20-22]. Data from RCTs demonstrated the improvement of joint involvement as assessed by British Isles Lupus Assessment Group (BILAG) index. In a real-life setting a significant reduction of DAS28 in patients treated by belimumab was shown and that polyarticular involvement is a predictive factor for response treatment [14,15].

Figure 1. Box and whiskers plot (median, quartiles, range) of ultrasound inflammatory score of 20 patients treated with belimumab at baseline (T0) and after 3 (T1), 6 (T2), 12 months (T3). *P* values refer to the comparison with baseline

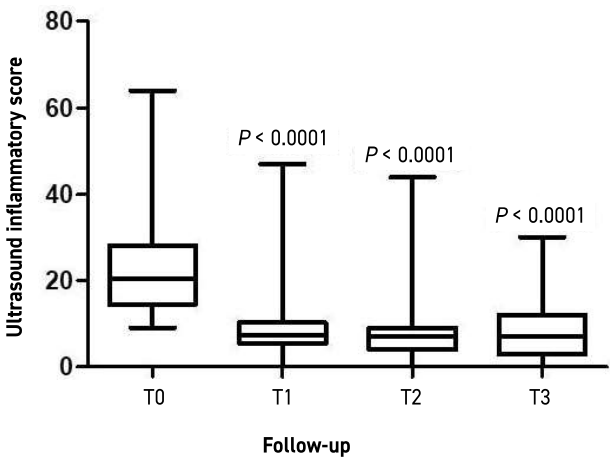

Table 2. Evaluation of disease activity and joint involvement activity in 20 systemic lupus erythematosus patients treated by belimumab

Activity index	T0 N=20	T1 N=20	T2 N=18	T3 N=18	*P* value
SLEDAI-2k, median (IQR)	6 (3.5)	2.0 (4.25)	2.0 (1.5)	0 (2.0)	T0 vs. T1 0.004 T0 vs. T2 0.01 T0 vs. T3 0.001
Tender joints count (IQR)	7 (7)	2 (4.7)	1 (2.7)	0.5 (3.0)	T0 vs. T1 NS T0 vs. T2 0.01 T0 vs. T3 0.02
Swollen joints count (IQR)	1 (3)	0 (1.2)	0 (0.7)	0 (0)	T0 vs. T1 NS T0 vs. T2 NS T0 vs. T3 0.03
DAS28, median (IQR)	4.4 (2.7)	3.4 (1.3)	2.9 (2.0)	2.4 (2.1)	T0 vs. T1 NS T0 vs. T2 0.02 T0 vs. T3 0.02
CDAI, median (IQR)	19 (13)	8 (9)	5 (4)	2.2 (5.5)	T0 vs. T1 0.02 T0 vs. T2 0.008 T0 vs. T3 0.004
SDAI, median (IQR)	18 (12.1)	8 (8.6)	5.8 (6.5)	3 (6.4)	T0 vs. T1 0.01 T0 vs. T2 0.006 T0 vs. T3 0.01
STR, median (IQR)	0.2 (0.5)	0 (0.4)	0 (0.3)	0 (0.0)	T0 vs. T1 NS T0 vs. T2 NS T0 vs. T3 NS

CDAI = clinical disease activity index, DAS = disease activity score, IQR = interquartile range, SDAI = simplified disease activity index, SLEDAI-2k = SLE disease activity index 2000, STR = swollen tender ratio

Global activity indices, such as SLEDAI-2k, are not able to capture the heterogeneity of joint involvement. The stringent definition included in this index is not able to identify patients with other phenotypes, such as inflammatory arthritis or mono-arthritis, leading to difficulty in the evaluation of activity status changes [1,7]. We proposed to use indices validated for rheumatoid arthritis to evaluate SLE-related joint involvement. We demonstrated the potential of using DAS28 and STR to identify patients with joint-related manifestations, not identifying by SLEDAI-2k, suggesting a greater sensitivity [8,9]. We also demonstrated a significant correlation between joint-specific activity indices in particular DAS28, STR, CDAI, SDAI, and ultrasound score, suggesting the usefulness of these composite indices in the assessment of inflammatory joint status [23].

In this study, we evaluated the effectiveness of belimumab in a real-life setting, focusing on joint involvement. The response to treatment was assessed by clinimetric indices and by ultrasound evaluation. In particular, by using this technique, we observed a response to belimumab as early as 3 months, which was was maintained after 6 and 12 months. This was demonstrated by the significant reduction of the ultrasound inflammatory score. In this score we evaluated the presence of inflammatory related modifications, in particular synovial effusion, synovial hypertrophy and power Doppler. Furthermore, we included the evaluation of different joint sites, to provide data about the patient's inflammatory status. Our results indicate the possibility to include ultrasound evaluation in the assessment of SLE patients treated with belimumab for musculoskeletal manifestations. We used different clinimetric indices. In particular, our results showed the ability of CDAI and SDAI to identify a significant improvement at 3 months, as compared to the other indices, which showed a significant reduction only after 6 months.

LIMITATIONS

The main limit of our analysis is the reduced number of enrolled patients; however, the 12-month follow-up represents the strength of the present study.

CONCLUSIONS

Treatment with belimumab resulted in a sustained improvement of ultrasound detected inflammatory status at the articular level. Moreover, joint-specific indices seem to be a valid tool to assess treatment response. However, the lack of correlation between the ultrasound inflammatory score and joint specific clinimetric indices suggests the need for a comprehensive patient's assessment to capture all aspects of musculoskeletal involvement, allowing the most appropriate treatment. This aspect is in agreement with the need for precision medicine for SLE patients [24].

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Capsule

Childhood vaccines and antibiotic use in low- and middle-income countries

Vaccines may reduce the burden of antimicrobial resistance, in part by preventing infections for which treatment often includes the use of antibiotics. However, the effects of vaccination on antibiotic consumption remain poorly understood,especially in low- and middle-income countries (LMICs), where the burden of antimicrobial resistance is greatest. **Lewnard** and colleagues showed that vaccines that have recently been implemented in the World Health Organization's Expanded Programme on Immunization reduce antibiotic consumption substantially among children under five years of age in LMICs. By analyzing data from large-scale studies of households, the authors estimated that pneumococcal conjugate vaccines and live attenuated rotavirus vaccines confer 19.7% (95% confidence interval 3.4–43.4%) and 11.4% (95% confidence interval 4.0–18.6%) protection against antibiotic-treated episodes of acute respiratory infection and diarrhoea, respectively, in age groups that experience the greatest disease burden attributable to the vaccine-targeted pathogens. Under current coverage levels, pneumococcal and rotavirus vaccines prevent 23.8 million and 13.6 million episodes of antibiotic-treated illness, respectively, among children under 5 years of age in LMICs each year. Direct protection resulting from the achievement of universal coverage targets for these vaccines could prevent an additional 40.0 million episodes of antibiotic-treated illness. This evidence supports the prioritization of vaccines within the global strategy to combat antimicrobial resistance.

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