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Clinical predictors of response and discontinuation of belimumab in patients with systemic lupus erythematosus in real life setting. Results of a large, multicentric, nationwide study

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ABSTRACT

Objective: To investigate efficacy, safety and survival of belimumab and to identify predictors of drug response and drug discontinuation in patients with active SLE in clinical practice.
Patients and methods: Data of SLE patients, treated with belimumab, from 11 Italian prospective cohorts were analyzed. SLEDAI-2K, anti-dsDNA, C3, C4, prednisone daily dose, DAS-28, 24-h proteinuria, CLASIa (Cutaneous LE Disease Area and Severity Index Activity) were recorded at baseline and every 6 months. SLE Responder Index-4 (SRI-4) was calculated at 12 and 24 months. Demographic and clinical features and comorbidities were included in the univariate and multivariate analysis. Adverse events were recorded at each visit. Statistics was performed using the SPSS software.
Results: We studied 188 SLE patients, mean follow-up 17.5 ± 10.6 months. The most frequent manifestations, which required the use of belimumab, were polyarthritis (45.2%) and skin rashes (25.5%). SRI-4 was achieved by 77.0% and 68.7% of patients at 12 and 24-months. Independent predictors of 12-month response were SLEDAI-2K $\geq$ 10 (OR 40.46, p = 0.001) and polyarthritis (OR 12.64, p = 0.001) and of 24-month response were SLEDAI-2K $\geq$ 10 (OR 15.97, p = 0.008), polyarthritis (OR 32.36, p = 0.006), and prednisone $\geq$7.5 mg/day (OR 9.94, p = 0.026). We observed a low rate of severe adverse events. Fifty-eight patients (30.8%) discontinued belimumab after a mean follow-up of 10.4 ± 7.5 months. The drug survival was 86.9%, 76.9%, 69.4%, 67.1%, and 61.9% at 6, 12, 18, 24, and 30 months, respectively. No factors associated with drug discontinuation were found.
Conclusion: Belimumab is effective and safe when used in clinical practice setting.

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1. Introduction

Despite the progresses in the treatment of systemic lupus erythematosus (SLE), the long term prognosis of patients is still unsatisfactory [1] and several urgent needs are still unmet. Indeed, a high percentage of patients experiences persistent disease activity or disease flares [2–4] requiring long term corticosteroid and immunosuppressive treatment which leads to progressive damage accrual and worsening of quality of life [2,5–14]. Among the immunological targets identified in SLE, soluble B lymphocyte stimulator (BLyS) seems to be very promising since excess of BLyS may rescue lupus autoreactive B cells [15–17].

In the BLISS-52 and BLISS-76 [18,19] phase 3 randomized controlled trials (RCTs), SLE patients treated with intravenous (IV) belimumab, a soluble BLyS inhibitor, added to standard treatment had a superior response rate (assessed by the SLE Responder Index-4; SRI-4) than those treated with standard therapy alone (placebo arm). These results led to the approval of belimumab by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of patients with SLE. In Italy belimumab is reimbursed in patients with active lupus manifestations despite standard therapy, positive anti-double stranded (ds)-DNA and low C3 or C4.

A number of *post-hoc* analysis which evaluated the pooled data of phase 2 and 3 RCTs, identified some manifestations which best responded to belimumab, such as musculoskeletal and mucocutaneous features, and some predictors of response including Safety of Estrogens in Lupus Erythematosus National Assessment - SLE Disease Activity Index (SELENA-SLEDAI) $\geq$10, low complement, positive anti-double stranded (ds)DNA, and prednisone intake $\geq$7.5 mg/day [20,21]. The results of the RCT carried out using subcutaneous belimumab in SLE patients have recently been published and the study met the primary endpoint [22], thus paving the way to a more practical route of administration.

Recent studies investigating the effectiveness of belimumab in clinical practice have confirmed it is capable of decreasing disease activity, corticosteroid intake and flare rate, thereby hindering the expected damage progression in patients with active SLE [23–31]. Moreover, belimumab use was associated with a low number of unscheduled visits and a reduced rate of visits in the emergency room (ER), being thus cost-effective [32–35].

So far, however, predictors of response to belimumab and survival of the drug have poorly been investigated in real life setting [36]. The aim of our study was to evaluate effectiveness and safety of belimumab and identify baseline predictors of drug response or discontinuation in a clinical practice-based, large, multicentre, nationwide cohort of patients with active SLE.

2. Patients and methods

2.1. Inclusion and exclusion criteria

We included in the study all SLE patients treated with belimumab up to April 20th, 2016 in eleven Italian SLE referral centers. All patients were prospectively followed according to the EULAR (European League Against Rheumatism) recommendations [37,38] and the inclusion of patients in this study did not interfere with current clinical practice.

Inclusion criteria were 1) fulfillment of 1982 American College of Rheumatology (ACR) revised criteria for SLE [39], 2) active (according to SLE Disease Activity Index-2000 - SLEDAI-2K > 6) and refractory SLE manifestations, 3) positive anti-dsDNA antibodies either by Farr, indirect immunofluorescence (IIF) or Enzyme Linked Immunosorbent Assay (ELISA) and 4) low C3 or C4 serum levels.

SLE manifestations were defined as refractory in case of drug intolerance, unresponsiveness or disease relapse in patients treated with corticosteroids, antimalarials and/or immunosuppressants. Patients with renal disease were considered as refractory if they had a persistence of 24 h proteinuria >1 g after at least 1 year from the start of the initial therapy or in case they experienced a renal flare (24 h proteinuria >1 g following a previous complete response or doubling of 24 h proteinuria in other cases) during the subsequent therapy.

Exclusion criteria were 1) severe and active lupus nephritis (24 h proteinuria >6 g and/or creatinine > 2 mg/dl), 2) severe and active neuropsychiatric lupus, 3) potentially life threatening SLE manifestations and 4) ongoing or planned pregnancy.

2.2. Treatment with belimumab

Belimumab was added to background therapy and was intravenously administrated at 10 mg/kg on day 1, 14, 28, and then every 28 days.

2.3. Clinical and serological variables

A complete medical history, physical examination and blood samples were collected in all patients prior to the first belimumab infusion; moreover, all patients underwent clinical examination before each belimumab administration. The following clinical and serological variables were collected at baseline and then every six months in all patients: SLEDAI-2K score, prednisone daily intake, complete blood count, anti-dsDNA antibody, C3 and C4. In addition, we assessed disease activity score (DAS)-28 in patients with arthritis, Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) activity score in patients with skin manifestations. Serum creatinine, 24 h proteinuria, and urinary sediment were also examined in patients with renal involvement.

Anti-dsDNA levels were measured by ELISA, IIF or Farr assay. As a measure of damage, Systemic Lupus International Collaborating Clinics-Damage Index (SLICC-DI) score was calculated at baseline and at 12, 18 and 24 months of follow-up. Being all patients prospectively followed-up, all centers were requested to provide the SLICC-DI calculated in the visit performed five years before the initiation of belimumab, when available.

2.4. Outcome measures

SRI-4 [40] was used to assess the response to belimumab at 12 and 24 months. Therefore, SELENA-SLEDAI, British Isles Lupus Assessment Group (BILAG)-2004 and physician global assessment (PGA) were assessed at baseline, at 12 and 24 month of follow-up.

Disease flares were determined and assessed by SELENA-SLEDAI flare index (SFI); number of flares was collected at 12 and 24 months before and after belimumab initiation.

Inadequate response was defined as severe flare according to SFI or the persistence of moderate/high disease activity by physician judgment.

2.5. Safety assessment

Adverse events (AEs) were carefully recorded at each clinical evaluation for all patients during the follow-up. AE was defined as follows: “any untoward medical occurrence in a patient treated with a pharmaceutical product which does not necessarily have a causal relationship with this treatment”. AEs were subdivided in noninfectious or infectious AEs, infusion and hypersensitivity reactions. Infusion reactions were defined as AE related to belimumab occurring within 6 h after drug administration; hypersensitivity reactions were defined as AE related to belimumab

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