Belimumab for the Treatment of Refractory Systemic Lupus Erythematosus: Real-Life Experience in the First Year of Use in 18 Italian Patients

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To date, it has been estimated that more than 50% of patients affected by systemic lupus erythematosus (SLE) have suboptimal disease control: while 40% of them have chronic active disease (CAD), the remaining 10% suffer from relapsing-remitting disease (RRD) with frequent exacerbations [1,2]. This situation requires frequent changes of therapy and, in particular, increased steroid dosage, along with the obvious risk of one or more of the well-known related side effects [3,4]. In this scenario the need for new treatment options is even more evident than in other rheumatic diseases.

After 50 years with no new drug licensed for SLE, belimumab was recently approved for the treatment of active and refractory SLE. Belimumab is a human immunoglobulin G (IgG)1λ monoclonal antibody specific for soluble human B lymphocyte stimulator protein (BLyS) able to inhibit the survival of B cells, including autoreactive B cells, and it reduces the differentiation of B cells into Ig-producing plasma cells. It is indicated in active SLE in the presence of hypocomplementemia and anti-ds-DNA antibody positivity, in addition to the standard treatment regimen. The recommended dose is 10 mg/kg belimumab in intravenous administration on day 0, 14 and 28, and once a month thereafter.

The development of belimumab represents the largest trial ever conducted in SLE patients, with 2200 patients enrolled in clinical studies with long-term treatment, in some cases for more than 7 years [5]. The aim of the study was to evaluate the efficacy and safety of belimumab in the real-life experience of a single tertiary referral center of rheumatology after the first year of licensed use in Italy.

METHODS

The study group comprised 18 SLE patients with active disease despite standard therapy. They met the American College of Rheumatology (ACR) classification criteria for SLE. The patients received belimumab (10 mg/kg) in addition to their current treatment. Hypocomplementemia was considered if serum levels of C3 and/or C4 were low. Anti-dsDNA antibodies were tested by Farr assay and classified as "high titer" if exceeding three times the normal values. CAD was defined as the presence of a SLEDAI-2K ≥ 2 (excluding isolated serology) in at least two of three evaluations performed in a single year, and RRD as a SLEDAI-2K ≥ 2 in at least one of three [2]. A disease flare was defined as measurable increases in disease activity in one or more organs and systems with the onset or a worsening of signs and symptoms and/or laboratory parameters [6]. SLE clinical and serological manifestations and mean steroid dosage were compared between baseline and different time points using the Mann-Whitney test for unpaired data.

RESULTS

All the patients were female, and their mean age at first drug administration was 39.6 years (range 25–55) and mean disease duration 12.3 years (range 1–26). At baseline, 15 patients (83.3%) presented hypocomplementemia and 15 (83.3%) had positive anti-dsDNA antibodies (7 at low titer, 8 at high titer).

Fourteen patients (77.8%) had positive antiphospholipid antibodies (in 9 cases a single test was positive, in 3 two tests, and in 2 patients all three tests were positive) but only 2 of the patients had a history of associated manifestations (deep vein thrombosis in one and HELLP syndrome in the other). At baseline, 17 patients (94.4%) were treated with one or more disease-modifying anti-rheumatic drugs (DMARDs) according to standard of care (12 patients were taking hydroxychloroquine, 7 mycophenolate mofetil, 4 methotrexate and 6 azathioprine), while 1 patient was treated solely with prednisone because she was intolerant or not responsive to immunosuppressive drugs.

Seven patients (38.8%) presented CAD while 11 (61.2%) showed RRD and experienced a disease flare in the year prior to belimumab administration (articular in 5 cases, cutaneous in 3, renal in 2 and constitutional – fever, malaise, weight loss – in 1 case). During the first 6 months of therapy we recorded five disease flares: one cutaneous, three articular and one cardiovascular (pericarditis). We also observed infectious adverse events in seven cases (four infections of the upper respiratory tract, in one case recurrent; two gastroenteric infections, and one urinary tract infection). A lower limb deep vein thrombosis (DVT) was diagnosed in a patient with high positive antiphospholipid antibodies (aPL) soon after the first infusion and warfarin was initiated. No significant differences were observed between anti ds-DNA, C3 and C4 values at baseline and after 3 (t3), 6 (t6), and 9 (t9) months from the start of therapy. SLEDAI-2K showed a significant decrease from t0 to t3 ($P = 0.002$), maintained also at t6 and t9 evaluation ($P = 0.012$). The mean dose of prednisone administered required 9 months of therapy to show a significant reduction ($P = 0.045$), even though it showed a trend towards decrease also at t3 (77.2 vs. 80 mg/week) and t6 (65 vs. 80 mg/week). The detailed data are shown in Table 1.

The administration of the drug was discontinued in 3 patients (16.7%), in 2 cases because of inefficacy and in 1 case due to recurrent infections of the upper respiratory tract (after 7 infusions). The two patients stopped belimumab after 6 months (seven infusions) because of the persistence of thrombocytopenia and hand vasculitis, and after 5 months (six infusions) because of persistent arthritis, respectively. One patient was lost to follow-up because she moved to another town.

CONCLUSIONS

Although SLE is a multifaceted disease, some disease patterns can be identified depending on the clinical and serological activity. CAD defines a patient whose activity persists for at least one year, while RRD, with alternating phases of activity and inactivity and quiescence, is identified when the disease remains inactive for at least one year [2]. A recent evaluation demonstrated that fewer than 50% of SLE patients reached and maintained a stable remission [1,2]. Despite the huge advances in diagnosis and therapy, an increase in mortality remains part of the natural history of SLE, with affected patients still having a three times higher risk of death than the general population [7]. Moreover, both disease activity and side effects of the drugs used to control SLE significantly influence the quality of life [8].

Table 1. Quarterly data on disease activity, serology and steroids intake from baseline to 9 months of treatment

	t0	t3	t6	t9
No. of treated patients	18	17	15	11
Prednisone (mg/week)	66.3 (58–100)	62.5 (45–105)	62.5 (43.1–96.9)	46.9* (30.3–64.1)
Anti-dsDNA Abs (normal < 7 UI/ml)	25.7 (13.7–76.5)	18.1 (8.5–78.1)	27.0 (18.1–55.3)	24.6 (12.4–34.5)
C3 (normal 80–160 mg/dl)	69 (55.3–83)	73.5 (62.4–91)	69.5 (59.3–89.2)	79 (65.5–86.3)
C4 (normal 10–40 mg/dl)	8 (7.1–13.8)	12.1 (8.3–15.4)	11.6 (9.6–16.6)	11 (7.6–15.8)
SLEDAI 2K	9 (8–10.8)	6* (5–8)	6* (5.3–7.8)	6* (4.3–6)

Values are expressed as median and interquartile range
*Significant reduction as compared to baseline ($P < 0.05$, Mann-Whitney test).

The recent introduction of belimumab has benefited patients who, despite the proper use of standard therapy, continue to present uncontrolled disease and are therefore exposed to the possible adverse events of the drugs taken as well as to the risk of developing chronic and irreversible damage of one or more organs or systems. Data on the use of the drug in real life are still limited, but our preliminary experience seems to confirm good tolerability and safety as shown in clinical trials.

Regarding effectiveness, based on our experience of the first few months of treatment we offer some relevant preliminary observations. We noted a significant reduction in the SLEDAI-2K score after 3 months of treatment followed by a significant decrease in steroids intake after 9 months of treatment, suggesting that the effects of belimumab can be seen over time for disease activity control and steroid-sparing at different time points. Changes in serology (reduction of anti-dsDNA and increase in complement levels) were not found to be significant as pooled data. However, this lack of significance can be due to the fact that nearly half the patients had low titers of anti-dsDNA and/or slightly reduced complement. In patients with an active serology these parameters improved markedly after a few months of treatment. The long-term follow-up will likely demonstrate the true effects of the drug in terms of clinical stabilization, improvement of laboratory parameters, lack of chronic damage accrual, and stable reduction of steroid intake.

Treatment dropouts occurred in patients whose clinical history had always been characterized by closely repeated relapses. High disease activity prompted the patients and physicians to discontinue the treatment, but we should question whether a 6 month period is sufficient to assess whether belimumab is working or not. It is also important to underline that a patient who discontinued the drug for ineffectiveness after 6 months was not taking any standard therapy except for steroids due to intolerance to multiple drugs. Belimumab was stopped as a cautionary measure in a patient with recurrent infection of the respiratory tract. However, no definite attribution to the drug could be made. In fact, the patient was concomitantly taking multiple immunosuppressive drugs and a generous steroid dosage, often spontaneously increased by the patient herself. Regarding the patient who developed a DVT soon after the

first infusion, we attributed this event to high disease activity rather than to belimumab itself.

In summary, although it is premature to draw firm conclusions, our preliminary observations suggest that the improvement in clinical and serological parameters seems to occur at least after 3–6 months of treatment. Perseverance with the treatment until the first 6–12 months, supported by its tolerability and safety, can provide benefit to the patient in terms of reduced steroid dosage as well.

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