

Successful treatment with belimumab of severe systemic lupus erythematosus not responding to standard therapy: a case report

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Abstract

Systemic Lupus Erythematosus (SLE) is an autoimmune disease characterized by complex pathophysiology and heterogeneous clinical picture. Belimumab is the first biological therapy licensed for SLE.

We report the case of a 24 years old woman affected by a severe form of systemic lupus erythematosus with arthritis, muscle weakness, cervical lymphadenopathy, cutaneous involvement, fever, leukopenia, low complement levels and positivity for anti-dsDNA antibodies. Treatment with high dose steroids, hydroxychloroquine, and mycophenolate mofetil did not induce remission and several disease flares were observed. Therapy with anti-BLyS monoclonal antibody belimumab leads to a fast clinical and laboratory response and to stable remission lasting for 30 months allowing steroid tapering to very low maintenance dose.

Keywords: Systemic lupus erythematosus (SLE); Belimumab; Biological therapy

Efficacia di belimumab nel trattamento di un caso di lupus eritematoso sistemico grave non rispondente alla terapia standard

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INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a systemic autoimmune disease, whose severity and clinical manifestations are highly variable. SLE pathogenesis is not completely known; however, genetic factors, as well as hormonal and environmental triggers, play a role in the development of the abnormal immune response [1]. SLE diagnosis is based on clinical features and laboratory findings according to current classification criteria [2,3]. SLE is a chronic disease and its course is characterized by relapses and remission periods. Therefore, the clinician should set up SLE treatment according to clinical manifestations and severity of flares [4].

Current therapy includes nonsteroidal anti-inflammatory drugs, corticosteroids, anti-malarial agents and immunosuppressive drugs. Belimumab, an anti-B lymphocyte

stimulator (BLyS) monoclonal antibody, is the first biologic drug licensed for SLE treatment.

CASE REPORT

We report the case of a 24 years old woman, who attended our outpatient clinic in February 2012 because of intense joint pain

Why we do describe this case:

- *A severe form of SLE with several disease flares*
- *Non-response to standard therapy*
- *Fast and long-term remission obtained with anti-BLyS monoclonal antibody belimumab*

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localized at knees, hands and wrists. She reported a history of asthma and allergic rhinitis (dust mites, dog dander, and olive tree pollen) for which she underwent sublingual immunotherapy in 2010. This therapy was withdrawn because a lack of benefit after two years.

Clinically, she complained of arthritis, muscle weakness, cervical lymphadenopathy and fever associated with leukopenia (white blood cells: $2,640 \times 10^9/\mu\text{l}$), low complement levels (C3: 75 mg/dl, C4: 19 mg/dl) and increased erythrocyte sedimentation rate (ESR: 55 mm/h) and C-reactive protein (CRP: 14 mg/l) levels. Urinalysis was unremarkable. Immunological investigations showed positivity of antinuclear (ANA, 1:1280 titer with homogenous pattern), anti-double stranded DNA (ds-DNA) and SSA-Ro antibodies; antineutrophil cytoplasm antibodies (ANCA) and antiphospholipid antibodies were negative. Clinical features and laboratory data lead to the diagnosis of systemic lupus erythematosus (SLE) according to current criteria [2,3].

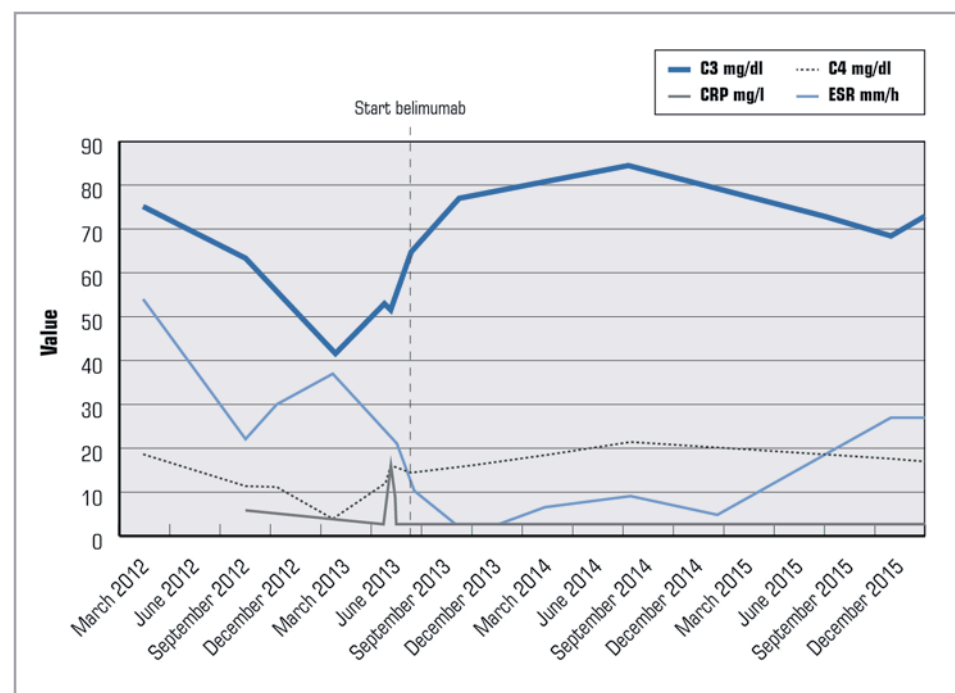
The patient was first treated with prednisone (1 mg/kg/day), gradually tapered to 12.5 mg/day, associated with hydroxychloroquine (HCQ) (200 mg twice a day), which did not provide clinical benefit. Then, after a cutaneous flare, in November 2012 HCQ was stopped and mycophenolate mofetil (MMF) (2 g/daily) was started in association with glucocorticoids at variable doses according to clinical needs. Despite these

medications, the disease was unsatisfactory controlled.

In May 2013, she presented fever (39°C), fatigue, intense knees' pain and swelling, and was admitted to our Department of Internal Medicine, Clinical Immunology Unit. Physical examination revealed severe knees' inflammation, tachycardia, and a soft systolic cardiac murmur. Chest X-ray was negative. She also presented cutaneous signs as *livedo reticularis* and dermatographism. Laboratory data showed worsening of leukopenia ($1.7 \times 10^9/\mu\text{l}$) with severe lymphopenia ($0.3 \times 10^9/\mu\text{l}$) associated with mild anemia and thrombocytopenia ($62 \times 10^9/\mu\text{l}$), abnormal liver function tests (AST 145 U/l; ALT 155 U/l) and increased LDH level (1680 U/l). The severe inflammatory status was confirmed by high CRP (17.1 mg/l) and ferritin ($29,799 \mu\text{g/l}$) levels. Blood and urine cultures were negative. A transthoracic Doppler echocardiography showed normal valvular structures without signs of endocarditis as well as normal systolic and diastolic functions. Serology resulted negative for Cytomegalovirus infection but was positive for a recent Epstein-Barr virus infection (positivity of VCA IgM and EBNA 1 IgG antibodies). A computer tomography scan showed liver and spleen enlargement, compatible with the viral infection, and no signs of malignancy. In accordance with these clinical features and laboratory results, we hypothesized an SLE flare triggered by EBV infection. During hospitalization, MMF was

Figure 1. Trend of laboratory parameters before and during belimumab treatment. The vertical line represents the start of belimumab

ESR = Erythrocyte Sedimentation Rate
CRP = C-reactive protein



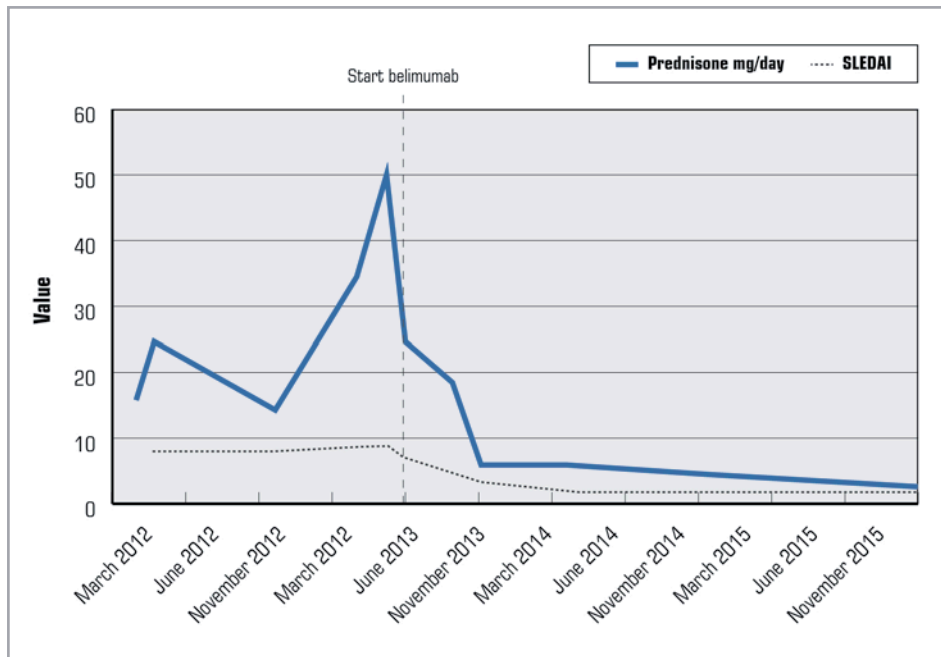


Figure 2. Trend of SLEDAI score (Systemic Lupus Erythematosus Disease Activity Index) and prednisone dose before and during belimumab treatment. The vertical line represents the start of belimumab

stopped, and the patient received methylprednisolone (five 500 mg i.v. infusions) followed by prednisone 1 mg/kg/day with transient but unsatisfactory clinical improvement (Figure 1).

On the basis of the poor disease control obtained with the previous treatments, we decided to start therapy with the anti-BLyS monoclonal antibody belimumab (10 mg/kg) according to the good results obtained by this biological drug in SLE patients refractory to standard therapy [4-8]. At the time of the first belimumab administration (June 2013) the patient was on treatment only with prednisone 25 mg/daily. No other lupus-specific medications were continued while she was on belimumab. The first three infusions were given 14 days apart and were followed by monthly infusions. We observed a disappearance of arthralgia and constitutional symptoms such as fatigue and fever, 30 days after belimumab was initiated. Hematological parameters and C3 and CRP values reached the normal level after three months of therapy. The amelioration of clinical and laboratory data allowed to decrease the prednisone daily dose from 25 mg to 18.5 mg after 4 months from the beginning of belimumab treatment.

Nowadays, the patient has received 33 belimumab monthly infusions which were well tolerated without any side effect. This therapy leads to a stable remission lasting for 30 months in the absence of disease flares and allowed a further tapering of the prednisone daily dosage to 2 mg (Figure 2).

Main questions the clinician should ask himself facing such a patient:

- Which are the clinical symptoms and laboratory data suggesting the lack of response to standard therapy?
- How many disease flares should arise to decide to switch from standard therapy to biological drugs?
- Which are the potential side effects of the long-term biological treatment?

DISCUSSION

Despite the current incomplete understanding of SLE pathogenesis, it is well known that B cells play a key role in the development of the disease mainly through the production of autoantibodies. Belimumab represents the first biological targeted therapy licensed for the treatment of SLE patients with active disease not responding to conventional therapies [5]. Belimumab is a fully human IgG1 λ recombinant monoclonal antibody directed against soluble B lymphocyte stimulator (BLyS, also known as BAFF), a member of the tumor necrosis factor (TNF) family. BLyS is involved in lymphocyte survival, activation, and proliferation. In the context of an autoimmune disorder such as SLE, elevated BLyS levels contribute to autoantibodies production and immune-complexes formation leading to inflammatory response and tissue damage. The interaction between belimumab and soluble BLyS prevents the binding of this growth

factor with its receptors thus decreasing B-cell survival and autoantibodies production.

Since 2013, we have treated with belimumab 10 SLE patients who were refractory to standard therapy. Among them, 7 showed a fast and long-standing response whereas 3 discontinued belimumab for inefficacy. Here we report the successful treatment with belimumab of a young woman with uncontrolled severe active SLE not responding to conventional treatment. Among the wide spectrum of drugs used for SLE therapy, corticosteroids are commonly used. Side effects of long-term corticosteroid intake as

hypertension, diabetes, weight gain and osteoporosis are well-known. These side effects could be reduced using a low maintenance daily dose < 7.5 mg [9]. Accordingly, the clinician should consider the best treatment strategy to reduce steroid dose to the lowest possible amount. In our case, belimumab allowed a quick tapering of prednisone without recurrence of the disease. Nevertheless, as belimumab is a relative young drug, more experience is required to ameliorate its management and to know its long-term efficacy and potential side effects.

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