

# Safety of belimumab in association with denosumab in a patient affected by Lupus Erythematosus: a case report

Case report

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## Abstract

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease characterized by multisystemic involvement. Owing to multifactorial etiologies, low bone mineral density (BMD) osteoporosis (OP) and fragility fractures (FFx) have been very frequently documented in these patients. Appropriate treatments to minimize underlying immunologic disease activity remain mandatory, and the development of strategies to prevent and treat important complications as osteoporosis is needed.

We present the clinical case of a female SLE patient treated simultaneously with belimumab (anti-BLyS) for the underlying disease, and denosumab (anti-RANKL) for concomitant severe osteoporosis. As these monoclonal antibodies have been recently introduced into the market, their combination has not been reported in literature yet. In this case, the combined administration proved a viable option for a SLE patient with osteoporosis and bisphosphonates contraindications.

**Keywords:** Lupus Erythematosus, Systemic; Belimumab; Denosumab

*Sicurezza di belimumab in associazione a denosumab in una paziente affetta da lupus eritematoso: un caso clinico*

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## INTRODUCTION

Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disorder characterized by multisystemic involvement. Although the exact etiology has not been determined, it has been shown that genetic, environmental, and hormonal factors play a role in its pathogenesis. SLE is characterized by disturbances of both innate and adaptive immune systems, with dysregulation of T and B cells, cytokines secretion, and autoantibodies production [1]. Its prevalence ranges from 40 to 200 cases per 100,000 [2]. Women are affected by SLE nine times more frequently than men, particularly after puberty and before menopause [2]. For reasons not entirely understood, SLE is also

more frequent in certain ethnic groups, e.g. African-Americans and Hispanics [2]. The broad spectrum of clinical presentations makes the SLE the prototypic multisystem

### Why we describe this case

*The occurrence of osteoporosis in SLE patients has been widely described in literature. However, often in SLE patients kidney dysfunction or kidney failure concur, for which bisphosphonates are contraindicated. Therefore, it is mandatory to find osteoporosis treatments compatible with the therapy for the underlying disease*

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Parameter	Detected value	Normal values
WBC (n/l)	2800	4000-10,000
Neutrophils (n/l)	1800	1500-8000
Lymphocytes (n/l)	800	1000-4000
PLTs (n/l)	98,000	140,000-450,000
ANA	1/160	< 1/80
Anti-dsDNA (UI/l)	89	< 10
C3 (mg/dl)	25	83
C4 (mg/dl)	8	15

**Table I.** Laboratory analyses performed in 2004

ANA = antinuclear antibodies;  
 Anti-dsDNA = anti-double-stranded DNA;  
 PLTs = platelets;  
 WBC = White Blood Cells

autoimmune disease. It may present with very different clinical manifestations, ranging from fatigue and mild skin rash to end-stage renal failure [2,3]. A wide spectrum of clinical and serological findings often misleads and delays the diagnosis. Therefore, SLE diagnosis still represents a challenge, remaining largely based on clinical judgment [3] and requiring often an interdisciplinary approach [4].

In 2012, the Systemic Lupus International Collaborating Clinics (SLICC) network presented a set of criteria (SLICC-12) to classify the disease [5]: in the validation set, the SLICC classification criteria resulted in fewer misclassifications compared with the revised 1997 American College of Rheumatology (ACR) classification criteria [6]; besides, it had a greater sensitivity (97% versus 83%) but a lower specificity (84% versus 96%) [5]. According to the SLICC criteria, the classification of SLE seems to be achieved more frequently than with the previous 1997 ACR criteria [3,7]. The clinical course of SLE is characterized by spontaneous or treatment-induced remissions and flares. Steroids and immunosuppressive drugs are the cornerstone of SLE treatment, but their use, especially in high doses and for long periods, may be burdened by the onset of medication-induced adverse effects.

The occurrence of osteopenia, osteoporosis (OP), and fragility fractures (FFx) in SLE patients has been widely described in literature [8-13]. Osteopenia and osteoporosis are reported in 25-74% and in 1.4-68% of SLE patients, respectively, and the occurrence of symptomatic fractures is increased 5-fold in women with SLE [14]. These frequencies vary widely as a consequence of differences in size, age, sex, ethnicity, disease severity, and medication use between the patient groups investigated [14].

The etiology of bone loss in SLE is supposed to be multifactorial, including traditional osteoporosis risk factors, inflammation, contraindications to sun exposure and subsequent reduction of activation of vitamin D, metabolic factors, hormonal factors, serologic factors, and medication-induced adverse effects [12,14,15].

We report the case of a woman affected by SLE and severe osteoporosis with osteoporotic fractures, contraindication to bisphosphonates due to a history of renal insufficiency, and concomitantly treated with belimumab and denosumab, two recently marketed monoclonal antibodies. Belimumab's mechanism of action is based on the known pathological functions of B lymphocyte stimulator (BLyS), a tumor necrosis factor (TNF) superfamily ligand. BLyS plays a critical role in the development and homeostasis of B lymphocytes. Under pathological conditions (as occurs in SLE), B lymphocytes produce the auto-antibodies responsible for the clinical features of SLE. By inhibiting BLyS, belimumab is able to effectively block this pathological pathway [8,16,17]. Denosumab is an anti-receptor activator of nuclear factor-kappaB (NFκB) ligand antibody, a fully human monoclonal antibody that binds the cytokine RANKL (receptor activator of NFκB ligand), an essential factor initiating bone turnover. RANKL inhibition blocks osteoclast maturation, function and survival, thus reducing bone resorption [18-20].

To date, there are no studies in literature on the efficacy and safety of combination therapy with belimumab and denosumab. This is probably due to the recent introduction on the market of these monoclonal antibodies.

## CASE PRESENTATION

We report the case of a 54-year-old female patient. In 2004, she came to our attention with malar rash, migratory arthralgias, recurrent epistaxis, and morning articular stiffness lasting more than one hour. Her previous medical history was significant for arterial hypertension, turbinate hypertrophy, and occasional leukopenia.

Laboratory analyses showed leukopenia, thrombocytopenia with antinuclear antibodies (ANA) = 1/160 with granular pattern on immunofluorescence, anti-dsDNA positive, hypocomplementemia (Table I), presence of

	March 2014 – first administration of belimumab	August 2014 – after 5 months of therapy with belimumab	December 2014 – first administration of denosumab	June 2015 – after six months of belimumab/denosumab combined therapy	December 2016 – last visit
SLEDAI	13	10	-	6	6
WBC (n/l)	3340	3216	3412	3945	6440
HB (g/dl)	10.9	11.1	11	11.4	10.4
PLTs (n/l)	130,000	126,000	146,000	126,000	254,000
Creatinine (mg/dl)	1.89	1.95	2.01	2.05	1.71
Proteinuria	no	no	no	no	no
C3 (mg/dl)	32	79	82	68	85
C4 (mg/dl)	11	18	21	17	12
Arthritis	yes	no	no	no	no
ANA	1/640	1/320	1/320	1/640	1/320
Anti-dsDNA (U/l)	72	22	40	64	38

lupus anticoagulant antibodies and anti-beta2-glycoprotein I IgG, and anticardiolipin IgG positive at low levels.

After a deep vein thrombosis with pulmonary thromboembolism, the patient had to start warfarin therapy. Furthermore, a MRI of the encephalon, requested for the suspicion of neurological involvement, showed signs of microischemic strokes.

According to the ACR 1997 criteria, a diagnosis of SLE was made, and the patient started a therapy with prednisone (initially at high dose, 25 mg/die) and hydroxychloroquine (200 mg/die), while awaiting the therapy with cyclophosphamide, which was started in September 2004 and shortly afterwards suspended owing to pancytopenia and gastrointestinal intolerance.

Due to incomplete disease control with steroid and hydroxychloroquine therapy (hypocomplementemia, anemia, and arthralgia were still present) she was given a therapy based on azathioprine, which was suspended, alongside hydroxychloroquine, because of the worsening of leukopenia (August 2005). From 2005 to 2013, the disease went to partial remission with steroid only therapy (treatment range between 10 and 12.5 mg/die).

In March 2013, during treatment with prednisone 12.5 mg/die, her renal function worsened: serum creatinine was 3.1 mg/dl and proteinuria increased to 0.9 g/24 hours. Even though lupus nephritis was suspected, renal biopsy was not performed because serum creatinine and proteinuria decreased after starting ACE-inhibitors; however, bisphosphonates, that she had been taking

since 2011 for a high risk of bone fracture documented by a dual-energy X-ray absorptiometry (DXA) with a vertebral T-score -3.0, were suspended. As osteoporosis-prophylaxis, the patient continued therapy with calcium carbonate and vitamin D (calcifediol).

Alongside ACE-inhibitor treatment, she started therapy with mycophenolate (500 mg twice a day) and her serum creatinine stabilized, reaching mean values = 1.2-1.4 mg/dl, denoting stage 2 renal insufficiency according to Kidney Disease Outcomes Quality Initiative (NKF KDOQI)<sup>TM</sup> classification.

In February 2014, mycophenolate was suspended for gastrointestinal intolerance and a mild non erosive polyarthritis; her renal situation was stable, with no proteinuria.

She presented in March 2014 with anti-dsDNA persistently positive (Table II), low complement levels, persistent fatigue, and oligoarthritis on wrists and small joints of the hand.

After proper literature searches and discussion with nephrologists, she was given a therapy with belimumab (Benlysta<sup>®</sup>) at the dosage of 10 mg/kg (600 mg) once every month.

After six infusions, in August 2014 the patient had a good clinical and serological response: no drug adverse event arose during treatment, arthritis reached clinical remission, renal function (creatininemia and proteinuria) remained satisfactory, and no flares of SLE had happened. Complement levels improved (Table II), anti-dsDNA reduced, no hematological alterations occurred, and total dosage of prednisone could be reduced to 7.5 mg/die.

**Table II.** Laboratory analyses performed from March 2014 to December 2016

ANA = antinuclear antibodies;  
Anti-dsDNA = anti-double-stranded DNA;  
HB = hemoglobin;  
PLTs = platelets;  
SLEDAI = Systemic Lupus Erythematosus Disease Activity Index;  
WBC = White Blood Cells

In December 2014, the patient had a spontaneous rib fracture and right metatarsal heads stress fractures. Dual-energy X-ray absorptiometry (DXA) showed reduced bone mineral density with vertebral T-Score = -3.2. At that time, her osteoporosis was treated with calcifediol 50.000/UI per month and calcium carbonate every day. Bisphosphonates were suspended due to contraindications for renal insufficiency. Given this clinical picture, the patient started denosumab (Prolia®) 60 mg administered as a single subcutaneous injection once every 6 months, in association with calcium 1000 mg daily and supplementation of already set vitamin D.

In February 2016, DXA documented a vertebral T-score = -1.7. No new spontaneous fractures occurred. The patient continued the treatment with belimumab 10 mg/kg/month and denosumab 60 mg/6 month, and we could reduce the dosage of prednisone to 5 mg/die. To date, she has had thirty-two infusions of belimumab and five injections of denosumab.

## DISCUSSION AND CONCLUSION

In literature, there are no case reports about the concurrent use of two monoclonal antibodies as belimumab and denosumab.

The etiology of bone loss in SLE is supposed to be multifactorial, including traditional osteoporosis risk factors, inflamma-

tion, metabolic factors, and medication-induced adverse effects. Osteoporotic fractures are present in 20-26.1% of SLE patients and often an appropriate treatment is mandatory. At the same time, a large number of SLE patients suffer from many comorbidities and many organ involvement by the underlying disease [2,3,11,12,14]: therefore, they need a basic therapy able to ensure an absent or a low SLE disease activity, and at the same time an appropriate therapy for the osteopenia/osteoporosis. Nowadays, an increasing number of patients are treated with belimumab, due to its proven efficacy in reducing flares. As a result, case reports and trials concerning this association and its interactions are required.

In this case report, the treatment with belimumab and denosumab resulted in improved patient's conditions. By considering the mechanisms of action of the two drugs (anti-RANKL and anti-BLyS), we do believe that the combined administration could be a viable option for patients with SLE, osteoporosis, and bisphosphonates contraindications. Finally, the six-month administration of denosumab is particularly suitable for patients who are exhausted because of their multiple chronic therapies; furthermore, it ensures an effective alternative therapy, since no side effects concerning kidneys (as opposed to bisphosphonates) and heart (a known side effect of strontium ranelate) were detected.

### Key points

- *Etiology of bone loss in systemic lupus erythematosus (SLE) is multifactorial, including traditional osteoporosis risk factors, inflammation, metabolic factors, and medication induced adverse effects*
- *In SLE patients, often kidney dysfunction or kidney failure concur, thereby contraindicating the use of bisphosphonates*
- *Considering the mechanisms of action of belimumab (anti-BLyS) and denosumab (anti-RANKL), two monoclonal antibodies acting upon two different molecular pathways, combined administration could be a worth option to be considered for patients with SLE, renal insufficiency, and osteoporosis*

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