Belimumab may not prevent lupus nephritis in serologically active patients with ongoing non-renal disease activity

Christopher Sjöwall and Lars Cöster

Linköping University Post Print

N.B.: When citing this work, cite the original article.

Original Publication:

http://dx.doi.org/10.3109/03009742.2014.887769
Copyright: Informa Healthcare
http://informahealthcare.com/

Postprint available at: Linköping University Electronic Press
http://urn.kb.se/resolve?urn=urn:nbn:se:liu:diva-107239
Title: Belimumab may not prevent lupus nephritis in serologically active patients with ongoing non-renal disease activity

Authors: Christopher Sjöwall* and Lars Cöster

1. Rheumatology/AIR, Department of Clinical and Experimental Medicine, Linköping University, Linköping

* Corresponding author:
Rheumatology Unit, University Hospital, SE-581 85 Linköping, Sweden
E-mail address: christopher.sjowall@liu.se
Telephone +46 10 1032416
Fax: +46 10 1031844

Running head: Debut of nephritis on belimumab treatment
LETTER

Systemic lupus erythematosus (SLE) is an inflammatory condition characterized by multiple organ involvement, antibodies against nuclear constituents and deposition and/or formation of immune complexes in affected organs (1). The current treatment strategies intend to relieve symptoms, induce remission, or at least allay the disease activity, and prevent future flares and organ damage (2). Belimumab, a monoclonal antibody that neutralize soluble B-lymphocyte stimulator (BLyS), is the first U.S. Food and Drug Administration-approved treatment for SLE in over 50 years (3). In Europe, belimumab is indicated as adjunctive therapy in adult patients with active SLE despite standard of care (4). Herein, we report one case with severe non-renal SLE that developed nephritis on belimumab treatment. Oral and written informed consent was obtained from the affected patient.

A non-smoking Caucasian woman born in 1951 with a history of cervical cancer in situ and enucleation of right eye due to malignant melanoma was referred to our unit in July 2004 on the suspicion of rheumatoid arthritis (RA). She had two successful pregnancies and one miscarriage, and suffered from arthralgias for many years. Interestingly, her mother was diagnosed with RA in her 60s but died due to rapidly progressive renal failure 10 years later (high levels of myeloperoxidase-ANCA were found, but renal biopsy was never performed). Autoantibody testing showed a positive homogeneous ANA, whereas anti-CCP and rheumatoid factor tests were negative. The consultant rheumatologist found symmetrical hand synovitis of metacarpophalangeal and proximal interphalangeal joints. No laboratory abnormalities, including complement, except for a low anti-dsDNA titre (1:10) detected by Crithidia luciliae test were recorded. Treatment
with a low daily dose oral prednisolone and hydroxychloroquine (HQ) 200 mg on the suspicion of SLE polyarthritis was introduced. Hand X-ray showed one single erosion. In 2007 the patient was affected by a conjunctival bleeding in her left eye. HQ was discontinued due to the patient’s wish. Six months later she was doing well without HQ. Anti-dsDNA was still positive at titre 1:10, whereas complement levels were normal.

In January 2008, the patient complained of stiffness and muscle pain. 20 mg prednisolone was temporarily re-introduced in tapering dosage. Two weeks later, she described chest pain with severe fatigue and arthralgias. Redness of the throat (no ulcers) was recorded, but no signs of synovitis. One week later, she still had flu-like muscle aches and fever. Classical complement function was slightly reduced to 70% (ref. 80–120%) and anti-dsDNA borderline positive. Another 10 days later, she presented with fever (38.2°C) and swelling of her left leg. Acute ultrasound showed a large thrombosis up to the groin. Computed tomography (CT) of the chest revealed no signs of embolization. LMW-heparin and warfarin were initiated. Coomb’s test was strongly positive whereas lupus anticoagulant test and IgG anti-cardiolipin were weakly positive; but importantly, high levels of IgM against cytomegalovirus (CMV) were found. In spring 2008, the patient had recovered and felt fairly well. Warfarin treatment was finished in January 2009, whereas other treatments were unchanged.

In January 2011, the patient experienced shortness of breath and chest pain. High-resolution CT showed pleural effusion on left side, but no embolization. 40 mg prednisolone daily was required to resolve symptoms. Azathioprine was added, but soon ended due to elevated transaminases. During the next year, it was very difficult to reach reasonable doses of prednisolone due to pleuritic chest pain. Anti-dsDNA rose and
anti-C1q antibody levels reached the highest level measured to date at our laboratory. Mycophenolate mofetil (MMF) was initiated, but ended due to nausea already after 1 month. Methotrexate was initiated, but terminated quickly due to headache.

In July 2012, the patient once again presented with pleural effusion and chest pain. Complement consumption was substantial with C3 0.40 (ref. 0.7–1.3 g/L) and C4 <0.05 (ref. 0.13–0.32 g/L), but urinalysis normal. Belimumab (520 mg/month) was introduced together with a lower dose of MMF (1 g/day). In October, the patient was doing better and prednisolone was gradually reduced. In December, she complained of loss of appetite and loss of weight. The pleuritic chest pain had disappeared although prednisolone had been reduced to 10 mg.

In May 2013, the patient returned to rheumatology ward after acute chest X-ray revealing new onset of pleural effusion. The anti-dsDNA titre remained high in combination with considerable complement consumption despite 10 months treatment with belimumab plus MMF and prednisolone. Albumin on urine dipstick, haematuria and high-moderate amount of urinary casts were detected. Urine albumin:creatinin ratio was 41 (ref. <3). Anti-dsDNA titre >1:20000; C3 0.60 and C4 0.10. Renal biopsy performed in June 2013 revealed proliferative lupus nephritis (LN) with extensive immune deposits, a high degree of inflammatory activity and segmental necrotic changes in 50% of the glomeruli (WHO class III). Limited chronic changes with fibrosis were found in the renal interstitium. Belimumab was discontinued, glucocorticoids increased and cyclophosphamide introduced according to Euro-Lupus regimen (5). At the evaluation-visit 3.5 months later, the chest pain was gone and the X-ray showed total regression of pleural effusion. Urinalysis and complement proteins were normal,
whereas anti-dsDNA titre had diminished from 1:20480 to 1:160 and anti-C1q levels from >1600 to 26 units. Cyclophosphamide was ended. A renal re-biopsy preformed in December 2013 confirmed the assumption of renal remission.

This case illustrates a patient with initially mild SLE. Possibly triggered by a CMV infection, her condition worsened and was subsequently mainly characterized by serositis resistant to any treatment but glucocorticoids. Although she fits well in the subgroup of patients who should benefit from belimumab (4) – clinically active, high anti-dsDNA and low complement – the treatment was unsuccessful and could not prevent the development of LN. Even in the BLISS-52 and -76 trials some individuals without signs of renal involvement at baseline received belimumab and developed LN during the study period (6, 7). Obviously, our patient was at high risk of renal involvement since she had been exposed to raised anti-dsDNA titres and complement consumption for a long time. The target for belimumab, BLyS, has indeed been detected in renal specimens of patients with active LN (8); and BLyS levels have been shown to associate with global lupus activity indices (9). Thus, it is not unlikely that belimumab delayed the onset of LN in this particular patient, but the active serology was not significantly improved until she received cyclophosphamide. This case underlines that the assortment of a patient subgroup suitable for belimumab automatically selects individuals that are prone to – and at high risk of – developing LN. This is important to take into account, both in the selection of the “right” patients to receive belimumab in the everyday clinical practice and when designing further belimumab clinical trials.
REFERENCES


FIGURE LEGEND

**Figure 1:** Panel A illustrates the patient's body weight and daily prednisolone dose; panel B, SLE disease activity index-2K (SLEDAI) and modified SLEDAI (with the exclusion of laboratory items for hypocomplementaemia and anti-dsDNA antibody binding); panel C, erythrocyte sedimentation rate and C-reactive protein levels; and D, haemoglobin and lymphocyte count. LN indicates the onset of lupus nephritis.
Figure 1: