Rituximab-refractory lupus nephritis successfully treated with belimumab

Sirs,

We report a case of a 25-year-old patient who was diagnosed with systemic lupus erythematosus (SLE) at the age of 11 on the basis of a history of arthritis, fever, vasculitic skin lesions, positive antinuclear antibodies (1:600), anti-dsDNA antibodies (1:200) and low complement (C3: 53 mg/dL, C4: 3 mg/dL). At the time of diagnosis, the urinalysis revealed nephrotic range proteinuria with active sediment. The renal biopsy showed a class IV LN, with an activity index (AI) of 3 and a chronicity index (CI) of 0. She received treatment with high-dose prednisone and cyclophosphamide (6 pulses of 1100 mg each) achieving complete remission. She continued therapy with azathioprine and medium doses of prednisone. Between 2002 and 2012 she suffered several nephritic flares, had two additional renal biopsies done and received a number of different therapies, including four courses of rituximab, finally achieving complete remission (Table I, Fig 1).

In January 2013, after one year in complete remission, the patient presented again with edema and hypertension. Blood tests revealed hypocomplementaemia (C3 45 mg/dL, C4 2 mg/dL), positive anti-ds-DNA antibodies (72 UI/mL) and hypoalbuminaemia (3 g/dL) with normal renal function. The urine had a Pr/Cr ratio of 5 with active sediment. Metilprednisolone pulses (500 mg x 3 days) and immunoglobulins (0.4 mg/kg x 5 days) were administered. However, proteinuria increased after therapy (Fig. 1). Three additional pulses of 500 mg CYC were given, with no effect. Taking into account the clinical history of the patient, with insufficient long-term response to several treatments, off-label therapy with belimumab (10 mg/kg at weeks 0-2-4, then every 4 weeks) was added to treatment with hydroxychloroquine, prednisone 5 mg/d, MMF (750 mg/day), tacrolimus (7 mg/day) and enalapril. Proteinuria started to decrease at month 2, and 4 months after the first infusion of belimumab complete remission was achieved. Since then, the patient has been on treatment with MMF, tacrolimus, low doses of prednisone, hydroxycloroquine and belimumab. In April 2015, tacrolimus was stopped after two years of her being in complete remission. Approximately 50% of patients with SLE are expected to suffer LN (1). Lupus patients with nephritis have lower survival rates (2), thus treatment should aim for complete renal response avoiding treatment-related damage (1).

Belimumab is a human immunoglobulin-G1 λ monoclonal antibody that inhibits the biologic activity of soluble B-lymphocyte stimulator (3). In 2011 belimumab was approved for autoantibody-positive SLE with disease activity despite standard therapy. (4, 5). Patients with severe active LN were not enrolled in the pivotal BLISS-52 and BLISS-76 trials, therefore, belimumab is not licensed to treat severe LN (6).

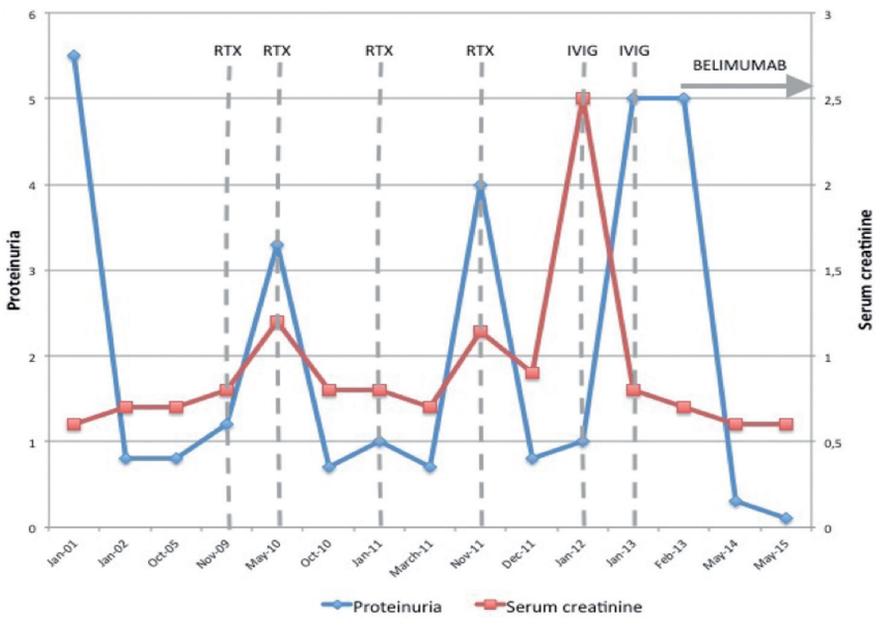

Fig. 1.

On the other hand, pooled subgroup analysis have shown that belimumab may be effective in patients with higher baseline SLE disease activity, identified as those with anti-dsDNA positivity, hypocomplementaemia, a SELENA-SLEDAI ≥10 and/or requiring treatment with corticosteroids (7). Patients with active LN usually fulfil these conditions.

Our patient had a longstanding relapsing LN, with biopsies showing persistent renal activity. She had been treated with many different schemes, all of them unsuccessful. Renal flares were repeatedly treated with rituximab, a drug frequently effective in this setting (8). However, in this case rituximab only helped to achieve partial remissions with early relapses. Thus, belimumab was tried as a last option.

Belimumab has been previously used in scarce patients with lupus nephritis, mainly to maintain remission (9, 10). As far as we know, our patient is the first one reported in whom belimumab could achieve complete remission after failure of several therapies, including rituximab. Awaiting the results of ongoing clinical trials, we believe that belimumab could be added to the list of potential treatments for patients with refractory forms of LN.

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Table I.

DATE	CLINICAL	LABORATORY	TREATMENT
2001		**FIRST RENAL BIOPSY:** Lupus nephritis class IV-G (A). Glomerular activity index: 3, chronicity index: 0	CYCLOPHOSPHAMIDE (6 x 1.1gr). Maintenance therapy: azathioprine + prednisone
2002-2005	Complete remission. Osteonecrosis of both knees. Obesity	Normal complement No proteinuria. No active sediment	Prednisone (10-20 mg/ day) Azathioprine 150 mg/day
October 2005	Polyarthralgia	Proteinuria: 0.8 g/24h. Haematuria Low complement (C4: 3 mg/dL)	Prednisone 10 mg/day STOP Azathioprine MMF 1g/12h
June 2009	Transferred from Paediatrics to Nephrology Department	Anaemia (Hb: 9.6 g/dL) AntiDNA antibodies: 241 UI/mL Proteinuria: 1.2 gr/24h. Active sediment	Prednisone < 7.5 mg/day MMF 1g/12h Tacrolimus 5 mg/12h HCQ 200 mg/day
November 2009		Anaemia (Hb: 9.2 g/dL) AntiDNA antibodies: 185 UI/mL Low complement (C3: 75 mg/dL, C4: 3 mg/dL) Proteinuria: 1.1 gr/24h. Active sediment	Prednisone < 7.5mg/day HCQ 200 mg/day MMF 1g/12h Tacrolimus 5 mg/12h RITUXIMAB (1g x 2 weeks apart)
November 09-May10	Partial renal remission	Proteinuria: 0.8 gr/24h. Active sediment	Prednisone < 7.5 mg/day HCQ MMF 1g/12h Tacrolimus 5 mg/12h
May 2010	Leg swelling Arterial hypertension	Renal failure (serum cretinine:1.2 mg/dL, GFR: 55 mL/min/1.73 m^2) Proteinuria: 3.3 gr/24h. Active sediment	RITUXIMAB (1gr x 2 weeks apart) CYCLOPHOSPHAMIDE 750 mg
		SECOND RENAL BIOPSY: Lupus nephritis class IV-G (A/C). Glomerular activity index: 6, chronicity index: 1	
May 2010-January 2011		GFR: >60 mL/min/1.73 m^2, Proteinuria: 0.7g/24h	Serum cretinine 0.7 mg/dL Prednisone < 7.5 mg/day HCQ MMF 1g/12h Tacrolimus 10 mg/24h
January 2011	Transferred to the Autoimmune Diseases Unit	Proteinuria 1gr/dL. Active sediment	RITUXIMAB (1g x 2 weeks apart) CYCLOPHOSPHAMIDE 750 mg
January-November 2011		Partial remission Proteinuria: 0.7 mg/dL	Prednisone < 7.5 mg/day HCQ MMF 1g/12h Tacrolimus 10 mg/24h Enalapril 2.5 mg/24h
November 2011	Leg swelling Fatigue	Serum creatinine: 1.14 mg/dL GFR: 45 mL/min/1.73 m^2 Proteinuria: 4g/24h. Active sediment	RITUXIMAB (1g x 2 weeks apart)
January 2012	Leg swelling Fatigue Arterial hypertension	Serum creatinine 2.5 mg/dL GFR: 33 mL7min/1.73 m^2 Proteinuria: 1gr/24h. Active sediment Low complement (C3: 60 mg/dL, C4: 8 mg/dL) **THIRD RENAL BIOPSY:** lupus nephritis class IV-G (A/C). Glomerular activity index: 12, chronicity index: 8.	Pulses of methyl-prednisolone (250 mg x3) IMMUNOGLOBULINS (0.4 mg/kg x 5 days)