Letters to the Editors

Efficacy of belimumab for the long-term maintenance therapy of thrombocytopenia in systemic lupus erythematosus

Sirs,

Thrombocytopenia in systemic lupus erythematosus (SLE) is usually mild and asymptomatic; nevertheless, in some cases it requires therapeutic intervention and the long-term management can represent a clinical challenge (1). Belimumab, an anti-BLyS human monoclonal antibody, has been licensed for the treatment of active SLE. To date, no clear data are presently available as regard thrombocytopenia in SLE under belimumab.

We describe the case of a 27-year-old woman suffering from SLE with skin, joint and haematological manifestations, anti-dsDNA and antiphospholipid positivity, and low complement. In February 2013, under antimalarial and low-dose aspirin therapy, the platelet count dropped to 17,000/μL. Prednisone 1 mg/kg/day and high-dose intravenous immunoglobulins (IVIG) were introduced with only transient improvement. Cyclosporine and tacrolimus was not tolerated due to systemic arterial hypertension and unremitting headache. Azathioprine 2 mg/kg/day was effective but burdened by liver toxicity. In September 2013 the patient was treated with prednisone 500 mg intravenously for three days, followed by rituximab 1 gram two weeks apart, associated with azathioprine 1 mg/kg/day, hydroxychloroquine and prednisone 0.5 mg/kg/day in tapering. At month +5, with CD19+B cell count still depleted, platelets dropped down to 40,000/μl and patient showed a cutaneous flare. High-dose IVIG was introduced with transient platelet increase but patient developed neutropenia and pleuro-pericarditis; SLEDAI-2k was 15. In April 2014, with platelet count 25,000/μl, patient received methylprednisolone 1000 mg/day for three days followed by prednisone 0.5 mg/kg/day and the second IVIG cycle. Belimumab 10 mg/kg was started soon after the second IVIG cycle and prednisone was slowly tapered. Platelet count rapidly increased and an improvement on skin and serositic manifestations was seen. A third and last course of IVIG was given and patient continued belimumab, OH chloroquine and low-dose prednisone. During the following 36 months no relapse of thrombocytopenia nor lupus flares were seen. At the last follow-up platelets were 178,000/μl and SLEDAI-2k score was 4 (Table I).

B-cells play a crucial role in the pathogenesis of SLE-related thrombocytopenia. Recently, directly targeting of the B-cells by rituximab has shown clinical efficacy in several SLE manifestations, including haematological manifestations (2), and it is currently used for the treatment of idiopathic thrombocytopenic purpura. However, relapse despite B-cell depletion may occur. Retreatment with rituximab may represent an option but possibly dangerous in the long term (*e.g.* chronic hypogammaglobulinaemia). Thus, other safer maintenance therapies would be advisable. Also, SLE may become resistant to rituximab, or time to relapse may become shorter over time (2). Long-lived plasma cells as well as local survival factors for B-cells may play a role in the resistance to B-cell depletion (3). Indeed, BLyS levels increase after rituximab.

Belimumab has recently showed to increase the efficacy of rituximab in chronic lymphocytic leukaemia (4), restoring the susceptibility to direct and rituximab-induced NK-cell killing. In addition, CD27 positive B-cells, which are targeted by BLyS inhibition (6), are the source of plasma cells. Therefore, targeting BLyS may prevent possible mechanisms of resistance to B-cell depletion and to inhibit long-lived plasma cell differentiation (5). Notably, belimumab given concomitantly or after rituximab proved effective in the mouse model of SLE (6), in patients with renal involvement (7) and is being investigated in SLE (SYNBIoSeNCT02284984). Belimumab preceding rituximab was also effective in Sjögren's syndrome (8).

In our case, we could demonstrate that targeting BLyS was effective as a maintenance therapy of SLE-related thrombocytopenia after induction with IVIG. Since SLE relapsed despite the persistent depletion of peripheral blood $CD20^+$ cells, the hypothesis of persistence of tissue pathogenic B-cells is supported (9, 10).

In conclusion, in some SLE patients, long-term targeting of tissue survival factors for B-cells might be effective and safe to maintain long-term remission.

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Table I. Summary of the laboratory features during belimumab therapy.

	Belimumab start	+3 mo.	+6 mo.	+12mo.	+24 mo.	+36 mo.
Platelets (/μL)	90,000	178,000	141,000	218,000	190,000	1178,000
CD19+cells (/μL)	4,3	-	12	12	23	39
Anti-dsDNA ab (UI/ml)	42	33	37	56	49	35
C3 (mg/dl)	60	79	69	66	70	72
C4 (mg/dl)	5	8	9	9	10	11
IgG (mg/dl)	1990	2190	1190	1100	1250	1400
IgM (mg/dl)	108	104	96	184	195	203
PDN dose	37.5	3.75	3.75	2.5	2.5	1.25

PDN: prednisone.