Letters to the Editor

Efficacy of rituximab in a patient with lupus nephritis despite low levels of CD19

Sir, A 35-year-old woman was diagnosed with SLE in 2002, with specific skin lesions and positive ANA (1/2500). She was treated with HCQ 400 mg/day.

In 2005, the treatment was changed for MTX and oral corticosteroid due to polyarthritis. Circulating B-cell level in the peripheral blood was normal at that time (CD19 < 25% by flow cytometry detection).

In April 2006, renal function started to deteriorate with a proteinuria of 5 g/day. A renal biopsy was performed and histology showed diffuse proliferative lupus GN. Arterial blood pressure, creatinaemia and renal ultrasonography were all normal. During this flare, she also had skin rash, polyarthritis and pericarditis. An initial induction period of intensive immunosuppressive therapy was started with i.v. cyclophosphamide (CYC) 0.7 g/m² every 28 days and high-dose i.v. methylprednisolone 1 g/day for 3 days, followed by oral prednisone (oral PDN) of 1 mg/kg. Proteinuria decreased to 1.78 g/day (Fig. 1A). After six courses of CYC with a cumulative dose of 6.8 g, mycophenolate mofetil (2 g/day) was proposed as maintenance therapy along with a progressive decrease in corticosteroid dose. In 2007, in view of the corticodependence, a 150 mg/day of AZA succeeded to mycophenolate mofetil. In May 2008, during the follow-up, proteinuria was increased to 3.31 g/day; she had polyarthritis, but serum creatinine [glomerular filtration rate (GFR) 90 ml/min/1.73 m²] remained normal. Nephrologist did not perform a new biopsy and proposed rituximab as an alternative to cyclophosphamide because of her age. She was then treated by four infusions (500 mg/week i.v.). AZA was replaced by ciclosporin 50 mg/day and steroids were continued. One week before the first rituximab infusion, a lymphocyte phenotype was performed and the CD19 level was surprisingly <1%. The cycle of rituximab was well tolerated but ciclosporin had to be stopped due to high arterial blood pressure 4 weeks after its initiation.

After 5 months, there was marked renal manifestation improvement with a decrease in proteinuria from 3.31 to 0.18 g/day and oral PDN could be reduced from 14 to 8 mg/day, the lowest dose ever reached since 2006 (Fig. 1B). She was also asymptomatic.

In February 2009, mycophenolate mofetil was restarted as maintenance therapy. In March 2009, during hospitalization for purulent meningitis, proteinuria increased to 3 g/day. A renal biopsy had concluded to an active diffuse proliferative lupus GN (Stage 4c). The i.v. immunoglobulin was started as a compromise to the infectious risk. At 6 months, proteinuria decreased to 0.64 g/day, serum creatinine (GFR 90 ml/min/1.73 m²) was normal and she did not have lupus manifestation.

SLE is a multisystem autoimmune disease, with GN as a severe and frequent complication. Conventional treatment of kidney impairment is based on a combination of steroids and other immunosuppressive drugs, such as cyclophosphamide. This intensive regimen may lead to partial or complete remission of lupus nephritis but is associated with partial resistance and significant morbidity. Hence, new treatments for severe SLE are currently being evaluated.

B-cell dysfunction has emerged as a key pathogenic component of SLE and is a prime target for the development of new agents [1]. Rituximab is a chimeric monoclonal anti-B-cell antibody directed against the CD20 molecule.

Following initial promising results, a large number of case reports and some observational studies have been undertaken, with variable results [2]. Despite the negative results of two recently randomized controlled trials (EXPLORER in non-renal and LUNAR in renal SLE), rituximab remains a potential drug for treatment of SLE according to daily clinical experience and limitations of these studies [3, 4].

Looney et al. [5] have emphasized that the degree of peripheral B-cell depletion in the blood was associated with the extent of clinical improvement. Peripheral blood B-cell reconstitution has, however, been found to precede relapse in the majority of patients [6].

We reported here the efficacy of rituximab in active GN lupus, despite low levels of B cells (CD19 <1%). CD19 level before injection of rituximab was <1%, and the result was checked in order to confirm that this was valid: chart, record, traceability of tubes in immunology laboratory. The CD19 level had been normal in the previous years, but its fall may have been caused by cyclophosphamide treatment [7]. Despite the low level of CD19, how can the effect of rituximab be explained?

Autoreactive B cells represent a small percentage of the total B-cell population. A significant clonal expansion of B cells has previously been identified in active SLE patients [8]. Lymphopenia is frequent in SLE patients; however, memory cells have often been overrepresented [9]. Patients with a long-term response to rituximab have been characterized by a dominance of transitional B cells (probably acting as regulatory and protective cell) that prevail for several years after depletion in the absence of significant re-expansion of memory B cells (more likely to mediate pathogenic effects) [10]. Hence, efficacy in our case may be explained by the action on a marginal clonal B-cell blood population (auto-reactive B cells).
Efficacy of rituximab may be explained by the action on a marginal clonal B-cell blood population.

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Fig. 1 Follow-up of the proteinuria after the first (A) and second (B) renal flare (GN Class 4) treatment.

Rheumatology key message

- Efficacy of rituximab may be explained by the action on a marginal clonal B-cell blood population.

References