Supplementary data

Supplementary data are available at *Rheumatology* Online.

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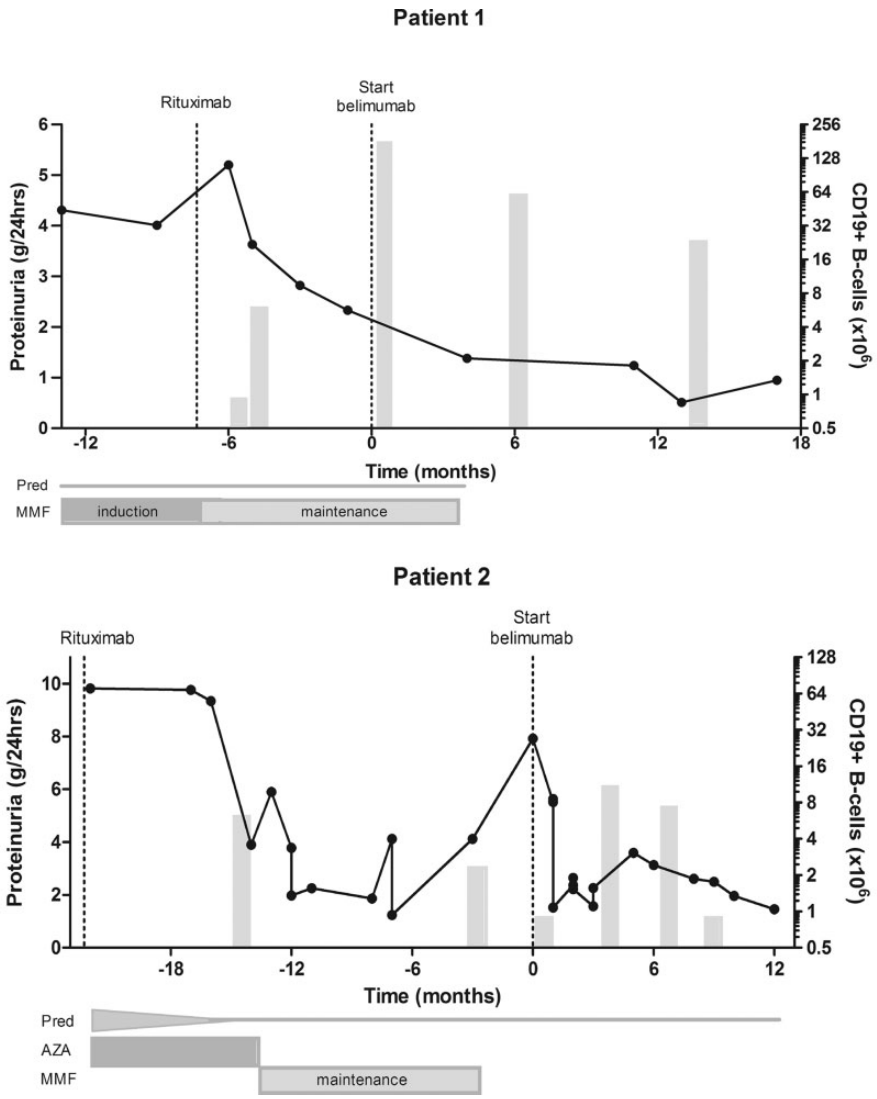
Belimumab after rituximab as maintenance therapy in lupus nephritis

SIR, Belimumab has been approved for autoantibody-positive SLE with persistent disease activity despite standard treatment [1]. With respect to LN, European League Against Rheumatism (EULAR) guidelines state that the position of belimumab needs further definition [2]. Previously another biologic, rituximab, failed to be superior over placebo when added to MMF and corticosteroids in LN [3]. However, retrospective cohort data suggest a role for rituximab in refractory LN [4]. Here we report our experience with rituximab followed by belimumab as maintenance treatment in two refractory LN patients.

Patient 1, a 32-year-old female, was diagnosed with SLE 3 years earlier based on a butterfly exanthema, discoid lupus, photosensibility, lymphadenopathy, GN and positive ANA (3+) and anti-dsDNA (3+). A kidney biopsy revealed diffuse and global proliferative GN class IV-S(A). Since her diagnosis she had received two induction regimens (MMF and Eurolupus CYC), despite which her disease flared. The latter manifested with discoid lupus, arthralgias, diffuse alopecia and persisting GN with urinary red blood cell (RBC) casts and proteinuria (SLEDAI score 22). She was re-treated with MMF induction and corticosteroids during which progressive proteinuria (8 g/day) developed (Fig. 1). Concomitant angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) induced symptomatic hypotension. At this time, pulse steroids and rituximab followed by MMF and prednisolone maintenance was initiated. This led to a partial response with a reduction of proteinuria to 3.5 g/day. Disease amelioration was hampered because MMF caused intractable nausea and weight loss that challenged her treatment adherence. Seven months after rituximab she was started on belimumab. The initiation coincided with the time B cells started to fully repopulate. In the following months her skin lesions, alopecia and arthralgia resolved. Moreover, she independently tapered her prednisolone to zero because of tremors that interfered with her daily work requiring highly developed fine motor skills. Currently, after 18 months, she remains in remission on belimumab monotherapy with proteinuria of 0.9 g/day, a reduction in ANA (1+) and anti-dsDNA (1+), C3 normalization (from a nadir of 0.7 to 1.0; normal range $>$0.9 g/l) and increasing C4 levels (from a nadir of 103 to 194; normal range $>$95 mg/l) and a reduced number of circulating B cells (SLEDAI score 6).

Patient 2, a 42-year-old male, was diagnosed with SLE 7 years earlier, presenting with nephrotic syndrome, urinary RBC casts, class IV-G(A) LN, positive autoantibodies (ENA 2+), complement usage, alopecia, anorexia and auditory hallucinations with psychosis, including cerebral white matter lesions confirming neuropsychiatric involvement. He was referred to our hospital 2 years ago with a therapy-refractory nephrotic syndrome (proteinuria 9.8 g/day, creatinine 150 μmol/l) while taking a combination of ACE inhibitors and ARBs. He was already treated with two previous induction treatments (CYC and MMF), each followed by MMF maintenance with concomitant prednisolone and HCQ. Another kidney biopsy confirmed the LN class IV-G(A) diagnosis with full-house immunofluorescence and additional focal global sclerosis and

FIG. 1 Overview of the two reported patients with respect to proteinuria and CD19$^+$ B cells



The vertical dotted lines represent the start of two courses of 1 g rituximab and the start of belimumab treatment (three 2-weekly infusions followed by monthly infusions of 10 mg/kg). Time scale is related to the start of belimumab treatment, i.e. $T = 0$ months, so the time interval between rituximab and belimumab initiation as well as the time to disease amelioration is illustrated. The vertical grey bars represent the absolute number of circulating CD19$^+$ B cells (right *y*-axis) after rituximab treatment (normal range for CD19$^+$ B cells: 60–1000 $\times$ 10^6 cells/l). The horizontal bars below the graph represent the (tapering of) concomitant immunosuppressive treatments through time. MMF dosages were titrated by measuring the area under the curve of serum levels, aimed at 60–90 mg/h/l during induction treatment and 45–60 mg/h/l during maintenance. Prednisone dosage was tapered from 1 mg/kg/day during induction (triangle) to 7.5 mg/day during maintenance treatment (line). Pred: prednisolone (triangles illustrate a tapering schedule).

arteriosclerosis. The patient was treated with pulse steroids and rituximab followed by MMF and prednisolone, leading to partial remission with a nadir of his proteinuria at 1.3 g/day (Fig. 1). Unfortunately, due to MMF-related gastrointestinal side effects he was unable to adhere to his anti-proteinuric and immunosuppressive therapy. A relapse occurred with nephrotic proteinuria (7.9 g/day), erythrocyturia and complement usage (SLEDAI score 10) while circulating CD19$^+$ B cells started to repopulate 20 months after rituximab initiation. To improve therapy adherence, MMF was tapered and belimumab was added to prednisolone. Thereafter proteinuria improved (1.5 g/day), ENA became negative, C3 normalized (from a nadir of 0.6 to 0.9 g/l), C4 increased (from a nadir of 210 to 386 mg/l) and circulating B cells remained reduced. At the 12 month follow-up he had low disease activity (SLEDAI score 4)

while continuing belimumab and tapering prednisolone to zero.

These cases illustrate the potential added value of belimumab after rituximab treatment in active LN. It should be noted that both patients continue to have low disease activity while on belimumab monotherapy. To our knowledge, this is the first report of LN patients treated with two consecutive B cell targeted treatments. In both patients, belimumab halted the full repopulation of circulating B cells after rituximab. From a pathophysiological point of view, it is well appreciated that autoantibody-positive disease is found specifically in LN and that B cell hyperactivity is a landmark in SLE [5]. It is tempting to speculate that the clinical improvement of these patients is due to a synergic effect of rituximab and belimumab.

Previously, two randomized trials (BLISS-52 AND BLISS-76) showed beneficial effects of belimumab in reducing concomitant immunosuppression in autoantibody-positive SLE without major organ involvement and without previous rituximab treatment. Recently one patient with active LN was reported to have a beneficial response to belimumab, albeit in conjunction with pulse steroids [6]. Currently we await the results of a randomized trial assessing belimumab's efficacy in LN (NCT01639339). This report describes belimumab as rescue treatment in refractory LN due to commonly seen gastrointestinal intolerance to MMF [7]. The present report encourages further research into the clinical yield of combining B cell targeted treatment in the difficult population of SLE patients with major organ involvement or refractory disease.

Rheumatology key message

- This report illustrates the potential added value of combining B cell targeted treatment in SLE patients with major organ involvement or refractory disease.

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Anti-adalimumab antibodies in paediatric rheumatology patients: a pilot experience

SIR, It has been reported that immunogenicity of anti-TNF agents is involved in treatment failure [1]. Despite its humanized structure, adalimumab may induce the formation of antidrug antibodies (ADAbs), although the percentage of positive cases, ~40%, depends on the assay used in its determination [2]. Experience in the paediatric population is poor [3].

Measurements of serum adalimumab levels and ADAbs from 25 children were available in our unit in March 2013. They received 0.8 mg/kg (S.D. 0.3, range 0.3–1.5) every 12 days (S.D. 3, range 7–14). The objective was to explore the relationship between the presence of ADAbs, the activity of the disease and therapeutic decisions through a cross-sectional retrospective study.

Adalimumab levels in serum were determined by capture ELISA, with >5 ng/ml being considered positive. ADAbs by two-site bridging ELISA, being considered positive at >10 arbitrary units (AU)/ml. Assays were similar to those described by our group to determine infliximab and anti-infliximab antibody values [4]. Samples were obtained within 24 h before drug administration. Since conventional analytical tests are not useful for determining the activity of uveitis, it was assessed by the physician visual analogue scale (VAS), with values ranging from