Ofatumumab: a novel treatment for severe systemic lupus erythematosus

Sir, Randomized controlled trials have not demonstrated a clear benefit of rituximab in refractory SLE, likely due to study design problems [1, 2]. However, numerous other studies have demonstrated efficacy, and B cell depletion with rituximab is now regarded as established treatment for SLE [3]. Unfortunately, infusion reactions may occur, hence alternative B cell-depleting agents need to be defined for patients with a previous clear response in whom further treatment is precluded due to a severe adverse reaction. Here we describe such a patient, the first report to our knowledge of a patient with SLE successfully treated with the anti-CD20 mAb ofatumumab.

Alternative anti-CD20 mAbs to rituximab include ocrelizumab and ofatumumab. While rituximab is chimeric and ocrelizumab is a humanized mAb, ofatumumab is a human IgG1k mAb that binds CD20 on B cells at a unique epitope. All are type I anti-CD20 mAbs, capable of B cell lysis through both complement-dependent and antibody-dependent cell-mediated cytotoxicity, but differences in structure and binding epitopes lead to differences in immunogenicity and intensity of B cell depletion. Ocrelizumab, while unlicensed, has been used to treat SLE, but has not been found to be significantly more efficacious than placebo, with an increased risk of infection [4]. Ofatumumab is approved for the treatment of chronic lymphocytic leukaemia and has shown efficacy in treating in RA [5]. There are no reports of its use in SLE.

Our patient is a 22-year-old woman of Nigerian descent who developed SLE at 11 years of age, when she presented with fever, arthritis, pericarditis and positive ANA, anti-dsDNA and anti-Sm antibodies with hypocomplementaemia. After AZA, mycophenolate and high-dose steroids failed to control her illness, she was treated with rituximab on two occasions 6 months apart in 2006/7 with good response, although she suffered anaphylaxis requiring adrenaline resuscitation on the second cycle. She remained well until 2011, when she developed a severe flare with rash, arthritis, pericarditis and proteinuria. Despite treatment with pulsed i.v. and high-dose oral steroids, CYC (cumulative dose 6 g), MTX, ciclosporin, belimumab for 5 months and IVIG, her disease remained persistently active over the next 2 years with recurrent fever, weight loss, rash, arthritis, an episode of pancreatitis, two episodes of macrophage activation syndrome (associated with infection), hypocomplementaemia and persistently high anti-dsDNA titres. In December 2013, the decision was made to treat her with ofatumumab off-licence, given her previous good response to rituximab. Ofatumumab was administered intravenously using the following regimen: 300 mg on day 0, 700 mg on day 7 and 700 mg on day 21. Each infusion was preceded by i.v. methylprednisolone 250 mg; no infusion reaction was noted.

Following ofatumumab, B cells were fully depleted and our patient responded extremely well: her pre-treatment SLEDAI score was 15 (December 2013), while 5 months after ofatumumab her SLEDAI score had fallen to 2 (May 2014). Her anti-dsDNA titre fell by >90% and C3 normalized (Fig. 1). Her oral prednisolone decreased from 30 mg/day pre-ofatumumab to 10 mg/day 5 months post-infusion. Six months later she has no symptoms of active SLE, has gained weight and has re-entered education. Her B cells remain depleted and there have been no infections or changes in serum immunoglobulins.

Although our patient was treated with both methylprednisolone and ofatumumab, previous i.v. steroid pulses did not achieve lasting disease control, so it is unlikely that these were responsible for her sustained improvement on this occasion. This report suggests that ofatumumab may be efficacious for severe SLE in patients who have responded to rituximab but in whom further treatment is precluded due to anaphylaxis. Randomized controlled trials of ofatumumab to treat SLE may be warranted. Our patient provided written informed consent to have her case published, in accordance with the Declaration of Helsinki.

Rheumatology key message

- Ofatumumab may be an effective alternative B cell-depleting agent in patients with SLE intolerant to rituximab.

![Fig. 1 Variation of anti-dsDNA titres and complement C3 levels with time](https://academic.oup.com/rheumatology/article-abstract/54/3/559/1796396/fig1)
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Long-term efficacy of alemtuzumab in polymyositis

SIR, We present a PM patient refractory to standard therapy, who showed effective clinical remission after a single treatment cycle with alemtuzumab for >3 years of follow-up. This is, to our knowledge, the first report of long-term efficacy of alemtuzumab in the treatment of PM.

This Caucasian male patient was born in 1957. PM manifested at the age of 52 with progressive symmetrical muscle weakness and myalgia of proximal limb musculature starting in 2009. At first consultation the patient showed a positive Gower’s sign and maximum walking distance was reduced to 500 m. The diagnosis of PM was established in May 2009 and was based on typical clinical presentation, elevated creatine kinase (CK) levels (3237 U/l), myopathic changes in the electromyogram and muscle biopsy showing endomysial CD8⁺ T cell infiltration (Fig. 1A). Ro-52 autoantibodies were positive; other myositis-specific autoantibodies (anti-Jo-1, anti-Mi-2 or anti-SRP) could not be detected. Therapy with oral prednisolone (80 mg/day) in combination with azathioprine (start dose 50 mg/day, end dose 225 mg/day) was initiated, significantly ameliorating muscle weakness and myalgia. Azathioprine therapy had to be withdrawn in August 2009 due to extremely elevated liver enzymes. Under subsequent therapy with cyclosporin (200 mg/day), it was not possible to further taper the prednisolone dose (<40 mg/day). The disease course showed sustained progression, as CK levels were still considerably elevated. Thus we started i.v. cyclophosphamide (monthly cycles at 2 x 1000 mg, followed by 2 x 1300 mg), which was not able to slow disease progress, decrease CK level or spare corticosteroid therapy. Walking distance further deteriorated to 150 m. A combination therapy of IVIG (start dose 5 x 40 g/day, followed by monthly cycles of 3 x 30 g/day) and MTX (start dose 7.5 mg/day, end dose 30 mg/day) was initiated in September 2010. After an initial favourable response, the disease progressed further despite increasing MTX doses to 30 mg/day, with CK levels increasing to 5242 U/l, and the patient reported significant deterioration of muscle strength. IVIG and MTX were subsequently withdrawn. After giving informed consent, the patient received alemtuzumab (one cycle at 5 x 30 mg) under premedication with clemastine, ranitidine, paracetamol, ondansetron and i.v. methylprednisolone (250 mg/day) in May 2011 (Fig. 1B). Alemtuzumab led to a rapid and long-lasting depletion of T cells, B cells and NK cells (supplementary Fig. S1, available at Rheumatology Online). At first application, the patient suffered from infusion-related reactions with fever and chills, while subsequent infusions were well tolerated. Afterwards the patient received famciclovir, fluconazole and cotrimoxazole for infection prophylaxis until CD4⁺ T cells reached >200 cells/µl. Approximately 12 weeks later the patient noticed an improvement in muscle strength, which was confirmed on physical examination and was slightly preceded by a continuous decrease in CK level. In addition, constant improvement of walking distance and prednisolone tapering to 7.5 mg/day was achieved. Until the beginning of July 2014 the disease course remained stable, when the patient reported progressive myalgia and deterioration of walking distance. No severe adverse events have been observed so far. We decided to administer another cycle of alemtuzumab.

Current therapeutic options of PM consist of corticosteroids, IVIG and immunosuppressants such as AZA or MTX [1]. These therapies are mainly non-specific, have various adverse effects and often show limited efficacy. Monoclonal antibodies are emerging as new therapeutic strategies for autoimmune myopathies, however, to date only limited evidence exists for their use [2]. Alemtuzumab is a monoclonal anti-CD52 antibody leading to rapid, long-lasting depletion of immune cells, but not of haematopoietic stem cells. After depletion, the reconstitution of immune cells follows a certain pattern, with T cells being the last to recover after years [3]. Here, anti-CD52 treatment was