

Ofatumumab for B cell depletion in patients with systemic lupus erythematosus who are allergic to rituximab

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Abstract

Objective. B cell depletion, most commonly with rituximab, is an evolving therapeutic approach in SLE. Infusion reactions after rituximab are common, and may prevent re-treatment in patients who previously demonstrated beneficial response. We have used ofatumumab, a fully humanized anti-CD20 mAb, as an alternative B cell-depleting agent in patients with SLE who are rituximab-intolerant due to severe infusion reactions.

Methods. A single-centre retrospective case series of 16 patients were treated with ofatumumab for SLE between 2012 and 2015.

Results. Ofatumumab infusion was well tolerated in 14/16 patients, in whom the median age was 34 (range 19–55) and the median duration of SLE 9.2 years (0.6–28.5). The cohort was heavily pre-treated, with 50% having prior CYC exposure, and a median cumulative dose of prior rituximab 4 g (1–6). Twelve patients were treated for LN, one for extra-renal flare and one for remission maintenance. B cell-depletion was achieved in 12/14 patients, with comparable reconstitution kinetics to a previous cohort treated with rituximab at our centre, and was associated with improvements in serological markers of disease activity, including ANA, anti-dsDNA antibody and complement levels. Half of the patients with LN achieved renal remission by 6 months. Progressive disease that was unresponsive to augmented immunosuppression with CYC was seen in five patients. During long-term follow-up (median 28 months), five grade III infections were reported, and there were no malignancies or deaths.

Conclusion. In this pre-treated cohort with long-standing SLE, ofatumumab was a well-tolerated, safe and effective alternative to rituximab for B cell-depletion therapy.

Key words: systemic lupus erythematosus, lupus nephritis, biologic therapy, monoclonal antibody, B cell depletion, rituximab, ofatumumab, anti-CD20, human-anti-chimeric antibodies

Rheumatology key messages

- Ofatumumab is an alternative to rituximab for B cell depletion in SLE.
- Reaction infusions to ofatumumab were uncommon in patients with SLE who had demonstrated intolerance to rituximab.
- Ofatumumab treatment was associated with serological and clinical response in the majority of patients with SLE.

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Introduction

SLE is a heterogeneous autoimmune condition with a variable and unpredictable course. Until recently, the mainstay of therapy had remained unchanged for decades, consisting of CSs, anti-malarials and non-specific immunosuppression. However, the challenges posed by refractory disease, and the adverse effects of these conventional therapies, particularly those of long-term

steroids, have led to a search for new treatments. B cell depletion, most commonly with rituximab, a chimeric monoclonal IgG1 directed against the CD20 antigen expressed on B lymphocytes, has emerged as a potential strategy [1]. While two controlled trials, the Exploratory Phase II/III SLE Evaluation of Rituximab (EXPLORER) and the Lupus Nephritis Assessment with Rituximab (LUNAR) studies [2, 3], did not show any additional benefit of rituximab as an add-on to standard therapy in non-renal and renal SLE, respectively, we have previously reported successful use of rituximab as a steroid-sparing agent when used with MMF in patients diagnosed with LN [4, 5]. In addition, there is a significant body of evidence, albeit uncontrolled, that rituximab may be beneficial in refractory or resistant disease, or in patients intolerant of standard therapy [6].

Infusion reactions after rituximab are common, occurring in 10–15% of patients in the randomized studies, and these may be sufficiently severe to preclude repeated treatment in patients who had previously demonstrated good clinical response. Fully humanized mAb may avoid these adverse immunogenic reactions. To date, three humanized anti-CD20 mAb have been developed; obinutuzumab, ocrelizumab and ofatumumab. Compared with rituximab, ofatumumab is directed against a distinct extracellular epitope of CD20, has slower dissociation kinetics, and is a more potent activator of complement-dependent cytotoxicity *in vitro* [7]. It is licensed for use in haematological malignancies, and has demonstrated biological activity in RA [8, 9]. We previously reported the use of ofatumumab in a cohort of patients with ANCA-associated vasculitis [10], and there is an individual case report, and one small series, describing successful use of ofatumumab in a total of four patients with SLE [11, 12].

Since 2012, we have offered ofatumumab to patients with SLE who are intolerant of rituximab and for whom B cell depletion is deemed an appropriate therapeutic strategy. Here, we report our experience in 16 patients, the majority of whom were treated for LN and had previously demonstrated beneficial responses to rituximab.

Methods

This is a retrospective case series of patients treated with ofatumumab for SLE/LN at the Imperial College Lupus Centre. Since 2012, we have offered ofatumumab off label on compassionate grounds to patients who are intolerant of rituximab and for whom B cell depletion is deemed a desirable treatment aim. Patients were classified as intolerant of rituximab if they developed angioedema, anaphylactoid or anaphylactic reactions despite the use of intravenous steroids and antihistamines as pre-medication.

Our treatment protocol was based on our previously published regimen using rituximab and MMF, without oral steroids (the Rituxilup regimen [4]). Herein, rituximab 2×1 g was replaced with ofatumumab 2×700 mg i.v. doses given 2 weeks apart, with 250–500 mg of i.v. methylprednisolone at each infusion. First-line

maintenance was with MMF, and we aimed to minimize the use of oral steroids.

Clinical and laboratory data were retrospectively extracted from case records, for at least 6 months after treatment until the last encounter prior to April 2016. Renal biopsy findings were classified according to the International Society of Nephrology/Renal Pathology Society system for LN. B cell counts were determined by CD19 flow cytometry, and a threshold of 20 cells/ μ l was used to define B cell depletion and repopulation. Complete renal remission was defined by the combination of a urine protein: creatinine ratio (uPCR) of <50 mg/mmol and serum creatinine not $>15\%$ above baseline, or by histological evidence of inactive disease on repeat biopsy. Partial remission was defined by uPCR <300 mg/mmol and 50% reduction in uPCR from baseline, with serum creatinine not $>15\%$ above baseline.

Unless otherwise stated, data are reported as median (range), and comparisons made by non-parametric testing. Graphs were constructed and statistical analysis performed using Prism 7.0 (GraphPad Software, La Jolla, CA, USA).

Informed consent was provided prior to initiation of therapy in all cases. In accordance with the UK National Health Service Research Ethics Committee guidelines, ethics approval was not required for this report, since all treatment decisions were made prior to this evaluation.

Results

Patient characteristics and treatment received

To date, 16 patients with SLE have been treated with ofatumumab at our centre. All had previously been treated with rituximab, and had demonstrated infusion reactions that were deemed sufficiently severe to preclude further rituximab challenge. Two of these 16 patients had significant infusion reactions to ofatumumab, such that they were unable to complete treatment, and are therefore excluded from this analysis.

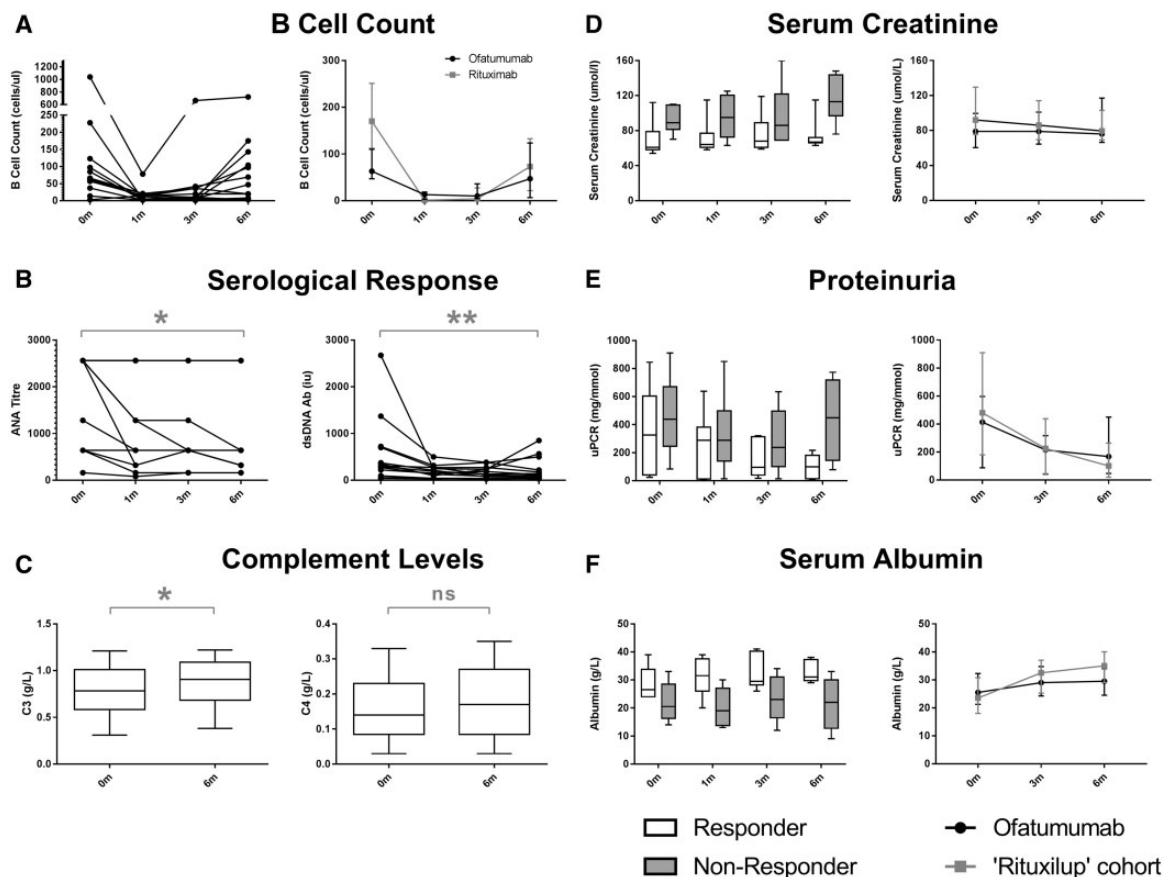
The clinical features of the 14 patients who completed treatment are summarized in Table 1. All were female, with a mean age of 34 years (range 19–55) and median disease duration of 9.2 years (0.6–28.5) before they were treated with ofatumumab. The majority of patients were of non-Caucasian ethnicity (5/14 African Caribbean; 4/14 south-Asian; 2/14 Caucasian; 3/14 other). Fifty percent of patients had previously received CYC, and the median time since last rituximab exposure was 192 days (9–1099), with a median cumulative prior dose of 4 g (1–6). The indication for ofatumumab treatment in 12 patients was active LN. Of the remaining two patients, one was already established on haemodialysis and treated for extra-renal flare; one was treated to maintain remission due to non-adherence with oral medications.

Following ofatumumab treatment, all patients were treated with maintenance MMF as per unit protocol, excepting the one patient who was non-adherent to oral medications. Five patients continued on pre-established oral CS therapy, and two patients had oral CSs added to their treatment regimen. Seven patients did not receive oral CSs during this cycle of treatment.

TABLE 1 Clinical characteristics, treatment received and outcome for individual patients

Case	Age, gender	Duration SLE, years	Previous therapies ^a	Previous RTX dose, g	Time since RTX, days	Indication ^b	Creatinine, $\mu\text{mol/l}$	uPCR, mg/mmol	Albumin, g/l	Ofatumumab dose, mg	Maintenance after ofatumumab	Outcome at 6 months
1	44 F	18.4	CS, MMF, HCQ, CYP	6	22	LN: IV-S (A/C)	79	325	32	1400	CS, MMF, HCQ	CRR
2	28 F	3.3	CS, MMF, HCQ	4	53	LN: III-S (A/C)	61	91	39	1400	MMF, HCQ	CRR
3	35 F	5.8	CS, MMF, HCQ	5	24	LN: V	58	41	24	1400	CS, MMF, HCQ	CRR
4	23 F	1.9	CS, MMF, CYP	3	134	LN: III-S (A) + V	79	604	25	1400	CS, MMF, HCQ	PRR
5	41 F	8.2	CS, MMF, HCQ	5	42	LN: IV-S (A/C)	60	845	24	1400	CS, MMF, HCQ	PRR
6	26 F	1.3	MMF, HCQ	4	9	LN: III-S (A)	70	84	33	1400	MMF, HCQ	NR: lost function
7	33 F	8.8	CS, MMF, AZA, MTX	4	355	LN: V	109	414	17	700	MMF, HCQ	NR: persistent proteinuria
8	31 F	7.3	CS, MMF, AZA, CYP	1	1099	LN: IV-G (A/C)	90	300	22	1400	CS, MMF	NR: lost function
9	55 F	1.7	CS, MMF, MTX, HCQ, CYP	5	332	LN: IV-S (A/C)	88	590	27	1400	CS, MMF, HCQ	NR: lost function
10	21 F	7.4	CS, MMF, CYP	5	174	LN: IV-S (A/C) + V	85	461	19	1400	MMF, HCQ	NR: persistent proteinuria
11	43 F	0.6	CS, HCQ	2	15	LN: III-S (A/C)	112	429	28	1400	MMF	PRR
12	48 F	28.5	CS, MMF, AZA, HCQ, CYP, FK	4	68	LN: V	110	911	14	1400	MMF, HCQ	NR: persistent proteinuria
13	34 F	11.5	CS, MMF, AZA, CYP, IVIG	5	151	Extra-renal Flare	-	-	-	700	CS, MMF, HCQ	Clinical improvement
14	19 F	15.4	MMF, HCQ	2	219	Maintenance	-	-	-	1400	Nil	Stable remission

^aPrevious treatment at any time point. ^bClassification according to the ISN/RPS system for LN. RTX: rituximab; uPCR: urinary protein: creatinine ratio; FK: tacrolimus; CRR: complete renal remission; PRR: partial renal remission; NR: non-responder.

Fig. 1 Laboratory and clinical responses in the first 6 months after ofatumumab treatment

(A) Individual B cell counts in this cohort (left panel), and compared with the Rituxilup cohort (right panel). There was no significant difference in B cell count between the two cohorts at 1, 3 or 6 months. (B) ANA titre ($n = 13$) and anti-dsDNA levels ($n = 12$) for individual patients during 6 months' therapy (ANA 1/2560 to 1/320, $P = 0.03$; anti-dsDNA 310 to 120 AU, $P = 0.01$). (C) C3 and C4 levels for the entire cohort during 6 months' therapy (C3 0.78 vs 0.91 g/L, $P = 0.03$; C4 0.14 vs 0.17 g/L, $P = 0.14$). (D–F) Changes in renal function (D), proteinuria (E) and serum albumin (F). Left panel compares responders and non-responders: at 6 months, responders had stable serum creatinine (61 vs 67 $\mu\text{mol/L}$, $P = 0.59$), improved proteinuria (uPCR 325 vs 99 mg/mmol, $P = 0.01$) and a trend towards increased serum albumin (26 vs 31 g/L; $P = 0.31$) that was not seen in non-responding patients (creatinine 89 vs 113 $\mu\text{mol/L}$, $P = 0.18$; uPCR 438 vs 449 mg/mmol, $P = 0.99$; serum albumin 21 vs 22 g/L, $P = 0.88$). Right panel compares parameters in this cohort with those in the Rituxilup cohort: there were no significant differences in any parameter at 0, 3 or 6 months (box-and-whisker plots describe median, IQR and range. Linear plots describe median and IQR. Statistical comparison between 0 and 6 month time-points in the ofatumumab cohort is by Wilcoxin signed-rank test for repeated measures of non-parametric data. Comparison between the ofatumumab and Rituxilup cohort is by multiple t -test.).

Serological and clinical response

Following treatment, 12 patients achieved B cell depletion, with a median time to documented depletion of 14 days (7–75) and to subsequent reconstitution of 185 days (64–553). The kinetics of B cell depletion and reconstitution were comparable with those of our previously reported cohort treated with rituximab ('Rituxilup' cohort; Fig. 1A). Treatment was associated with significant improvements in the serological markers of disease activity, including ANA titres, anti-dsDNA antibody levels and circulating complement levels, in the first 6 months (Fig. 1B and C).

At this time-point, 6 of the 12 patients who were treated for LN had achieved complete (cases 1, 2 and 3) or partial (cases 4, 5 and 11) renal remission (Fig. 1D–F, left panels). One partial-responder subsequently achieved complete remission by 12 months (case 4). Six patients were deemed non-responders at month 6: three due to persistent nephrotic-range proteinuria (cases 7, 10 and 12) and three due to deteriorating renal function (cases 6, 8 and 9). During the 6-month follow-up, we observed similar improvements in serum creatinine, albumin and proteinuria in this cohort compared with in the 'Rituxilup' cohort (Fig. 1D–F, right panels).

One non-responder was retreated with ofatumumab, and subsequently achieved complete remission (case 6). The remaining five non-responders were subsequently treated with pulsed i.v. CYC (in the context of a systemic flare 7–9 months after initial ofatumumab treatment), although none of these five patients achieved renal remission during follow-up.

Systemic flares were subsequently observed in four cases. Three of these occurred in the aforementioned non-responding patients (cases 6, 7 and 8, occurring at 10, 7 and 9 months after ofatumumab, respectively). One occurred in a patient who had achieved complete remission (case 3) 20 months after ofatumumab treatment. One patient (case 7) progressed to ESRD 21 months after ofatumumab treatment.

In the remaining two patients treated for non-renal disease, resolution of clinical symptoms was observed in case 13: ECLAM [13] Index improved from 3 (fatigue, rash, arthritis, hypocomplementaemia) to 0 over 6 months, and stable remission was maintained without any oral maintenance immunosuppression in case 14.

Adverse events

Two of 16 patients who have received ofatumumab developed angioedema during drug administration, such that they were unable to complete treatment. They were subsequently treated with MMF and CS therapy. The median duration of the total follow-up of the 14 patients who completed ofatumumab treatment was 28 months (range 9–43). During this period, five severe infections (requiring hospital admission or treatment with i.v. antibiotics) were observed in three patients: 2× lower respiratory tract infections; 2× dialysis access infections, 1× gastroenteritis. Non-severe infections were also reported: 1× lower respiratory tract infection; 2× upper respiratory tract infections; 1× urinary tract infection; 1× folliculitis. No atypical or opportunistic infections were observed. There were no new cases of hypogammaglobulinaemia or persistent neutropenia. No malignancies, cases of progressive multifocal leucoencephalopathy or deaths were observed during follow-up.

Conclusions

This is the largest published series of patients treated with ofatumumab for SLE/LN. Our experience suggests that ofatumumab is a well-tolerated and effective alternative for patients who are intolerant of rituximab, but for whom B cell depletion is deemed a desirable therapeutic strategy, with 14 of 16 patients receiving treatment without infusion reactions, and 12 of these 14 patients achieving peripheral B cell depletion. This was associated with a serological and clinical response within 6 months, with half of the patients with active LN progressing to remission by this time-point. Of note, B cell kinetics and clinical response rates were comparable with those seen in our previously reported cohort of newly diagnosed patients treated with rituximab for LN.

In contrast to the Rituxilup cohort, the majority of patients in this series had long-standing SLE and were

heavily pre-treated. As such, it included a number of patients with aggressive or resistant disease, reflected in our observations that in those patients who did not respond to ofatumumab, the response to augmented immunosuppression with CYC was similarly limited, and of subsequent disease flares in four cases. Reassuringly, however, we did not detect any unexpected adverse events in this cohort with a significant burden of prior and concomitant immunosuppression.

Infusion reactions to rituximab are common, occurring in 10–15% of patients in randomized controlled studies in SLE, and it is likely that the frequency of infusion reactions increases with repeated exposure. Indeed, all but one of our patients had more than one prior exposure to rituximab. Human anti-chimeric antibodies (HACA) develop in 5–10% of patients treated with rituximab for RA [14], though at an apparently higher frequency of 15–26% in patients with SLE [2, 3], perhaps reflecting an enhanced state of ‘immunoreactivity’ in these patients. The role of HACA in the development of infusion reactions is unclear, though the presence of HACA has been associated with incomplete B cell depletion and poorer clinical response in some SLE cohorts [15, 16]. As a fully-humanized mAb, ofatumumab has low immunogenicity, with no patients developing demonstrable anti-ofatumumab antibodies in haematological or RA studies [17, 18]. Ofatumumab may therefore be a preferred alternative to rituximab in patients with SLE who are likely to require repeated treatments due to the chronic and relapsing nature of their disease.

Ofatumumab has also shown efficacy in rituximab-resistant cases of paediatric nephrotic syndrome and haematological malignancy [19–21]. It has been suggested that differences in epitope specificity, pharmacokinetics and ability to activate both complement- and antibody-dependent cell-mediated cytotoxicity may account for this differential response. Whether ofatumumab might likewise provide benefit in patients with SLE who fail to have a primary response to rituximab is unclear. Of note, a phase III study investigating the utility of ocrelizumab, another humanized anti-CD20 antibody, suggested that renal responses were numerically (though not statistically) higher in patients treated with ocrelizumab vs controls, though a higher than expected rate of infectious episodes were reported, such that the study was terminated early [22]. Clearly, not all B cell-depleting strategies are equal, and controlled studies are ideally needed to better define the safety and potential value of ofatumumab in resistant SLE. A randomized control trial investigating the use of obinutuzumab in LN is underway (NCT02550652).

Our study has obvious limitations—it is small, uncontrolled, and includes a heterogeneous case mix in whom there was non-uniform use of maintenance immunosuppression and CSs. While we observed that non-responding patients tended to have poorer renal function, lower serum albumin and higher urinary protein loss at baseline, we were unable to identify clear predictors of response in this small cohort. In addition, as a retrospective series, we were unable to perform detailed analysis of B cell subsets or reconstitution, B cell survival factors or the presence of

HACA, and it would be of value to investigate these in any future study.

Our experience, however, suggests that, in patients who are intolerant of rituximab, ofatumumab is a potential alternative agent, which in this heavily pre-treated cohort was well-tolerated, safe and effective in inducing B cell depletion, with subsequent clinical responses in a significant proportion of patients with long-standing and aggressive SLE.

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