Obinutuzumab in rituximab-refractory or intolerant systemic lupus erythematosus: a real-world case series

Sirs,

Rituximab (RTX) is used for treatment-refractory systemic lupus erythematosus (SLE). However, multiple mechanisms contribute to RTX unresponsiveness (1-4). Obinutuzumab (OBZ), a next-generation anti-CD20 antibody that overcomes key RTX resistance mechanisms (4, 5), has demonstrated improved renal outcomes when added to standard care in proliferative lupus nephritis (6, 7). Despite this, real-world data on OBZ use in RTX-refractory or RTX-intolerant SLE remain limited. We report seven SLE patients treated with OBZ after RTX failure or intolerance.

Our cohort comprised seven patients (median age 28; 2 males) with lupus nephritis (n=5; Classes III, V, and III/V), enteritis (n=1), and inflammatory arthritis (n=1). Indications for switching to OBZ included RTX non-response (n=4) and infusion reactions (n=4). Over a median of 3 courses, 3/5 nephritis cases achieved complete or partial remission, while enteritis and arthritis cases reached sustained remission. Two patients (Cases 1 and 7) were non-responders. Notably, OBZ was well-tolerated with no infusion reactions under standard premedication, and no new-onset hypogammaglobulinaemia or severe infections were observed.

Case 1 (28F, Class III/V LN) remained refractory to OBZ despite prior failure of cyclophosphamide, RTX, and triple immunosuppression (MMF/tacrolimus). Conversely, Case 2 (26M, Class III/V LN with APS) achieved complete remission (proteinuria <0.5 g/day) after two OBZ courses, having switched due to recurrent RTX infusion reactions and persistent nephrotic-range proteinuria. Case 3 (28M, Class V LN) showed a rapid response, reaching clinical remission after a single OBZ course following a suboptimal one-year response to MMF/RTX/tacrolimus.

Regarding non-renal disease, Case 4 (refractory arthritis) and Case 5 (recurrent enteritis) both achieved sustained remission on OBZ after RTX was discontinued due to hypersensitivity. Case 6 (39M, Class III LN and myocarditis) demonstrated significant improvement, with stabilised cardiac function and >50% reduction in proteinuria after switching to OBZ during an RTX-refractory relapse. Finally, Case 7 (38F, Class V LN) failed to respond to two OBZ courses after developing new-onset nephritis while on MMF and experiencing severe RTX rechallenge reactions.

Our experience with OBZ addresses a significant gap in the literature: its use in late-stage, multi-refractory SLE, which differs fundamentally from the early-stage populations evaluated in randomised trials (6, 7). Real-world data in such heavily pre-treated patients remains sparse and clinically valuable. Arnold *et al*. reported a nine-patient case series of SLE treated with OBZ for infusion reaction-associated secondary non-depletion, non-response to RTX, showing 6-month clinical remission in 6/9, robust peripheral B-cell depletion, and significant reductions in SLEDAI-2K; aside from one death due to COVID-19 in an unvaccinated patient, no other serious adverse events were observed (8). However, individual patient details (sequential labs, C3/C4, anti-dsDNA) were not extractable (Table II). Additionally, in a letter reporting on four cases of recurrent lupus nephritis, OBZ treatment led to good disease control. Prior RTX therapy was noted in only one patient, and one individual experienced CMV and herpes zoster infections, both successfully managed with antiviral agents (9).

Our findings align with the broader therapeutic shift emphasised in the recent *Clinical and Experimental Rheumatology* 'One Year in Review': the prioritisation of glucocorticoid minimisation, attainment of low disease activity (LLDAS), and the essential role of real-world evidence in complex SLE (10). Within this evolving framework, our data demonstrate that OBZ remains a rational, well-tolerated option for achieving these goals even in late-stage, multi-refractory disease – an area underrepresented in clinical trials and in need of further characterisation. Nonetheless, treatment sequencing in advanced disease limits attribution of outcomes to OBZ alone. Prospective multicentre cohorts with standardised endpoints, biomarker assessments, and long-term follow-up are needed to refine patient selection and define optimal role of OBZ in the treatment pathways of SLE.

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Table I. Clinical and laboratory features of seven cases of systemic lupus erythematosus who were non-responsive to RTX/ RTX intolerance.

Case n. (sex/age)	Indication for OBZ	C3/C4 level before OBZ (g/L)	C3/C4 level after OBZ (g/L)	Anti-dsDNA status, pre- / post-OBZ	OBZ courses (n)	Proteinuria, pre- / post-OBZ (g/day)	Hypogamma-globulinaemia	SLEDAI-2K before / after OBZ treatment
1. F / 28	Non-responsive to RTX	0.37*/0.04*	1/0.18	300/300 IU/ml	4	7.3/4.3	Pre-existing	20/18
2. M / 26	Non-responsive to RTX, RTX intolerance (infusion/ hypersensitivity reactions)	0.63*/0.02*	1.0/0.05*	+++/72.8 IU/ml	2	1.6/0.223	Absent	20/4
3. M / 28	Non-responsive to RTX	0.98/0.12	0.97/0.12	Negative/ Negative	3	1.7/0.27	Absent	4/0
4. F / 32	RTX intolerance (infusion/ hypersensitivity reactions)	1.02/0.17	1.14/0.17	Negative/ Negative	3	N/A	Absent	4/0
5. F / 25	RTX intolerance (infusion/ hypersensitivity reactions)	0.37*/0.02*	0.59*/0.06*	++/45 IU/ml	3	N/A	Absent	4/4
6. M / 39	Non-responsive to RTX	1.08/0.14	1.39/0.31	+/13.5 IU/ml	2	2.0/0.9	Absent	18/18
7. F / 38	RTX intolerance (infusion/ hypersensitivity reactions)	0.41*/0.04*	0.68*/0.15	Negative/N/A	2	2.9/2.5	Absent	6/6

C3/C4 levels, which were lower than the reference range. F: female; M: male; OBZ: obinutuzumab; RTX: rituximab; N/A: not applicable.

Table II. Comparison of real-world case series evaluating obinutuzumab in patients with conventional treatment resistance or secondary rituximab non-response/non-depletion.

	Age, F/M	SLE manifestations	Indication for OBZ	C3/C4 level before / after OBZ (g/L)	Anti-dsDNA status, pre- / post-OBZ	OBZ courses (n)	Proteinuria, pre- / post-OBZ (g/day)	LEDAI-2K before / after OBZ treatment	Adverse event
Teoh *et al*. (9)									
Patient 1	24, F	Class IV lupus nephritis	Fourth renal relapse occurred while on MMF	Low/improved to near normal	Positive/improved to near normal	1	50 /not detectable	N/A	No major side effects
Patient 2	49, F	Class III + V lupus nephritis, cerebral lupus with optic neuritis	Non-responsive to RTX	Low/Normal	Positive/Negative	1	2.2/0.21	N/A	No major side effects
Patient 3	60, F	Class III + V lupus nephritis	Tapering steroids and MMF led to a flare-up	Low/Low	Positive/Positive	1	0.63/0.48	N/A	CMV pneumonitis, colitis, herpes zoster
Patent 4	37, F	Lupus podocytopathy and class II lupus nephritis	Recurrent nephrotic syndrome during steroid tapering despite the addition of belimumab and tacrolimus	Normal/Normal Normal/Normal	Negative/Negative	1	2.29/0.12	N/A	No major side effects
Arnold *et al*. (8)									
Patient 1	36, F	NR	Secondary non-depletion non-response to RTX	NR	NR	1	NR	14/8	NR
Patient 2	24, F	NR	Secondary non-depletion non-response to RTX	NR	NR	1	NR	12/4	NR
Patient 3	34, F	NR	Secondary non-depletion non-response to RTX	NR	NR	1	NR	10/4	NR
Patent 4	41, F	NR	Secondary non-depletion non-response to RTX	NR	NR	1	NR	6/0	NR
Patient 5	29, F	NR	Secondary non-depletion non-response to RTX	NR	NR	1	NR	18/14	NR
Patient 6	37, F	NR	Secondary non-depletion non-response to RTX	NR	NR	1	NR	8/8	NR
Patient 7	30, F	NR	Secondary non-depletion non-response to RTX	NR	NR	1	NR	12/8	NR
Patent 8	44, F	NR	Secondary non-depletion non-response to RTX	NR	NR	1	NR	13/0	NR
Patent 9	21, F	NR	Secondary non-depletion non-response to RTX	NR	NR	1	NR	16/6	NR

F: female; M: male; OBZ: obinutuzumab; RTX: rituximab; N/A: not applicable; NR: not reported

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