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Efficacy and safety of obinutuzumab in systemic lupus erythematosus patients with secondary non-response to rituximab

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KEY MESSAGES

1. In a multicentre cohort, SLE patients with secondary non-depletion and non-response to rituximab had high rates of severe life- or organ-threatening disease
2. In these patients, switching from rituximab to obinutuzumab restores clinical responses previously achieved with rituximab with high rates of low disease activity

ABSTRACT

Objectives

Secondary inefficacy with infusion reactions and anti-drug antibodies (2NDNR) occurs in 14% of SLE patients receiving repeated rituximab courses. We evaluated baseline clinical characteristics, efficacy and safety of obinutuzumab, a next-generation humanised type-2 anti-CD20 antibody licensed for haematological malignancies in SLE patients with 2NDNR to rituximab.

Methods

We collated data from SLE patients receiving obinutuzumab for secondary non-response to rituximab in BILAG centres. Disease activity was assessed using BILAG-2004, SLEDAI-2K and serology before, and 6 months after, obinutuzumab 2x1000mg infusions alongside methylprednisolone 100mg.

Results

All 9 patients included in the study received obinutuzumab with concomitant oral immunosuppression. At 6 months post-obinutuzumab, there were significant reductions in median SLEDAI-2K from 12 to 6 (p=0.014) and total BILAG-2004 score from 21 to 2 (p=0.009). Complement C3 and dsDNA titres improved significantly (both p=0.04). Numerical, but not statistically significant improvements were seen in C4 levels. Of 8/9 patients receiving concomitant oral prednisolone at baseline (all >10mg/day), 5/8 had their dose reduced at 6 months. 4/9 patients were on 5mg/day and were in Lupus Low Disease Activity State following obinutuzumab. After obinutuzumab, 6/9 patients with peripheral B-cell data achieved complete depletion including 4/4 assessed with highly-sensitive assays. 1/9 obinutuzumab non-responder required cyclophosphamide therapy. 1 unvaccinated patient died from COVID-19.

Conclusions

Obinutuzumab appears to be effective and steroid-sparing in renal and non-renal SLE patients with secondary non-response to rituximab. These patients have severe disease with few treatment options but given responsiveness to B-cell depletion, switching to humanised type-2 anti-CD20 therapy is a logical approach.

INTRODUCTION

B-cells play a critical role in the pathogenesis of SLE via autoantibody production, antigen-presentation and proinflammatory cytokine production(1). Therefore, they represent a logical therapeutic target. Rituximab, a chimeric anti-CD20 monoclonal antibody that depletes B-cells, is recommended by EULAR for treatment-refractory renal and non-renal SLE patients(2).

As rituximab is a chimeric antibody, some rituximab-treated patients who initially respond well develop neutralising antibodies with repeat cycles on treatment. Infusion reactions followed by failure of B-cell depletion and treatment inefficacy, termed as secondary non-depletion nonresponse (2NDNR) occur in approximately 14% of patients(3). This is associated with high levels of anti-rituximab antibodies, high levels of pre-treatment plasmablasts and a lack of concomitant immunosuppression(3).

Following 2NDNR, a variety of other anti-CD20 therapies (ofatumumab, ocrelizumab and obinutuzumab) overcome the immunogenicity problems associated with 2NDNR, restoring depletion and clinical response. Switching from rituximab to these agents appeared more effective than treatment with a B-cell activating factor inhibitor, belimumab in a small study of 14 patients(4).

Obinutuzumab may be the most promising anti-CD20 therapy for SLE. While all of the next generation CD20 therapies are humanised or fully human, obinutuzumab is a type-2 CD20 antibody that is glycoengineered to have a stronger interaction with Fc gamma receptors and a stronger resistance to internalisation than rituximab. *In vitro* studies have shown that it is 2-fold more efficient than rituximab in inducing B-cell cytotoxicity in whole blood assays which provides a mechanistic basis for its increased potency(5). It is currently under investigation as part of the ongoing REGENCY and ALLEGORY Phase III randomised clinical trials in renal and non-renal SLE respectively. In contrast, a trial of the humanised anti-CD20 monoclonal ocrelizumab was halted due to an increased rate of opportunistic infections(6).

Only a single case of obinutuzumab for 2NDNR has been reported in the literature as described above. Here, we summarise data from all patients receiving obinutuzumab for 2NDNR in BILAG centres.

METHODS

Patient and design

We undertook a retrospective observational longitudinal cohort study and collated data from 9 patients across 6 centres managed with obinutuzumab following 2NDNR reactions after rituximab therapy (Leeds n=4, Bradford n=1, York n=1, London n=1, Birmingham n=1, Nottingham n=1). All patients had initially been treated with cycles of rituximab 2 x 1000mg but this had been discontinued due to 2NDNR. These patients had all then been switched to obinutuzumab 2 x 1000mg infusions 2 weeks apart, each preceded by methylprednisolone 100mg.

Ethical approval

According to NHS Research Ethics Committee guidelines, this study was considered as a service evaluation and formal ethical approval was not required because all treatment decisions were made prior to evaluation of data. Off-label use of obinutuzumab was approved by each participating NHS trust's Drugs and Therapeutic Committee.

Data and outcomes

Clinical information on the last rituximab cycle and the first obinutuzumab cycle was collected from a review of local medical notes including other therapies and safety (deaths and hospitalisations). Disease activity was assessed using BILAG-2004 and SLEDAI-2K and serology in local diagnostic laboratories before, and 6 months after each relevant cycle.

Laboratory measures

Peripheral B-cell subsets (naïve, memory and plasmablasts) were measured as a part of routine care in accredited diagnostic laboratories using either high-sensitive flow cytometry protocol as previously described at the Leeds Haematological Malignancy Diagnostic Service(7) or conventional flow cytometry in other participating centres. Complement C3 and C4 levels and anti-double-stranded DNA levels were measured according to standard laboratory protocols.

Statistical analysis

All analysis and data visualisation were carried out in R v3.6.0 with ggplot2. Changes in clinical and serological parameters were evaluated using the Wilcoxon signed-rank test.

RESULTS

Baseline characteristics

Baseline characteristics of all 9 patients included in this study are shown in Table 1

Table 1: Baseline characteristics of study participants

Baseline characteristic	
Age mean (SD), years	33.22 (7.26)
Disease duration mean (SD), years	9.34 (4.67)
Female n/N (%)	9/9 (100%)
Ancestry - South Asian - Afro-caribbean - European	 5/9 (56%) 2/9 (22%) 2/9 (22%)
Baseline BILAG A/B - Mucocutaneous n/N (%) - Musculoskeletal n/N (%) - Renal - Other domains n/N (%)	 4/9 (44%) 3/9 (33%) 5/9 (56%) 0/9 (0%)
SLEDAI mean (SD)	14.22 (7.71)
Total numeric BILAG mean (SD)	21.3 (11.5)
Prednisolone use n/N (%)	8/9 (89%)
Prednisolone dose mean (SD), mg	17.5mg, (11.7)
Previous cycles of rituximab mean (SD)	2.78 (1.40)
Concomitant immunosuppresants - Mycophenolate - Azathioprine - Tacrolimus - None	 4 (44%) 2 (22%) 5 (56%) 1 (11%)
Concomitant hydroxychoroquine	6 (67%)

All patients had signs and symptoms and laboratory tests consistent with 2NDNR to rituximab in their last course of therapy. 1 patient also had hospitalisation due to sepsis shortly after their last rituximab infusion. The median number of rituximab cycles before 2NDNR was 2.78.

Clinical response

Changes in numeric BILAG-2004 and SLEDAI-2K are shown in figure 1A and B. Individual patient responses are shown in supplementary table S1. At 6 months post-obinutuzumab, there were significant reductions in median SLEDAI-2K score (from 12 to 6 points, p=0.011) and numeric BILAG-2004 score (from 21 to 2 points, p=0.002). Before obinutuzumab, 6/9 patients had BILAG A/B grade for mucocutaneous, 6/9 had BILAG A/B musculoskeletal and 4/9 had BILAG A/B renal disease. After obinutuzumab 1/9 patients had BILAG B mucocutaneous, no patients had BILAG A/B musculoskeletal and 2/9 patients had BILAG A/B renal disease.

1/9 patient demonstrated a partial renal response and underwent a successful renal transplant. 1/9 patient who was not initially improving required escalation of oral prednisolone then rescue therapy with cyclophosphamide prior to month 6. In the available long-term follow-up data, the other 6/9 patients remain well controlled with repeat obinutuzumab cycles without requiring additional immunosuppression.

Prednisolone reduction and LLDAS

Prednisolone dose is shown in figure 1c. Before obinutuzumab therapy,all 9patients were on concomitant oral prednsiolone of ≥10mg/day. Following obinutuzumab therapy, 5/9 patients had their dose reduced of which 4/9 reduced to 5mg/day and achieved a Lupus Low Disease Activity State (LLDAS; defined as SLEDAI<4 without major organ activity, no new disease activity, physician's global Assessment ≤ 1 and prednisolone ≤ 7.5mg/day with standard immunosuppressant dosage)(8).

Serological and B-cell response

Changes in anti-dsDNA, complement C3 and C4 levels are shown in figure 1. There was a statistically significant reduction in anti-dsDNA; mean dsDNA titre reduced by 41.56 IU/ml (p=0.036). Mean C3 levels increased significantly by 0.23g/L (p=0.039). A numerical, but not statistically significant increase was seen in mean complement C4 levels following Obinutuzumab therapy (p=0.109).

B-cell depletion after obinutuzumab data were available in 6/9 patients. In 4/6 patients, this was assessed using highly sensitive flow cytometry (HSFC). All 6 of these patients achieved complete B-cell depletion following treatment with Obinutuzumab.

Safety

No significant infusion reactions occurred following obinutuzumab treatment. 1 unvaccinated patient became acutely well with COVID-19 infection and died. No case of progressive multifocal leucoencephalopathy was observed.

DISCUSSION

This is the first case series to report the effectiveness and safety of humanised anti-CD20 antibody obinutuzumab in the management of treatment-refractory SLE. Obinutuzumab was shown to be effective in patients who had failed to respond to conventional immunosuppressants, as well as rituximab due to 2NDNR. This was a group of patients with the greatest unmet clinical need due to limited therapeutic options available, high baseline disease activity and glucocorticoid requirements. It is also notable that the 2NDNR problem was predominantly observed in patients with non-European ancestry, disproportionate to the overall population of patients with SLE in the UK. Patients with non-European ancestry are well recognised to experience worse SLE and demonstrate poorer responses to conventional therapies(9). Hence this loss of therapeutic response to the UK's most commonly used biologic appears to occur in those with the greatest need. For this reason, our description of an effective therapy for this highly resistant population is important.

The superior responses to obinutuzumab we observed are consistent with evidence comparing rituximab and obinutuzumab in haematology, as well as *in vitro* data in autoimmunity(10,11). Given the severity and resistance of this population, the achievement of LLDAS in almost half of our patients is impressive. LLDAS represents a clinically meaningful SLE outcome measure that predicts low rates of damage if sustained and has already been applied retrospectively to another therapeutic trial in SLE(8). Our findings therefore suggest that obinutuzumab may be relatively cost-effective, although longer-term follow-up and a formal health economics analysis are needed to confirm this.

There is an increasing range of therapeutic classes available in SLE(12–14). The mechanism of most conventional immunosuppressants for SLE is, at least in part, due to their effects on B-cells (e.g. azathioprine, mycophenolate or cyclophosphamide). The most commonly used biological therapies in SLE, rituximab and belimumab, also target B-cells. However, more recently licensed and emerging therapies have other targets. These include anifrolumab, which targets the type I IFN receptor, voclosporin, which is a novel calcineurin inhibitor, or several inhibitors of JAK/TYK signalling. It will therefore be increasingly important for rheumatologists to develop a rationale to sequence these therapies. The data in this manuscript help with these decisions.

Several biologic switches can be considered based on our understanding of the mechanism of non-response: (i) some patients have primary non-response to rituximab due to failure to adequately deplete B-cells. These patients may still have B-cell-mediated disease and potentially benefit from the more potent B-cell killing offered by obinutuzumab, but that will require further research to test(7,15). (ii) Other patients, such as those with certain

cutaneous lesions, have primary non-response to rituximab due to seemingly non-B-cell mediated disease. These patients may benefit more from a switch to a non-B-cell-targeted therapy(16). (iii) In most primary responders to rituximab, relapse is explained by B-cell repopulation and they will continue to benefit from repeat cycles of the same therapy. (iv) some patients with primary response to rituximab exhibit secondary loss of response due to immunogenicity (i.e. 2NDNR) and these patients should switch within the CD20 class, particularly the humanised agents.

Obinutuzumab was generally well tolerated. Infusion reactions did not occur or were mild. 2 serious adverse events were noted, one episode of SLE enteritis and a death from severe COVID-19 infection. Rituximab has been previously associated with poorer outcomes in COVID-19 infection and attenuated vaccination responses. The timing of anti-CD20 therapy in the context of initial and booster COVID-19 vaccination represents another therapeutic challenge(17). Our patient was unvaccinated due to other significant health conditions and was severely unwell with SLE driven vasculitis when they contracted COVID-19. Therefore, it is difficult to comment as to whether Obinutuzumab contributed to their deterioration and beyond this whether obinutuzumab carries a higher risk than rituximab. Evidence is however emerging on how to manage these patients with antiviral medications and those conferring passive immunity(18,19).

Limitations of this study were the relatively low numbers and open-label design. However, it is difficult to obtain larger cohorts or to conduct formal trials in such highly resistant populations with unlicensed therapies, and we drew from a large group of collaborating SLE experts to obtain our data. Notably, our patients had high disease severity and resistance to prior treatments, so spontaneous improvements (as seen in the placebo arms of many non-renal RCTs) are less likely.

Apart from the post-rituximab population described here, obinutuzumab appears effective in lupus nephritis in the NOBILITY trial and is currently being assessed further as part of the ALLEGORY and REGENCY trials in renal and non-renal SLE (20). Moreover, as the range of therapeutic classes and molecules increases in SLE, questions about the appropriate sequence in which they should be used become more salient. Such questions are difficult to answer in randomised trials. We therefore propose that studies explaining the mechanism of response and small trials of mechanistically logical switches such as ours will be essential to begin to address these questions.

REFERENCES

1. Md Yusof MY, Vital EM, Emery P. B-cell-targeted therapies in systemic lupus erythematosus and ANCA-associated vasculitis: current progress. Expert Rev Clin Immunol [Internet]. 2013 Aug [cited 2022 Jan 4];9(8):761–72. Available from: https://pubmed.ncbi.nlm.nih.gov/23971754/

2. A F, M K, A A, M A, I B, JN B, et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. Ann Rheum Dis [Internet]. 2019 Jun 1 [cited 2021 Jul 12];78(6):736–45. Available from: https://pubmed.ncbi.nlm.nih.gov/30926722/

3. Yusof MYM, Shaw D, El-Sherbiny YM, Dunn E, Rawstron AC, Emery P, et al. Predicting and managing primary and secondary non-response to rituximab using B-cell biomarkers in systemic lupus erythematosus. Ann Rheum Dis [Internet]. 2017 Nov 1 [cited 2021 Jul 12];76(11):1829–36. Available from: https://ard.bmj.com/content/76/11/1829

4. Hassan SU, Md Yusof MY, Emery P, Dass S, Vital EM. Biologic Sequencing in Systemic Lupus Erythematosus: After Secondary Non-response to Rituximab, Switching to Humanised Anti-CD20 Agent Is More Effective Than Belimumab. Front Med [Internet]. 2020 Aug 27 [cited 2021 Dec 17];7. Available from: https://pubmed.ncbi.nlm.nih.gov/32984378/

5. Reddy V, Klein C, Isenberg DA, Glennie MJ, Cambridge G, Cragg MS, et al. Obinutuzumab induces superior B-cell cytotoxicity to rituximab in rheumatoid arthritis and systemic lupus erythematosus patient samples. Rheumatol (United Kingdom) [Internet]. 2017 Jul 1 [cited 2020 Oct 7];56(7):1227–37. Available from: https://pubmed.ncbi.nlm.nih.gov/28407142/

6. Mysler EF, Spindler AJ, Guzman R, Bijl M, Jayne D, Furie RA, et al. Efficacy and Safety of Ocrelizumab in Active Proliferative Lupus Nephritis: Results From a Randomized, Double-Blind, Phase III Study. Arthritis Rheum [Internet]. 2013 Sep 1 [cited 2020 Dec 8];65(9):2368–79. Available from: http://doi.wiley.com/10.1002/art.38037

7. Vital EM, Dass S, Buch MH, Henshaw K, Pease CT, Martin MF, et al. B cell biomarkers of rituximab responses in systemic lupus erythematosus. Arthritis Rheum [Internet]. 2011 Oct [cited 2020 Oct 12];63(10):3038–47. Available from: https://pubmed.ncbi.nlm.nih.gov/21618204/

8. Morand EF, Trasieva T, Berglind A, Illei GG, Tummala R. Lupus Low Disease Activity State (LLDAS) attainment discriminates responders in a systemic lupus erythematosus trial: post-hoc analysis of the Phase IIb MUSE trial of anifrolumab. Ann Rheum Dis [Internet]. 2018 May 1 [cited 2021 Nov 24];77(5):706–13. Available from: https://ard.bmj.com/content/77/5/706

9. Lewis MJ, Jawad AS. The effect of ethnicity and genetic ancestry on the epidemiology, clinical features and outcome of systemic lupus erythematosus. Rheumatology (Oxford) [Internet]. 2017 Apr 1 [cited 2021 Dec 22];56(suppl_1):i67–77. Available from: https://pubmed.ncbi.nlm.nih.gov/27940583/

10. Reddy V, Klein C, Isenberg DA, Glennie MJ, Cambridge G, Cragg MS, et al. Obinutuzumab induces superior B-cell cytotoxicity to rituximab in rheumatoid arthritis and systemic lupus erythematosus patient samples. Rheumatology (Oxford) [Internet]. 2017 Jul 1 [cited 2021 Nov 24];56(7):1227–37. Available from: https://pubmed.ncbi.nlm.nih.gov/28407142/

11. Freeman CL, Sehn LH. A tale of two antibodies: obinutuzumab versus rituximab. Br J Haematol [Internet]. 2018 Jul 1 [cited 2021 Dec 13];182(1):29–45. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/bjh.15232

12. Morand EF, Furie R, Tanaka Y, Bruce IN, Askanase AD, Richez C, et al. Trial of Anifrolumab in Active Systemic Lupus Erythematosus. N Engl J Med [Internet]. 2020 Jan 16 [cited 2021 Jun 29];382(3):211–21. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1912196

13. Furie R, Rovin BH, Houssiau F, Amoura Z, Santiago M, Contreras G, et al. BLISS-LN: A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 3 TRIAL OF INTRAVENOUS BELIMUMAB IN PATIENTS WITH ACTIVE LUPUS NEPHRITIS. Ann Rheum Dis [Internet]. 2020 Jun 1 [cited 2020 Oct 12];79(Suppl 1):103–103. Available from: http://ard.bmj.com/

14. Rovin BH, Teng YKO, Ginzler EM, Arriens C, Caster DJ, Romero-Diaz J, et al. Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet [Internet]. 2021 May 29 [cited 2021 Nov 30];397(10289):2070–80. Available from: http://www.thelancet.com/article/S014067362100578X/fulltext

15. Md Yusof MY, Shaw D, El-Sherbiny YM, Dunn E, Rawstron AC, Emery P, et al. Predicting and managing primary and secondary non-response to rituximab using B-cell biomarkers in systemic lupus erythematosus. Ann Rheum Dis [Internet]. 2017 Nov 1 [cited 2020 Sep 2];76(11):1829–36. Available from: http://ard.bmj.com/

16. Vital EM, Wittmann M, Edward S, Md Yusof MY, MacIver H, Pease CT, et al. Brief report: Responses to rituximab suggest B cell-independent inflammation in cutaneous systemic lupus erythematosus. Arthritis Rheumatol [Internet]. 2015 Jun 1 [cited 2021 Jul 7];67(6):1586–91. Available from: https://pubmed.ncbi.nlm.nih.gov/25707733/

17. Arnold J, Winthrop K, Emery P. COVID-19 vaccination and antirheumatic therapy. Rheumatology [Internet]. 2021 Mar 12 [cited 2021 May 7]; Available from: https://pubmed.ncbi.nlm.nih.gov/33710296/

18. Malsy J, Veletzky L, Heide J, Hennigs A, Gil-Ibanez I, Stein A, et al. Sustained response after remdesivir and convalescent plasma therapy in a B-cell depleted patient with protracted COVID-19. Clin Infect Dis [Internet]. 2020 Oct 26 [cited 2021 Dec 6]; Available from: https://pubmed.ncbi.nlm.nih.gov/33103195/

19. Wood EM, Estcourt LJ, McQuilten ZK. How should we use convalescent plasma therapies for the management of COVID-19? Blood [Internet]. 2021 Mar 25 [cited 2021 Dec 6];137(12):1573–81. Available from: https://pubmed.ncbi.nlm.nih.gov/33202419/

20. Furie RA, Aroca G, Cascino MD, Garg JP, Rovin BH, Alvarez A, et al. B-cell depletion with obinutuzumab for the treatment of proliferative lupus nephritis: a randomised, double-blind, placebo-controlled trial. Ann Rheum Dis [Internet]. 2021 Oct 6 [cited 2021 Nov 30];0:1–8. Available from: https://ard.bmj.com/content/early/2021/10/06/annrheumdis-2021-220920

SUPPLEMENTARY DATA: INDIVIDUAL PATIENT RESPONSES

Patient	Ancestry	Disease duration (Years)	Age (Years)	Total BILAG-2004 before Obi	Total BILAG-2004 after Obi	SLEDAI-2K before Obi	SLEDAI-2K after Obi	Prednisolone before Obi (mg)	Prednisolone after Obi (mg)
1	South Asian	10.8	36.4	18	2	14	8	10	5
2	South Asian	6.3	24.4	24	2	12	4	30	10
3	South Asian	11.9	34.8	29	1	10	4	10	10
4	South Asian	8.2	41.9	21	1	6	0	15	15
5	South Asian	6.8	29.4	32	21	18	14	50	60
6	White European	17.5	37.0	12	8	8	8	15	5
7	White European	16.9	30.0	12	1	12	8	10	5
8	Caribbean	6.2	44.2	25	2	13	0	10	15
9	Caribbean	2.6	21.0	9	2	16	6	10	5
Median (Q1, Q3)	**NA**	**8.2 (6, 12)**	**34.8 (29,37)**	**21 (12, 25)**	**2 (1, 2)**	**12 (10, 14)**	**6 (4, 8)**	**10 (10, 15)**	**10 (5, 15)**