Extremely Long-Lasting B-cell Depletion and BAFFling Effects Following Obinutuzumab-Based Regimen in Lupus Nephritis

To the Editor: A 47-year-old man diagnosed with class V lupus nephritis in 1993 has been treated over the years with cyclophosphamide, azathioprine, mycophenolate, and rituximab. In 2017, 2 years after the last (effective) rituximab infusion, a renal relapse occurred (proteinuria up to 11 g/24 h with class III nephritis at repeat biopsy). He received obinotuzumab (obi)[1] 1000 mg on day 1 and weeks 2, 24, and 26 as an add-on therapy to mycophenolate and corticosteroids.[2] He has been on complete peripheral B-cell depletion (BCD) (< 0.4 cells/mcl) for over 72 months with stable clinical response (SLEDAI-2k = 29 to SLEDAI-2k = 4) (Figure 1) despite the occurrence of a severe SARS-CoV-2 infection. Three bone marrow biopsies from 2021 and 2023 were unremarkable. Circulating levels of B-cell activating factor progressively increased during the follow-up (Figure 1).[2–4]

In Supplementary Figure S1, and Supplementary Tables S1 and S2, we provide a comparison of the BCD duration with obi and rituximab in different randomized controlled trials in systemic lupus erythematosus. In a *post hoc* analysis of the NOBILITY study,[5] of 63 patients who received two 1000 mg infusions of obi at baseline and week 2, 59 (93.7%) achieved BCD by week 24, that is, before obi redosing. Of the 51 patients who had sufficient follow-up data, 37 (72.5%) attained B-cell recovery within 93 weeks after last dose of obi. At week 104, 23 of 37 (62.2%) achieved an overall renal response. In the 11 patients requiring more than 93 weeks to achieve B-cell recovery it occurred within a median time of 114 weeks. Two of these 11 cases, including our patient, had not yet achieved B-cell recovery at the time of that last evaluation.

The results of the NOBILITY trial[2] strongly support the concept that obi is superior to rituximab at inducing BCD, leading to a higher rate of remissions

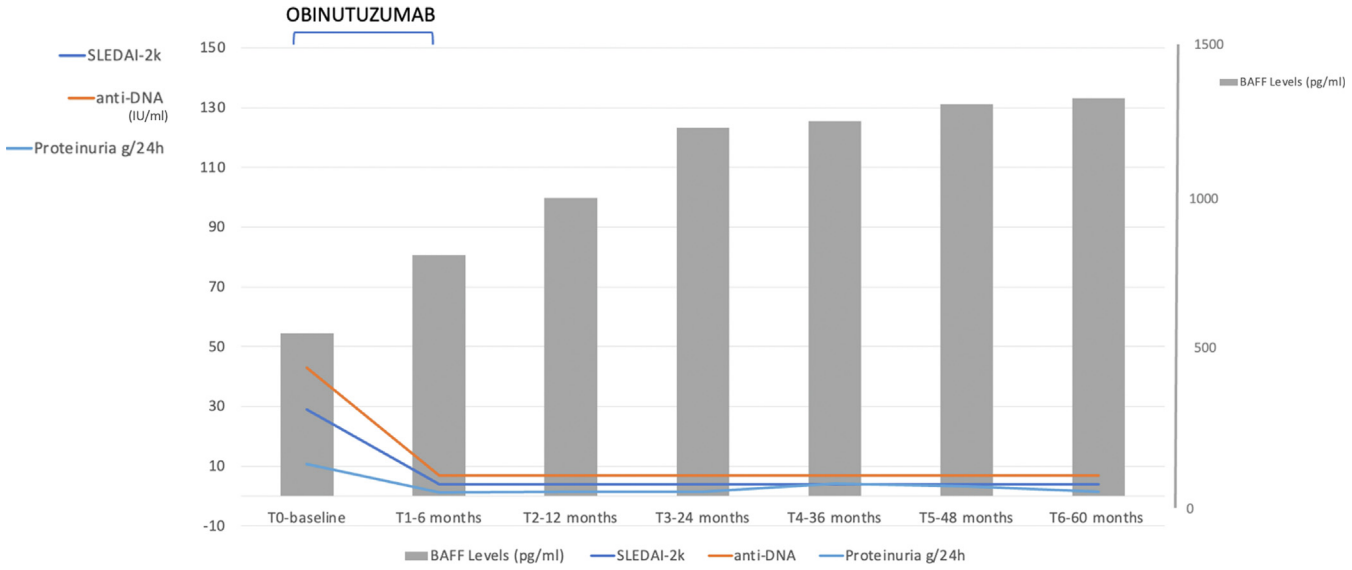

Figure 1. Clinical and laboratory response to obinutuzumab as monitored by SLEDAI-2K, anti-DNA antibodies and proteinuria levels. B-cell activating factor (BAFF) levels were monitored and increased during the follow-up. Obinutuzumab was administered as an i.v. infusion of 1000 mg on day 1 and weeks 2, 24, and 26, after premedication for prophylaxis against infusion-related reactions. B-cell depletion has been shown to distort BAFF homeostasis in patients with systemic lupus erythematosus, and an association between BAFF levels and disease exacerbation has been suggested. The loss of B cells following treatment with anti-CD20 agents reduces BAFF consumption by the major "users" of BAFF, thereby raising the steady state serum BAFF levels. This mechanism, as well as a potential compensatory, increased production of BAFF as a major cytokine regulating B-cell survival, maturation, and differentiation of B cells, could contribute to the increased levels of BAFF observed in patients who relapse after rituximab therapy compared with both those in remission and those who experience flare before B-cell depletion. Nevertheless, these observations do not apply to our patient, who experienced a progressive increase in circulating BAFF after obinutuzumab treatment while clinically in remission with persistent B-cell depletion, possibly pointing to a bystander effect instead of a causal relationship between increases in BAFF levels upon B-cell depletion and disease recurrence.

(Supplementary Tables S1 and S2). Adverse effects were mild and unrelated to duration of BCD (5 - Supplementary Figure S1). Although concerns may arise about the long-term effects of lack of B-cell repopulation over years, data show that clinical remission persists as long as BCD lasts despite increases in peripheral B cell activating factor levels.

PATIENT CONSENT

Written informed consent has been obtained from the involved patient.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Reference.

Figure S1. B-cell depletion time of the reported cases.

Table S1. The CD19-positive lymphocyte depleting effects of different therapeutic schemes using rituximab compared to obinutuzumab treatment.

Table S2. Comparison of rate of B-cell depletion at different time points after treatment with anti-B cell agents in different randomized controlled trials in systemic lupus erythematosus.

1. Mössner E, Brünker P, Moser S, et al. Increasing the efficacy of CD20 antibody therapy through the engineering of a new type II anti-CD20 antibody with enhanced direct and immune effector cell-mediated B-cell cytotoxicity. *Blood*. 2010;115:4393–4402. https://doi.org/10.1182/blood-2009-06-225979
2. Furie RA, Aroca G, Cascino MD, et al. B-cell depletion with obinutuzumab for the treatment of proliferative lupus nephritis: a randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis*. 2022;81:100–107. https://doi.org/10.1136/annrheumdis-2021-220920
3. Carter LM, Isenberg DA, Ehrenstein MR. Elevated serum BAFF levels are associated with rising anti-double-stranded DNA antibody levels and disease flare following B cell depletion therapy in systemic lupus erythematosus. *Arthritis Rheum*. 2013;65:2672–2679. https://doi.org/10.1002/art.38074
4. Scholz JL, Cancro MP. Resolve, revise, and relax: the 3 Rs of B cell repertoire adjustment. *Immunol Lett*. 2012;143:2–8. https://doi.org/10.1016/j.imlet.2012.01.014
5. Furie RA, Aroca G, Cascino MD, et al. B-cell depletion with obinutuzumab for the treatment of proliferative lupus nephritis: a randomised, double-blind, placebo-controlled trial. *Annals of the Rheumatic Diseases*. 2021;81:100–107. https://doi.org/10.1136/annrheumdis-2021-220920

Dario Roccatello[1,3], Savino Sciascia[1,3], Emanuele De Simone[1], Thomas Schindler[2], Elsa Martins[2], Huiyan (Ashley) Mao[2], Daniela Rossi[1] and Roberta Fenoglio[1]

[1]University Center of Excellence on Nephrological, Rheumatological and Rare Diseases (ERK-net, ERN-Reconnet and RITA-ERN Member) Including Nephrology and Dialysis Unit and Center of Immuno-Rheumatology and Rare Diseases (CMID), Coordinating Center of the Interregional Network for Rare Diseases of Piedmont and Aosta Valley (North-West Italy), San Giovanni Bosco Hub Hospital, ASL Città di Torino and Department of Clinical and Biological Sciences of the University of Turin, Turin, Italy; and [2]F. Hoffmann-La Roche AG, Basel, Switzerland

Correspondence: Dario Roccatello, University Center of Excellence on Nephrological, Rheumatological and Rare Diseases (ERK-net, ERN-Reconnet and RITA-ERN Member) Including Nephrology and Dialysis Unit and Center of Immuno-Rheumatology and Rare Diseases (CMID), Coordinating Center of the Interregional Network for Rare Diseases of Piedmont and Aosta Valley (North-West Italy), San Giovanni Bosco Hub Hospital, ASL Città di Torino and Department of Clinical and Biological Sciences of the University of Turin, Turin, Italy. E-mail: dario.roccatello@unito.it

[3]DR and SS contributed equally to this work.

Received 14 June 2024; revised 1 August 2024; accepted 5 August 2024; published online 10 August 2024

Kidney Int Rep (2024) **9,** 3079–3080; https://doi.org/10.1016/j.ekir.2024.08.008