

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

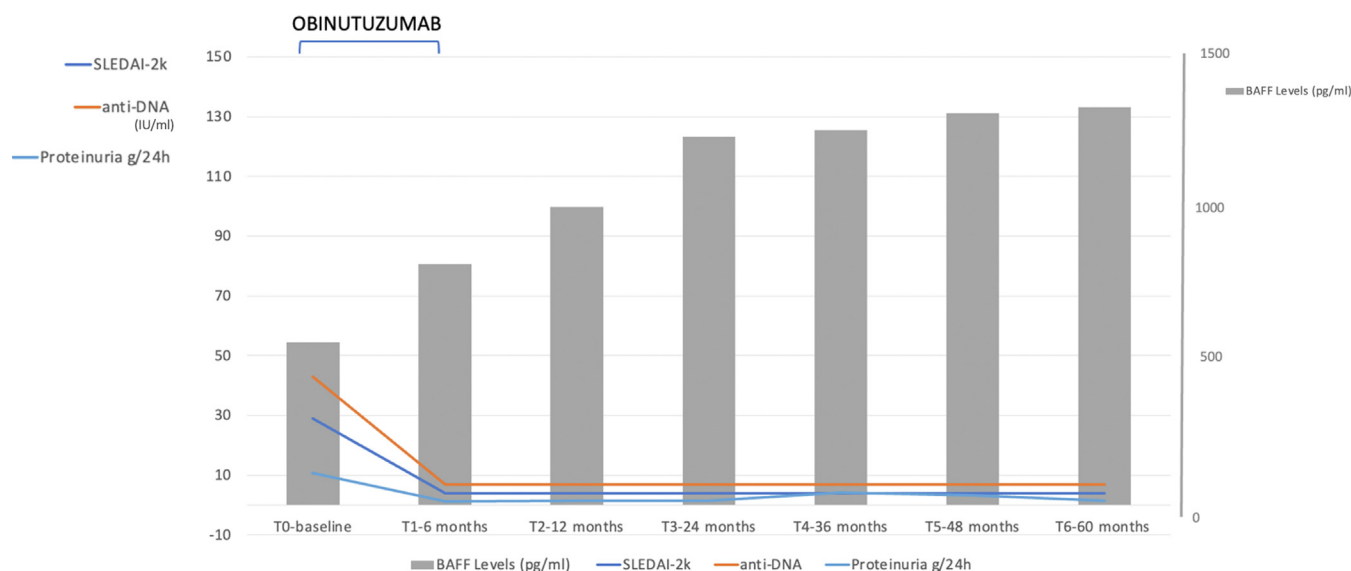


**To the Editor:** A 47-year-old man diagnosed with class V lupus nephritis in 1993 has been treated over the years with cyclophosphamide, azathioprine, mycophenolate, and rituximab. In 2017, 2 years after the last (effective) rituximab infusion, a renal relapse occurred (proteinuria up to 11 g/24 h with class III nephritis at repeat biopsy). He received obinutuzumab (obi)<sup>1</sup> 1000 mg on day 1 and weeks 2, 24, and 26 as an add-on therapy to mycophenolate and corticosteroids.<sup>2</sup> 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).<sup>2-4</sup>

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,<sup>5</sup> 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<sup>2</sup> 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.

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