EDITORIAL

Obexelimab and the Promise of Nondepleting B-Cell Therapy in IgG4-Related Disease

Thomas Dörner, M.D.[1]

IgG4-related disease has emerged as one of the clearest human models for understanding the role of B-lineage cells in immune-mediated inflammation. Although glucocorticoids remain effective for inducing remission, relapse during tapering is common, cumulative toxic effects are substantial, and durable disease control remains difficult to achieve. Della-Torre et al.[1] now report in the *Journal* the findings of the INDIGO trial. This phase 3 INDIGO trial of obexelimab is notable, not only because it showed a significantly lower risk of disease flare and significantly less glucocorticoid exposure than placebo, but also because it advances a mechanistically distinct approach to pathogenic B-cell responses.

The glucocorticoid-sparing implications of obexelimab may be as important as its effect on prevention of flare. This monoclonal antibody does not rely on broad B-cell depletion. Instead, it coligates CD19 and the inhibitory receptor FcγRIIb (CD32B) (Fig. 1), which results in suppression of B-cell activation without producing substantial B-cell aplasia. CD19 ligation inhibits B-cell receptor activation, along with antigen uptake and presentation to T cells.[2] FcγRIIb binding inhibits B-cell proliferation and differentiation through interleukin-4, lipopolysaccharide, and other stimulatory pathways.[2,3] Their coligation results in enhanced inhibition of B-cell activation, proliferation, and differentiation into antibody-secreting cells.

The case for B-lineage pathogenicity is strong. Rituximab first established B-cell targeting as a powerful therapeutic principle, and subsequent analyses identified predictors of relapse after B-cell depletion.[4] Controlled data on inebilizumab have reinforced the importance of the B-cell axis by showing substantial protection against flare in a phase 3 trial.[5] Translational studies have shown marked expansion of circulating plasmablasts during active disease and relapse, findings that support the view that B-cell activation, differentiation, and downstream effector products play a central role in pathogenesis. The results seen with obexelimab extend this framework by suggesting that complete B-cell depletion may not be necessary to interrupt clinically important biologic processes associated with disease.

One can envision at least three broad strategies for B-cell–directed treatment in IgG4-related disease: depletion of B-cell populations, functional inhibition of B cells without broad depletion, and interference with intracellular signaling pathways that sustain B-cell activation. For anti-CD19 depletion, we have evidence for inebilizumab; for nondepleting inhibitory coligation, we now have evidence for obexelimab; and for Bruton's tyrosine kinase inhibition, an early phase 2 trial indicates promise for rilzabrutinib,[6] and a phase 3 trial is ongoing (ClinicalTrials.gov number, NCT07190196). Preservation of more of the normal B-cell compartment could, in principle, lessen the risk of infection, reduce perturbation of humoral immunity, and decrease the risk of long-term complications.

The appeal of a nondepleting strategy does not by itself establish superior long-term safety, nor does it define the patients who are most likely to benefit. Questions remain about durability of response, optimal sequencing with other B-cell–directed agents, and the effects of treatment in patients with multisystem disease, advanced fibrosis, or repeated relapses. Even so, the mechanis-

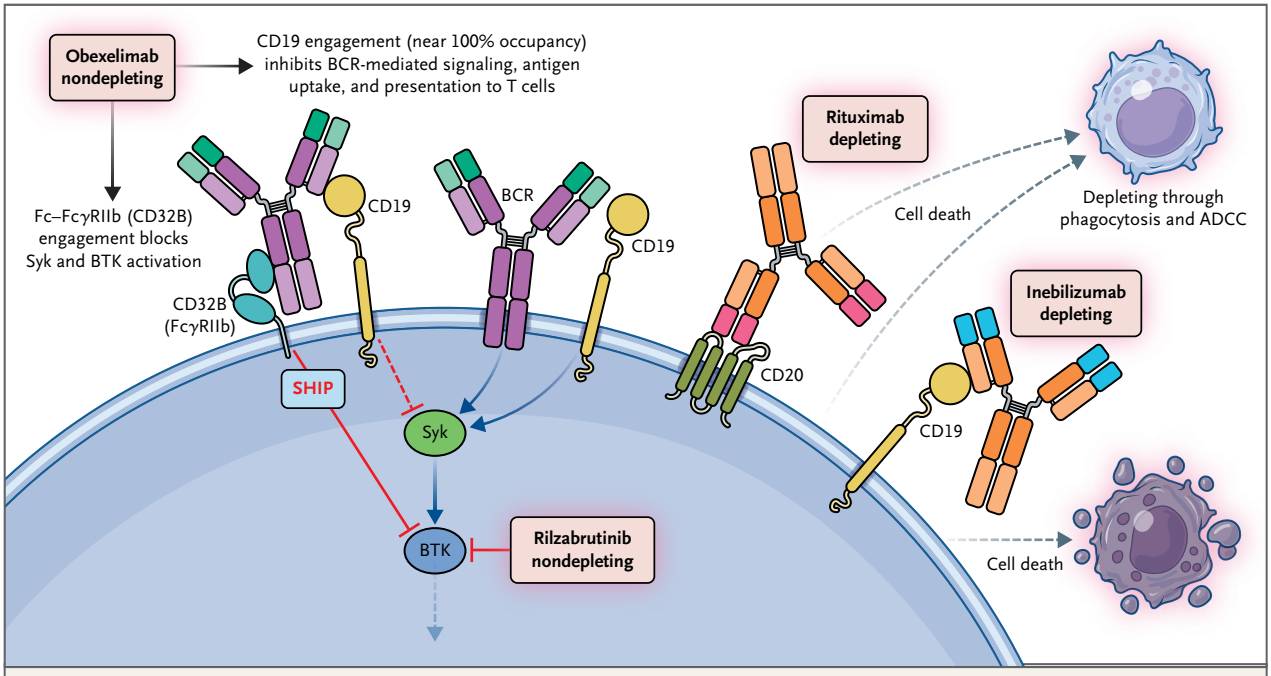

Figure 1. B-Cell–Targeted Therapies and Their Mechanisms of Action in IgG4-Related Disease.

B-cell–directed therapies can be classified on the basis of whether they deplete B cells or functionally inhibit B-cell activation, albeit often with a reduction in the number of circulating B cells. Rituximab targets CD20 and induces B-cell depletion through phagocytosis and antibody-dependent cellular cytotoxicity. Inebilizumab targets CD19 and depletes CD19-expressing B-lineage cells. Obexelimab coengages CD19 and the inhibitory receptor FcγRIIb, which leads to inhibition of B-cell–receptor signaling through blockade of spleen tyrosine kinase (Syk) and Bruton's tyrosine kinase (BTK) activation. Near-complete CD19 occupancy may also reduce antigen uptake and presentation to T cells. Rilzabrutinib inhibits BTK and thereby blocks downstream B-cell activation without directly depleting B cells. ADCC denotes antibody-dependent cellular cytotoxicity, BCR B-cell receptor, FcγRIIb Fc gamma receptor IIb, and SHIP SH2-containing inositol 5′-phosphatase.

tic message is important. With many autoimmune and fibroinflammatory disorders, the field has tended to equate successful B-cell therapy with depletion. The INDIGO trial challenges that assumption, suggesting that, in at least some cases, the critical therapeutic objective may be selective silencing of pathogenic B-cell function rather than elimination of the lineage itself. If so, the therapeutic goal shifts from aplasia to recalibration, two distinctly different approaches for achieving immune homeostasis.[7,8]

Inhibition of critical B-cell functions, however, may require more time to achieve immune homeostasis than would aplasia followed by B-cell repletion. Such inhibition may also depend to a great extent on selecting patients whose disease remains driven by reversible B-cell activation with the possibility of transiently unbalancing regulatory and effector immune circuits and requiring repeated doses. Options that do not involve B-cell depletion, however, hold promise for unique opportunities in autoimmunity to disentangle biologic processes associated with disease in order to personalize treatments that may enhance benefits and reduce risk.

In this sense, IgG4-related disease may serve as a model for rational drug development across immune-mediated diseases. Identification of upstream immune abnormalities that ultimately converge into abnormal B-cell activation — an approach that characteristically combines innate and adaptive activation pathways within B lymphocytes — holds promise.[7] Obexelimab provides proof that mimicking natural inhibition of B-cell activation and function is a therapeutic option. Depletion is no longer the only credible B-cell therapeutic paradigm.

The results of the INDIGO trial add to a growing body of evidence that precise manipulation of the B-cell compartment can alter the course of IgG4-related disease while also reducing reliance on glucocorticoids. The value of different treat-

ment options for patient subpopulations and various disease stages (e.g., inflammatory or fibrotic or as determined on the basis of the duration of disease) remains to be delineated. The next generation of studies should investigate whether selective B-cell inhibition can deliver sustained disease control, less treatment-related injury, and safer long-term immune preservation.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

[1]Department of Medicine, Charité Universitätsmedizin Berlin, Deutsches Rheuma-Forschungszentrum, Berlin.

This editorial was published on June 2, 2026, at NEJM.org.

1. Della-Torre E, Baker MC, Zhang W, et al. Obexelimab for the treatment of IgG4-related disease. N Engl J Med. DOI: 10.1056/NEJMoa2601337.
2. Perugino CA, Wallace ZS, Zack DJ, et al. Evaluation of the safety, efficacy, and mechanism of action of obexelimab for the treatment of patients with IgG4-related disease: an open-label, single-arm, single centre, phase 2 pilot trial. Lancet Rheumatol 2023;5(8):e442-e450.
3. Chu SY, Vostiar I, Karki S, et al. Inhibition of B cell receptor-mediated activation of primary human B cells by coengagement of CD19 and FcgammaRIIb with Fc-engineered antibodies. Mol Immunol 2008;45:3926-33.
4. Carruthers MN, Topazian MD, Khosroshahi A, et al. Rituximab for IgG4-related disease: a prospective, open-label trial. Ann Rheum Dis 2015;74:1171-7.
5. Stone JH, Khosroshahi A, Zhang W, et al. Inebilizumab for treatment of IgG4-related disease. N Engl J Med 2025;392:1168-77.
6. Stone JH, Martinez Valle F, Carruthers M, et al. Efficacy and safety of rilzabrutinib, an oral Bruton's tyrosine kinase inhibitor, in patients with IgG4-related disease: results from a 52-week, phase 2, open-label, proof-of-concept study. Ann Rheum Dis 2025;84:155 (https://ard.eular.org/article/S0003-4967(25)01232-4/abstract).
7. Dörner T, Lipsky PE. The essential roles of memory B cells in the pathogenesis of systemic lupus erythematosus. Nat Rev Rheumatol 2024;20:770-82.
8. Junt T, Calzascia T, Traggiai E, et al. Defining immune reset: achieving sustained remission in autoimmune diseases. Nat Rev Immunol 2025;25:528-41.

DOI: 10.1056/NEJMe2605617