Published in final edited form as:

Transplantation. 2020 January ; 104(1): e3–e4. doi:10.1097/TP.0000000000002993.

Anti-BAFF Therapy: A New Tool to Target B Cells in Antibody-mediated Rejection?

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Maintaining long-term renal allograft survival remains a major challenge in kidney transplantation. Chronic active antibody-mediated rejection (AMR) accounts for the majority of late renal allograft failures. In AMR, B cells both generate donor-specific antibody (DSA) as well as present antigen, produce cytokines, and promote allograft injury. The efficacy of therapeutics commonly used to treat AMR demonstrate mixed results in clinical practice. Thus, clinicians and researchers have an interest to better understand the role of B cells in AMR and to identify effective targeted therapeutics.

To this end, novel agents targeting B cells are becoming a focus of study. One such mediator is a member of the B cell survival cytokines, called B-cell Activating Factor of the Tumor Necrosis Factor Family (BAFF). BAFF is a critical B cell survival factor that promotes B-cell maturation and activation.¹ Therapeutics targeting BAFF are now in use clinically. Belimumab is a humanized monoclonal antibody that targets circulating BAFF and results in B-cell apoptosis. Much of the clinical research regarding belimumab comes from the field of rheumatology, where it has proven effective to treat systemic lupus erythematosus. As a result of clinical trials in 2011, belimumab became the first FDA-approved agent for treatment of systemic lupus erythematosus in over 50 years (the previous FDA-approved addition was hydroxychloroquine in 1958).² This progress was largely the result of a guidance document from the FDA in 2005 that sparked numerous clinical trials. The efficacy of belimumab to treat lupus nephritis remains unclear; post hoc analysis suggests improved proteinuria and serologic activity. Clinical trials specifically designed to test the efficacy of belimumab for renal outcomes in lupus nephritis are ongoing.

Along similar lines, there is a sparsity of effective and approved medications for the treatment of AMR in renal transplantation. Recent studies show promise and rationale for targeting B-cell survival cytokines such as BAFF in transplantation. Studies have associated higher levels of BAFF with increased DSA, risk of AMR, worsened allograft pathology, and development of survival niches for B cells within the renal allograft.^{3–7} A recent phase 2 clinical trial including belimumab in addition to standard immunosuppression in kidney transplantation demonstrated safety; however, had limited impact on naive B cell populations.⁸ Whether this finding was due to concurrent immunosuppression or failure to achieve adequate BAFF suppression remains an open question.

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The author declares no conflicts of interest.

In this issue of *Transplantation*, Steines et al⁹ examined the impact of administering a monoclonal anti-BAFF antibody in a rat kidney transplant model. Anti-BAFF treatment demonstrated efficacy to reduce B-cell populations in lymphoid tissues, circulation, and the allograft. Pronounced effects on lymphoid tissues were observed. BAFF suppression reduced CD40, inducible costimulator (ICOS) ligand, and interleukin (IL)-6 levels in splenic tissue. Splenic germinal center formation was reduced and, as a functional consequence, DSA levels were reduced. Mechanistic explanations for the humoral responses to anti-BAFF treatment include (1) reduced costimulatory molecules for antigen presentation; (2) reduced splenic IL-6 levels to promote germinal center formation; and (3) a reduced naïve B cell pool to form germinal centers. The authors hypothesize targeting BAFF could reduce B-cell and plasmablast-mediated production of IL-6, which would lessen germinal center formation and DSA production.

Surprisingly there were 2 cases of chronic active AMR out of the 5 recipients in the anti-BAFF treated group. Pathologic characterization of the 2 cases demonstrated chronic active AMR (as evidenced by transplant glomerulopathy and microvascular inflammation); 1 of the cases also had grade IIB cellular rejection and the other case had borderline cellular rejection. Further analysis revealed these cases had persistent DSA, with DSA levels similar to the group that did not receive anti-BAFF treatment. The authors note that the 2 cases with chronic active AMR did not have abnormal B cell numbers or cytokine levels. The reasons for the 2 cases of chronic active AMR in the anti-BAFF treated group are unclear. Did these cases of rejection manage to escape BAFF suppression and, as a result, was B-cell maturation and DSA generation allowed to continue? The data indicate DSA were generated, supporting B-cell maturation and activation was intact in these 2 cases. Would similar results be seen with an alternative dosing schedule? In many cases, the belimumab dosing schedule for lupus is applied to transplant. Whether a different dosing schedule is required to maintain B-cell suppression in the setting of transplantation is unclear and warrants further study. Was B-cell development driven through an alternative signaling pathway that is not exclusively mediated by BAFF? This is a consideration due to several features of the BAFF pathway. First, there are membrane and soluble forms of BAFF. Anti-BAFF antibody, such as belimumab, targets the soluble form of BAFF, not membrane-bound BAFF. Whether targeting membrane-bound versus soluble BAFF would yield different results is not established. Second, other mediators of B-cell maturation exist, such as A Proliferation Inducing Ligand (APRIL). The BAFF/APRIL system share signaling through two receptors on B cells (B-cell maturation antigen and Transmembrane Activator and Cyclophilin Ligand Interactor). Thus, it is possible to maintain APRIL mediated signaling to B cells even in the face of BAFF suppression. In fact, due to the redundancy in the BAFF/APRIL system, some propose targeting multiple arms of the pathway.

B cell survival cytokines such as BAFF hold promise as a new targeted therapeutic in the transplant immunosuppressive armamentarium. There are certainly issues to sort out in terms of effectiveness and durability of B-cell suppression and the necessity of BAFF/APRIL pathways in DSA responses. Experimental models such as animal models are important tools to help in this regard to better dissect the mechanisms at play. Clinical trials investigating belimumab in transplantation are currently underway, which will bring a new understanding of these therapeutics to the field in the near future.

Acknowledgments

S.E.P. was supported by NIH grant K23DK122136.

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