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Response

Friend or foe in GVHD: a matter of targeting the right B-cell subset

We thank Davis and Ritchie for their interest in our review and their comments. In their letter they suggest that other mechanisms than B-cell depletion could underlie the observed benefit of rituximab in graft-versus-host disease (GVHD). In addition, they raise the concern that use of rituximab could also cause harm by depleting regulatory B cells, which suppress allogeneic T-cell responses.

Unfortunately, due to space constraints, we were not able to discuss these aspects fully in our review. We consider it unlikely that Fc receptor–mediated immunomodulatory effects are responsible for the therapeutic activity of rituximab in GVHD. High-dose intravenous immunoglobulins are of questionable use for the prophylaxis or treatment of GVHD.[1] Furthermore, the dose of intravenous immunoglobulins, typically 500 mg/kg, that is required to observe an immunomodulatory effect is much higher than the 375 mg/m^2 of rituximab generally used for the treatment of GVHD. Several other potential mechanisms have been suggested to explain the effectiveness of rituximab in nonmalignant disorders such as autoimmune disease. For instance, recently it has been shown that rituximab also depletes CD20$^+$ T cells, which constitute a small subpopulation of T cells with proinflammatory properties.[2] Another proposed mechanism is the formation of immune complexes of anti-CD20 antibodies and B cells, which act as decoys and sequester Fcγ receptor–expressing effector cells such as macrophages.[3] In addition, rituximab can also interfere with B-cell receptor signaling.[4] Despite these potential nonspecific effects of rituximab, multiple independent lines of evidence both from experimental animal models as well as clinical data strongly link B lymphocytes to GVHD pathogenesis.[5-7] Therefore, even though other mechanisms might contribute to the effectiveness of rituximab, we believe that the depletion of pathogenic B lymphocytes themselves and not nonspecific effects of rituximab such as depletion of CD20$^+$ T cells, FcγRIII-dependent immunomodulation, or the tolerogenic effect of apoptotic lymphocytes are the main mode of action of rituximab in GVHD.

We fully agree with the authors' concern that the use of rituximab also could lead to the depletion of regulatory B cells. As we pointed out in our review, certain regulatory B cells can suppress T-cell immune responses and some subsets of B lymphocytes are associated with a reduced incidence of GVHD.[6] Administration of rituximab therefore bears the risk of destruction of protective regulatory B cells and thereby might trigger or worsen GVHD. To our knowledge there are so far no reports of acute exacerbation of GVHD after administration of rituximab, indicating that the benefits of depleting the pathogenic B-cell subsets generally outweighs the harm of depleting regulatory B cells. Interestingly, it was reported recently that administration of rituximab within the first months after stem cell transplantation is associated with an increased risk of cytopenias, which possibly resulted from an autoimmune response.[8] Thus, agents that more specifically deplete the pathogenic B-cell subset while sparing regulatory B cells could provide superior results in the treatment of GVHD.

A better characterization of human B-cell subsets and the spatial and temporal dynamics of their pathophysiologic contribution to the graft-versus-host reaction will enable us to maximize the benefit of B cell–targeted therapeutic approaches for the prevention and treatment of acute and chronic GVHD.

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