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To the editor:

B cells in GVHD: friend or foe?

We were pleased to read the recent review by Shimabukuro-Vornhagen et al, "The role of B cells in the pathogenesis of graft-versus-host disease," which highlights the importance of B cells after bone marrow transplantation, as B cells have tended to be overlooked as a contributor to transplantation immunology.[1] This review comprehensively describes the use of the humanized chimeric CD20 monoclonal antibody, rituximab, for the prophylaxis and treatment of acute and steroid-refractory chronic graft-versus-host disease (GVHD).[1] Three key observations have been made: (1) the use of rituximab as part of pretransplantation conditioning results in the in vivo depletion of donor B cells after transplantation; (2) pretransplantation rituximab is associated with reduced incidence and severity of acute GVHD in a cohort of patients; and (3) elevated B-cell numbers in donor grafts are associated with the development of both acute and chronic GVHD. Whether B-cell depletion per se is the mechanism underlying reduced GVHD rates, and whether this reflects a direct role of B cells in stimulating allogeneic T-cell expansion and effector function remains unknown.

It is important to also consider the potential nonspecific effects of rituximab therapy on the activation of allogeneic T cells. Nonspecific IgG treatment, such as high-dose intravenous immune globulin, can inhibit interferon-γ (IFN-γ) responses in macrophages via a FcγRIII-dependent mechanism, and induce natural killer cell–mediated antibody-dependent cellular cytotoxicity of dendritic cells (DCs).[2,3] Apoptotic lymphocytes also have a regulatory effect upon DCs, by down-regulating costimulatory molecules and inducing the production of the immunosuppressive cytokine interleukin-10 (IL-10).[4,5] In GVHD, these events stimulate the generation and proliferation of regulatory T cells (Tregs), thus suppressing allogeneic T-cell activation.

Both T and B lymphocytes play a role in tolerance induction to autoantigens, whereby $CD4^+$ T cells regulate early allogeneic T-cell activation and expansion, and B cells control their differentiation into effector T cells.[6] Host B cells have also been shown to play a protective role in GVHD, via the secretion of IL-10 after total body irradiation, thus inhibiting alloreactive T-cell expansion and subsequent acute GVHD induction.[7] Donor B cells can also inhibit acute GVHD in a major histocompatibility complex class II– and Treg-dependent manner. Mice receiving BM from B cell–deficient mutant mice (B6.μMT) developed rapid-onset acute GVHD, contributed by faster donor $CD8^+$ T-cell engraftment and production of IL-2 and IFN-γ (J.E.D., V. Watt, and D.R.S., manuscript in preparation), and indirect alloantigen presentation to $CD4^+$ T cells.[8] This is supported by recent in vitro human data, indicating that activated B cells directly suppress allogeneic $CD4^+$ T-cell proliferation through the expansion of alloantigen-specific suppressor Tregs.[9]

While clinical observations indicate that rituximab has a beneficial effect in the prophylaxis of acute GVHD, it is worth considering that an alternate mechanism of its action may exist over and above simple B-cell depletion. Furthermore, the potential benefit of regulatory B cells may be lost if rituximab is adopted wholesale into pretransplantation conditioning regimens.

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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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