Dual cytokine blockade in acute GVHD

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In this issue of Blood, Khuat et al report that the dual blockade of both tumor necrosis factor α (TNF-α) and interleukin-6 (IL-6) receptor (IL-6R) provided a significant advantage over single-cytokine blockade in protection from lethal murine graft-versus-host disease (GVHD).1

Preclinical and clinical evidence points to the important contribution of proinflammatory cytokines, including TNF-α and IL-6, in GVHD pathogenesis (as reviewed by Henden and Hill2). Preclinical studies reporting TNF-α3 or IL-64 blockade for murine GVHD prevention and treatment prompted clinical studies. Despite case series and phase 1/2 trials with encouraging results, confirmation of the efficacy of TNF-α or IL-6 blockade in GVHD from phase 3 clinical trials is still lacking. A phase 3 study of initial treatment of acute GVHD reported no improvement with combined infliximab and corticosteroids compared with corticosteroids alone.5 Similarly, a recent phase 3 double-blind randomized study showed only a trend toward reduction in grade 2 to 4 acute GVHD after the addition of tocilizumab to standard GVHD prophylaxis, with no impact on long-term outcome.6

In the current study, Khuat et al tested the hypothesis that blocking both the TNF-α and the IL-6 pathways would provide superior GVHD prophylaxis over single-cytokine blockade. The authors employed several murine GVHD models, including a classical acute GVHD major histocompatibility complex–mismatch model and a minor mismatch model they had recently reported using diet-induced obese recipient mice7 (see figure). Animals receiving dual TNF-α and IL-6R blockade had significantly reduced signs of acute GVHD and better survival compared with untreated mice or mice receiving single-cytokine blockade. Conversely, in a model of sclerodermatous chronic GVHD, dual TNF-α and IL-6R blockade did not provide an advantage over single-cytokine blockade. Importantly, dual-cytokine blockade did not affect the graft-versus-tumor effect in either murine model. GVHD is a result of the activation of multiple cellular and molecular pathways ultimately leading to tissue damage. Khuat et al selected 2 actionable targets, the combined modulation of which is possible through routinely available therapies, thus allowing rapid clinical evaluation of these preclinical findings.

Cellular and molecular mechanisms underlying the additive or synergistic effect of TNF-α and IL-6 blockade are not fully understood. A potential limitation of TNF-α blockade in GVHD is that TNF-α signaling through TNF receptor 2 (TNFR2) is essential for the homeostasis and function of CD4+ FOXP3+ regulatory T cells (Tregs) after allogeneic hematopoietic cell transplantation.8 Conversely, IL-6R blockade augments both thymic-dependent and thymic-independent Treg reconstitution.4 Addition of IL-6R blockade might thereby prevent Treg depletion and functional impairment secondary to single TNF-α blockade. This hypothesis was supported by a trend toward increased Foxp3 transcript in the small intestine of mice receiving dual-cytokine blockade.1 Future mechanistic and correlative studies are needed to elucidate the importance of this and other pathways and to understand fully the effect of dual-cytokine blockade.

Mouse models remain essential tools for GVHD studies but are not useful for the evaluation of the risk of infection that arises from the use of new immunomodulatory strategies. TNF-α blockade using infliximab was associated with a significant number of severe infectious complications in patients with steroid-refractory acute GVHD.9 Carefully conducted clinical studies will reveal whether patients receiving dual TNF-α and IL-6R cytokine blockade will have an acceptable level of infection.

Over the last decade, the use of cytokine blockade has been extended to new indications both within and beyond the hematological field, namely for the treatment of cytokine release syndrome after adoptive immune effector cellular therapies and for severe COVID-19. Future studies will

![Diagram of Dual cytokine blockade in acute GVHD](https://example.com/diagram.png)

Dual anti–TNF-α and IL-6R blockade mitigated acute GVHD without interfering with the graft-versus-tumor effect in 2 different mouse models (major histocompatibility complex [MHC]-mismatch model BALB/c into C57BL/6 and minor mismatch model B10.D2 into diet-induced obese [DIO] BALB/c recipients). Professional illustration by Patrick Lane, ScEYEnce Studios.
assess whether combined cytokine blockade might provide additional benefits while retaining an acceptable safety profile in these inflammatory settings and others.

In summary, the work by Khuat et al offers compelling evidence that dual TNF-α and IL-6R blockade provides a marked advantage in terms of acute GVHD prevention over single-cytokine blocking approaches in murine models of GVHD. The results of this study should contribute to the design of future clinical trials assessing the safety and efficacy of dual TNF-α and IL-6R blockade for GVHD prevention and treatment.

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REFERENCES

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