need to be treated with a DOAC rather than a vitamin K antagonist to avoid one event of intracranial bleeding is 588 and is 1250 for fatal bleeding. In view of the large number of patients who present with VTE each year,[2,3] and the devastating nature of these bleeding events, these are important effects on population health.

Regarding the key patient subgroups evaluated, the noninferior efficacy of the DOACs was consistent across all subgroups, with possibly superior efficacy in the elderly and in cancer patients.[1] The safety advantage of reduced major bleeding was also consistent across the subgroups, except possibly in cancer patients, in whom the pooled estimate of a 23% RR reduction did not achieve statistical significance (supplemental data).[1]

What are the implications for clinical practice? The DOACs should now replace vitamin K antagonists in most patients with VTE. The exceptions are patients with severe renal impairment (creatinine clearance <30 mL/min) because they were not included in the clinical trials, and cancer patients because only relatively small numbers of selected cancer patients were included and because clinical trials comparing the DOACs with currently recommended standard therapy with low-molecular-weight heparin have not been done. The lack of a specific reversal agent for the DOACs should not be a reason to withhold from most patients the benefit of significantly reduced risks of major bleeding, intracranial bleeding, and fatal bleeding. In the near term, vitamin K antagonists may be preferred in patients in whom prompt and measurable reversal of the anticoagulant effect will be required as a result of planned surgery or invasive procedures. The availability of an effective reversal agent for the DOACs is eagerly awaited and will further enhance their clinical utility. Because the DOACs do not require laboratory monitoring, patients receiving DOACs may have less frequent contact with their physician or anticoagulation clinic, and nonadherence to the prescribed therapy may not be detected as quickly. Physicians and health systems should use evidence-based strategies to enhance adherence, and they should evaluate patients at intervals to assess whether ongoing anticoagulant therapy is appropriate and maintained.

Some practical questions remain. Rivaroxaban and apixaban can be used as a single drug approach,[4,7-9] whereas dabigatran and edoxaban are preceded by at least 5 days of heparin or low-molecular-weight heparin treatment.[5,6,10] Is DOAC monotherapy sufficient for the full spectrum of VTE severity, or is "lead-in" heparin treatment preferred in some patients, such as those with PE who have right ventricular dysfunction?[10] How does the effectiveness and safety of the DOACs compare with low-molecular-weight heparin treatment in cancer patients with VTE? If the DOACs are at least as effective and safe, they may improve the quality of life for such patients by avoiding daily subcutaneous injections. Clinical trials are urgently needed to address these questions.

Despite these questions, the results gained by van Es and colleagues[1] provide further evidence that the DOACs are a major therapeutic advancement that simplifies anticoagulant therapy and improves patient safety outcomes in patients with VTE.

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● ● ● **TRANSPLANTATION**

Bringing out the DCs' softer side in GVHD

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In this issue of *Blood*, Capitini et al use mouse models to demonstrate that STAT1 loss or inhibition causes dendritic cell (DC) modulation, resulting in lesser GVHD.[1]

Graft-versus-host disease (GVHD) remains a significant cause of morbidity following allogeneic hematopoietic stem cell transplantation (HSCT). Much of the earlier research and approaches focused on the alloreactive donor T cell itself as the principal driver and mediator of GVHD. Approaches have ranged from simple removal of all T cells (which unfortunately also abrogates graft-versus-tumor [GVT] responses), blockade of costimulation or cytokine pathways, interfering with lymphocyte trafficking to GVHD target tissues, use of purified T-cell subsets (ie, memory cells,
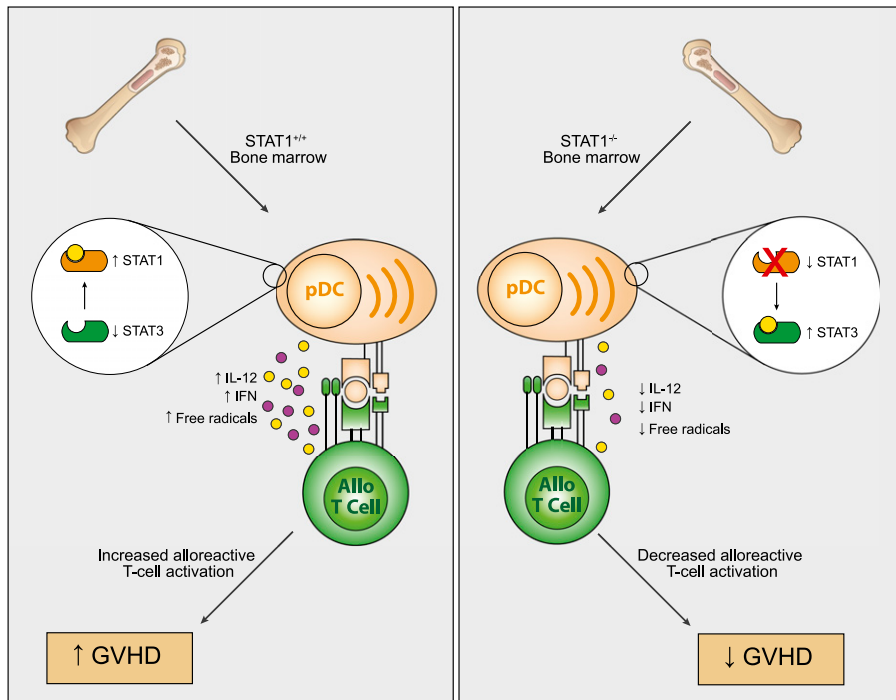
Impact of STAT1 on GVHD. STAT1$^{-/-}$ bone marrow cells give rise to pDCs with a tolerogenic phenotype after allogeneic HSCT in mice. This results in increased STAT3 and lesser production of interferon, IL12, and free radical formation culminating in lesser activation of alloreactive T_h1 cells and GVHD pathology.

T regulatory [Treg] cells, or T-helper [T_h]2 subsets), and modulation of T cells ex vivo to targeting intracellular signaling via Janus kinase (JAK) and signal transducer and activator of transcription (STAT) pathways.[2] Recently, more attention has been given to a principal and pivotal collaborator in the fueling of alloreactions after HSCT: the dendritic cell (DC). Once viewed as simple antigen-presenting vehicles, it is clear there is a tremendous complexity among DC subpopulations that profoundly affects T cells through promoting, inhibiting, and modulating T-cell responses. Initial studies in allogeneic HSCT focused on the host DC as the culprit in sensitizing the donor T cell,[3] but subsequent investigations demonstrated that both donor and host DCs can contribute to GVHD and GVT responses.[4] This may be the case particularly with chronic GVHD, which is becoming a more prominent complication in allogeneic HSCT. The study by Capitini et al[1] nicely demonstrates the role of STAT1 in this process. STAT1 is a critical transcriptional regulator of T_h1-type pathways and has been shown to directly impact CD4 T-cell responses in GVHD.[5]

However, when using bone marrow from STAT1 knockout mice (STAT1$^{-/-}$), Capitini et al showed, across several strain combinations, a significant diminution of acute GVHD when normal donor T cells were later given as a delayed lymphocyte infusion (DLI). They further demonstrated that the absence of STAT1 markedly altered the development of donor-derived DCs as CD9$^-$ SiglecH^{hi} plasmacytoid DCs (pDCs) predominated. These STAT1$^{-/-}$ pDCs also displayed important functional alterations and exhibited a tolerogenic phenotype by expressing elevated STAT3. STAT1$^{-/-}$ pDCs produced less interleukin (IL)12, type I interferon, and free radicals (see figure). Not only did this impair the T_h1-driven GVHD processes when the normal T cells were later given as DLI, but the lesser free radical formation likely also diminished tissue damage so often associated with fueling the GVHD cascade. Tregs were also expanded. Importantly, the investigators demonstrated maintenance of GVT effects and that pharmacologic STAT1 inhibition also prevented GVHD. These studies offer a new pathway that can be targeted in GVHD

modulating DC generation after HSCT. Using small molecule inhibitors or small interfering RNA, it may offer means to modulate STAT1 in a transient fashion, making it a more clinically applicable approach.

Several important questions remain to be considered. What are the long-term effects on GVT when the systemic STAT1 inhibitor is used? Is prolonged suppression of STAT1 required or is the induction of CD9$^-$ SiglecH^{hi} pDCs enough to maintain the protective effect of STAT1 inhibition? Can it be used to modulate ongoing GVHD? The study used a DLI model where the role of the donor-derived DCs may be greater compared with host DCs. It is important to determine effects on chronic GVHD as in other murine models; the effects of STAT1 deficiency on the development of chronic GVHD have been contradictory.[6,7] All of these questions are critical next steps before clinical application can be attempted. The study by Capitini et al indicates that bringing out the "softer side" to the DC may be an attractive approach in GVHD prevention through indirect control of donor T cells following DLI.

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