Some practical questions remain. Rivaroxaban and apixaban can be used as a single drug approach,
2,3 whereas dabigatran and edoxaban are preceded by 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?11 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 colleagues1 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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The study which is becoming a more prominent the case particularly with chronic GVHD, targeting intracellular signaling via Janus kinase (JAK) and signal transducer and activator of transcription (STAT) pathways. 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, but subsequent investigations demonstrated that both donor and host DCs contribute to GVHD and GVT responses. 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 nicely demonstrates the role of STAT1 in this process. STAT1 is a critical transcriptional regulator of T cell-type pathways and has been shown to directly impact CD4 T-cell responses in GVHD. 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+ SiglecHhi plasmacytoid dendritic cells (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 T3-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+ SiglecHhi 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. 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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Bringing out the DCs' softer side in GVHD

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