turnover in which circulating proteins are constantly subjected to the activity of glycosidases, including sialidases that remove sialic acids.[7] Thus, the longer a protein circulates in plasma, the more hyposialylated it will become. In the case of VWF, this would mean that hyposialylated VWF becomes a target for MGL, contributing to the removal of aged VWF from the circulation (see figure). As such, MGL would be different from other macrophage receptors, like LRP1 (known to interact with VWF in a shear stress–dependent manner) and scavenger-receptor AI (recently reported to contribute to basal VWF clearance).[8,9] The data presented by Ward et al further indicate that MGL would have a larger contribution to the clearance of hyposialylated VWF as compared with the AMR.

A final point of interest relates to the increased clearance of VWF that has been observed in VWD-type 1. Recent studies showed that specific mutations may increase the binding of such VWF mutants to LRP1 and/or scavenger-receptor AI.[9,10] In addition, another study also showed that many VWD-type 1 mutations are associated with reduced sialylation of *O*-linked glycan structures.[5] In light of the report by Ward et al, it now seems conceivable that the increased clearance observed in VWD-type 1 patients can originate from premature binding of these mutants to MGL, due to hyposialylation of the *O*-linked glycan structures (see figure fast lane). In this regard, it would be of interest to investigate whether polymorphisms in the gene encoding MGL are associated with modified VWF levels, particularly in VWD-type 1 patients. Another relevant avenue to explore would be the role of MGL in the clearance of FVIII. Is MGL-mediated clearance limited to VWF, or does it also include the VWF/FVIII complex? And if so, would making VWF resistant to desialylation improve its half-life and that of FVIII? Upon further studies on these matters, it is without doubt that MGL is another player in the complicated pathway of VWF clearance.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

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TRANSPLANTATION

Comment on Fox et al, page 917

HSCT for PID: not just for children

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In this issue of *Blood*, Fox et al summarize their experience with allogeneic bone marrow transplantation for adults with a variety of primary immunodeficiencies, describing excellent outcomes with reduced-intensity conditioning.[1]

The number of adults diagnosed with primary immunodeficiencies (PIDs) continues to increase.[2] This is likely due to a variety of factors, including improved supportive care of those without definitive treatment in childhood, recognition of milder clinical phenotypes, and marked progress in our ability to identify genetic defects. Although diagnostic methods have greatly improved, treatment considerations have been slow to follow. Most of these diseases are not typical adult indications for allogeneic transplantation. Long-term natural history is lacking for many newly identified disorders (though life expectancy is diminished for those diagnosed early in life) such as chronic granulomatous disease (CGD).[3] Moreover, most adult patients with PIDs have substantial comorbidities,[4] as defined by the hematopoietic cell transplantation–comorbidity index (HCT-CI). These patients are therefore considered to be at high risk for transplant-related mortality, though there are few data specific to this population to corroborate the presumption.

Although there is a tremendous amount of new data showing the success of transplantation in pediatric-onset PIDs, adult reports are scarce. One of the first reports of a significant number of adults with PIDs undergoing transplantation was for patients affected with CGD.[5] It included 14 patients older than 17 years, showing excellent survival and very low rates of graft-versus-host disease and graft failure. Similar outcomes have been obtained by other teams treating adult CGD.[6] However, a summary on patients with severe complications attributed to common variable immunodeficiency undergoing transplantation[7] showed very poor outcomes, mostly due to transplant-associated mortality.

With 29 adult subjects and over 10 diseases represented, the cohort described

by Fox et al is the biggest to date. Despite its heterogeneity, survival outcomes are impressively good, with resolution of most clinical indicators for transplant despite instances of mixed chimerism. Interestingly, the authors note that HCT-CI scores did not correlate with patient outcomes. The previously summarized reports[4,5] share this conclusion. Although HCT-CI has been validated in patients with hematological malignancies and in pediatric populations, it has not been evaluated in patients with PIDs.

The results of this article argue that allogeneic bone marrow transplantation can be safely performed, with good results, in young adult patients with PIDs and that the presence of multiple comorbidities should not deter from providing definitive treatment. It remains to be determined whether all PIDs will be as responsive to transplant, as well as what level of donor chimerism will be required for full resolution, but this is a notable first step in opening the door for further studies.

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