Other possibilities may be pertinent. A previously undetected inhibitor, for example, from childhood, during long periods with intermittent or less frequent FVIII treatment (exposure), could be first recognized when a 60+ year-old requires high-intensity FVIII treatment for surgery or severe bleeding, resulting in an anemnestic response to FVIII, thereby uncovering a new inhibitor antibody. This would seem unlikely as most severe hemophilia patients would be unlikely to go untreated, although adult patients often have fewer bleeds and reduce factor use as they age, potentially allowing for relapse of an old inhibitor after resumption of heavy treatment, such as for a bleed or surgery. In that regard, factor treatment records, with dates and intensity of FVIII exposure, will be indispensable in determining if late, high-intensity exposure during danger is an important risk in late age inhibitor detection.

It is also possible that inhibitor formation in the elderly could accompany a switch to a new generation FVIII product that the immune system might recognize as foreign, triggering immune activation. After a lifetime of multiple product exposures and negative inhibitor tests, and in whom inhibitor formation would be unanticipated, this seems unlikely. Yet, it is not known whether a transient inhibitor could accompany a switch to a new product, or, under danger and immune stimulation, might persist. Unless regular inhibitor monitoring is conducted from birth, with uniform assessment no less than 48 hours off treatment to avoid inhibitor neutralization, and is performed each time a new product is introduced, it remains difficult to assess the contribution of immune response to new products in the aging adult with hemophilia to new inhibitor formation. We look forward to future analyses to illuminate the intriguing findings of Hay et al.

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● ● ● TRANSPLANTATION

Comment on Socié et al, page 6375

T-cell depletion in GVHD: less is more?

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A critical hurdle in the successful clinical application of hematopoietic stem cell transplantation (HSCT) is graft-versus-host disease (GVHD). Socié and colleagues report that in a randomized trial of unrelated donor HSCT, adding a polyclonal anti–T lymphocyte globulin (ATG-Fresenius) to conventional GVHD prophylaxis before stem cell infusion after myeloablative conditioning results in a reduction of both acute and chronic GVHD without compromising antileukemia activity.[1]

Acute GVHD is a clinical syndrome caused by T cell–mediated recognition of minor histocompatibility antigens followed by organ-specific vascular adhesion, migration, proliferation, cytokine release, and direct cell-mediated attack on normal tissues. Chronic GVHD is more complex, incorporating both conventional T-cell effector functions, as well as humoral and antigen-presenting effects of B cells. GVHD can be modulated by interfering with T-cell activation and proliferation using calcineurin inhibitors (cyclosporine, tacrolimus), mTOR inhibitors (sirolimus), and antiproliferative agents (methotrexate, cyclophosphamide, or mycophenolate). Alternatively, donor T cells can be eliminated in toto or in part from the stem cell product using monoclonal antibodies or physical techniques. Despite excellent control of acute GVHD with conventional immunosuppressants, 50% to 70% of patients develop chronic GVHD. Extensive chronic GVHD is associated with significant morbidity and mortality—a problem that is increasingly relevant as this complication becomes more prevalent. Higher rates of chronic GVHD result from improvements in HSCT technology allowing the use of older donors to transplant older patients, use of peripheral blood as a stem cell source, use of more alternative donors because relatively few patients have the luxury of a matched sibling donor, and improvements in supportive care resulting in less nonrelapse mortality. More patients are alive in the late time periods when chronic GVHD occurs. Understanding the relative advantages of different strategies for GVHD prophylaxis is made more difficult by the complex interactions between donor type (related vs unrelated), degree of match, stem cell source (peripheral blood vs marrow vs cord blood), disease stage, differing susceptibility of specific diseases to graft-versus-leukemia or lymphoma (GVL), polymorphous effects of different immunosuppressants, and the intensity of the conditioning regimen.

It is important to recognize that the T cells that mediate GVHD are behaving normally in context; that is, they identify antigens to which they are not tolerant and generate an immune response that is essentially the same as if the recognized antigen were viral. If the immune response is completely abrogated, the risk of infection must increase proportionately. Moreover, because the GVL effect functions by the same mechanism, complete elimination of GVHD also risks increasing the relapserate. Thus, a balance must be established to allow enough immunologic function to provide GVL and to control infection until the immune system has a chance to reconstitute. While in some situations ex vivo T-cell depletion can be very effective, the complete elimination of T cells has generally not improved survival. For instance, a recent trial conducted by the Blood and Marrow Transplantation Clinical Trial Network showed that in first remission AML, there was no disadvantage to using a CD34 selection strategy in myeloablative HSCT with regard to relapse or infection, and there was the expected reduction in both

acute and chronic GVHD; however, survival was not improved compared with a historical cohort.[2] Moreover, the failure to improve survival in the small number of randomized trials of T-cell depletion has limited interest in this technology.[3]

An alternative to ex vivo T-cell depletion is in vivo T-cell depletion using monoclonal antibodies (eg, alemtuzumab) or heteroantisera. There are 3 commercial sources of anti–T cell heteroantisera. ATG-Fresenius is made by immunizing rabbits to the Jurkat cell line, while Thymoglobulin (Genzyme) is made by immunizing rabbits to human thymocytes. Atgam (Pfizer) also uses human thymocytes, but in contrast to the other 2 products, it is made in horses. These preparations differ in the degree of lymphocyte depletion, the duration of effect, and the target antigens. Thus, they are far from interchangeable, and it is clear that in the absence of comparative trials we cannot expect outcomes to be similar. For instance, in randomized studies by Bacigalupo and colleagues Thymoglobulin also reduced the rate of acute and chronic GVHD, but there was an increased infection rate and no improvement in therapy-related mortality.[4] Similarly, an observational study of 1676 patients treated with alemtuzumab (Campath), Thymoglobulin, Atgam or no antibody before reduced intensity HSCT from sibling or unrelated donors showed an agent-specific reduction in acute and chronic GVHD. However, in this analysis the concomitant increase in relapse resulted in lower disease-free and overall survivals when antibodies were used.[5]

The data presented by Socié and colleagues using ATG-Fresenius are encouraging, but cannot be interpreted as definitive. Properly powered, confirmatory, randomized studies, while expensive and time-consuming, are critical in transplantation, where selection bias can strongly influence outcome. It is particularly important to understand that these data apply to myeloablative transplantation from unrelated donors, with ATG-Fresenius only. It is by no means clear that the data can be generalized to related donor transplantation, reduced intensity procedures, or other in vivo T-cell depletion products without subsequent studies. However, these data do suggest that control of chronic GVHD without a proportionate increase in infection and relapse is possible. It is fair to say that if there is no reduction in survival, control of chronic GVHD is an important goal. The morbidity of chronic GVHD has a substantial effect on the quality of life of long-term survivors. If we are to improve survival, future studies must determine whether relapse and infection rates can be reduced. Strategies such as tumor vaccines,[6] newer generation viral vaccines, selective infusions of memory T cells,[7] and specific cytotoxic lymphocytes[8] are in development and show promising early results. Well-conducted large studies such as this one are critical if we are to continue to move the field forward.

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