Furthermore, investigation of transgenic β2GPI-null mice reported evidence for impaired in vitro thrombin generation but the absence of any obvious phenotypes other than the interesting finding of the births of fewer than expected homozygous null mice to heterozygous parents.3

Last year, Agar et al reported that plasma β2GPI has a circular conformation that is maintained by affinity of its carboxyterminal domain V for amniontermal domain I and that the protein opens into a fish hook conformation when it becomes bound to phospholipid via its hydrophobic “barb” on domain V.4 They showed that this alteration exposes an epitope on domain I that is cryptic in the circu-

An interesting aspect of their results was the finding that β2GPI binds to LPS at sites other than the lipid A core, where the molecule’s endotoxin activity resides. In addition, β2GPI does not neutralize the endotoxin activity of LPS directly. Rather, the β2GPI-LPS complexes are bound and endocytosed via low density lipoprotein-related protein receptors on cell surfaces—monocyte-macrophages in their experiments—but they propose that vascular endothelial cells can have a similar function. They also show that this uptake occurs via affinity of receptors for the open, but not the circular, conformation of β2GPI.

Agar and colleagues provide convincing evidence for the biologic significance of this β2GPI-LPS affinity in humans.1 Under a protocol approved by their institutional scientific and ethics committees, healthy human volunteers were intravenously infused with low doses of LPS. A rapid decline of plasma β2GPI levels was observed. In addition, febrile responses and serum levels of inflammatory cytokines correlated inversely with the subjects’ baseline β2GPI levels. Also, plasma β2GPI levels of hospital patients with Gram-negative sepsis were reduced during the acute event and increased after recovery.

In addition to shedding new light on the bio-

REFERENCES


4. Agar C, van Os GM, Morgelin M, et al. Beta2-Glycoprotein I can exist in two conformations: implications for our understanding of the antiphospholipid syn-


To “close the circle,” these results regarding LPS also return our attention to the APS disease process because clinical studies indicate that infections may be one of the triggers for APS. This is particularly true for a severe form of the disorder, catastrophic APS, that is marked by disseminated small vessel occlusions and multorgan failure. It is possible, as Agar and colleagues suggest, that in susceptible patients, the binding of β2GPI to Gram-negative bacteria leads to a conformational change in β2GPI with exposure of former cryptic epitopes that in turn lead to the immunologic response and the devastating thromboembolic sequelae.1 This article by Agar et al represents a significant advance in the biology of β2GPI and in the elucidation of innate host defenses against microorganisms. We can hope for even more solid confirmation of the hypothesis with addi-
tional clinical studies of the β2GPI-deficient patients to learn whether they might be more susceptible to sepsis and when investigators return and to the β2GPI-null animal model to determine whether these mice might have an altered response to LPS challenge.

Conflict-of-interest disclosure: The author declares no competing financial interests.

Sergio Giralt MEMORIAL SLOAN-KETTERING CANCER CENTER

It has been more than 50 years since Professor George Mathe explored the use of non-specific immunotherapy to treat secondary disease after allogeneic transplantation.1 Weiden et al then began exploring the use of antithymocyte globulin (ATG) as prophylaxis of acute GVHD.2 Bacigalupo et al have reported a series of randomized trials in which 109 patients with hematologic malignancies undergoing myeloablative bone marrow
transplantations from unrelated donors were randomized to receive ATG or not. In these studies, although GVHD risks were reduced with ATG, survival rates were comparable in the ATG and non-ATG groups for patients who received total body irradiation (56% vs 59%) with a trend toward improved survival in patients not receiving total body irradiation (33% vs 18%). In a more recent trial, Finke et al reported the results of a randomized trial comparing in vivo T-cell depletion with a different ATG preparation (Fresenius) in 202 patients with hematologic malignancies. In this study, acute and chronic GVHD was lower with ATG; however, no significant differences in overall survival rates between the groups were seen. The above studies would suggest that in the setting of myeloablative unrelated donor transplantation, ATG therapy is a therapeutic element that can reduce the risk of GVHD without negatively affecting and potentially improving transplantation outcomes.

In this issue of Blood, Soiffer et al examined the outcomes of reduced intensity conditioning (RIC) according to the use of in vivo T-cell depletion using either antithymocyte globulin (ATG) or alemtuzumab. A total of 1676 patients with hematologic malignancies were identified and analyzed within the Center for International Blood and Marrow Transplant Research (CIBMTR). Half of the patients received allografts from a human leukocyte Ag-matched sibling and half from an unrelated donor. ATG was given before transplantation to 584 patients; 213 received alemtuzumab and 879 received a T-replete graft. Grade 2-4 acute GVHD was 19% with alemtuzumab compared with 38% and 40% for ATG and unmanipulated grafts, respectively. Chronic GVHD was also lower with alemtuzumab and ATG compared with unmanipulated grafts (24% vs 40% and 52%). Because of increased rates of relapse with ATG and alemtuzumab, disease-free survival was lower with alemtuzumab and ATG compared with unmanipulated grafts (30%, 25%, and 39%, respectively with corresponding survival probabilities of 50%, 38%, and 46%, respectively).

With all the caveats and limitations of a retrospective analysis, this study should move the transplantation field to reflect on the routine use of ATG in the context of RIC regimens. Although ATG and alemtuzumab have been routinely used in the setting of RIC transplantation, no randomized trials have been performed looking at their impact on transplantation outcomes when less intense conditioning regimens are used. The data from the CIBMTR support the protective effect of alemtuzumab and ATG in regard to acute and chronic GVHD prevention, but in contrast with previous smaller studies that demonstrated either no benefit or a beneficial effect on event-free survival, this analysis suggested worse outcomes for recipients of ATG after RIC. Unfortunately, unless well-designed randomized trials are performed with a less heterogeneous population receiving more homogeneous therapies comparing the impact of ATG, alemtuzumab, and modern ex vivo T-cell depletion methods on transplantation outcomes in the RIC setting, optimizing treatment outcomes will be difficult. In the meantime, it would be reasonable to minimize the use of ATG in the RIC setting to patients at higher risk of developing GVHD (alternative donor or mismatched transplantation) and to those with lower risk of relapse. In regard to alemtuzumab, most of the experience is in the context of lymphoid malignancies, and its use in this setting is appropriate. Finally, the CIBMTR should continue to be commended for being the invaluable resource for the stem cell transplantation community and the patients it serves.

Conflict-of-interest disclosure: The author is on Speakers bureaus for Amgen, Genzyme (maker of a brand of ATG), Novartis, Celgene, and Millennium.

REFERENCES
ATG and RIC: not such a good match?
Sergio Giralt