Acquired Severe Aplastic Anemia: Progress and Perplexity

By E. Donnell Thomas and Rainer Storb

The pathophysiology and treatment of acquired severe aplastic anemia (ASAA) has been the subject of recent reviews. Whether idiopathic or idiosyncratic, ASAA is a “likely-to-be-fatal” disease. However, it has long been recognized that some patients will recover spontaneously, and a few lucky ones may do so with surprisingly rapid restoration of hematopoiesis. The inherent unpredictability of the natural course of this disorder has made evaluation of therapeutic efforts most difficult. In particular, the commonly used agents—steroids and androgens—have never been shown to be of value in a prospective study, and their toxic side effects can contribute to the patient’s problems.

Some insight into the pathogenesis of this disorder was acquired through studies of bone marrow transplantation. In Seattle, three patients with ASAA were infused with syngeneic bone marrow from a normal identical twin, without any preparative regimen. All three patients recovered bone marrow function over the course of the subsequent few weeks. These observations indicated a rather simple pathogenetic mechanism, that is, that ASAA is due to something that damages or destroys the hemopoietic stem cells and that the disorder can be corrected by infusion of normal stem cells. Further, success in these patients indicated that ASAA is not due to a disorder of the microenvironment, lack of a humoral factor, persistence of a toxin, or to an autoimmune disorder.

However, the plot began to thicken when it was recognized that some patients with ASAA did not recover following a simple infusion of syngeneic bone marrow. When conditioned with an immunosuppressive regimen (cyclophosphamide, 50 mg/kg on each of four days), most of these patients did recover following a second infusion of syngeneic marrow. The observations of these patients suggested that the ASAA might well be an autoimmune disorder that could be overcome by an intensive immunosuppressive regimen.

Further, the more recent demonstration that marrow engraftment may include the grafting of macrophages, osteoclasts, and the cells that constitute the feeder layer in long-term marrow cultures in vitro revived the possibility that marrow grafting might actually restore the microenvironment in vivo.

Additional confounding clinical data began with the observation by Mathé et al that some patients with ASAA could recover following the administration of antilymphocyte globulin (ALG). Initially, there was skepticism about these observations, which might have been explained by the unpredictable natural history of the disease. However, Speck and colleagues produced convincing clinical data that ALG therapy may result in recovery of an appreciable fraction of patients with ASAA, with 12 of 29 patients showing sustained hematologic improvement.

A subsequent study in Seattle showed that the administration of Upjohn (Kalamazoo, Mich) antithymocyte globulin (ATG) results in long-term survival of some patients (six of 19 responders). A randomized study was carried out at UCLA that demonstrated that 11 of 21 patients given Upjohn ATG responded as compared to 0 of 21 control patients during the three-month observation period. A cooperative randomized study demonstrated an improved recovery rate following administration of Swiss ALG (76% survival at two years compared to 31% for the controls). A recent unexplained increment in the survival of patients with ASAA led to the hypothesis that ASAA might be a disorder that results from something that damages or destroys the hemopoietic stem cells, and that the disorder can be corrected by infusion of normal stem cells. Further, success in these patients indicated that ASAA is not due to a disorder of the microenvironment, lack of a humoral factor, persistence of a toxin, or to an autoimmune disorder.

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trolled study in Seattle showed a 66% long-term survival for 53 patients given Upjohn ATG. Although the apparent response of some patients treated with ALG or ATG may lend credence to the “autoimmune” etiology of ASAA, it should be emphasized that the mechanism of the effect is entirely unknown. Unfortunately, many patients who “respond” to ATG or ALG do not regain normal counts, and four of the responders in Seattle have reverted to ASAA more than one year after treatment. The need for further randomized studies is evident because of the unpredictable course of the disease and because of the difficulty in reproducing the apparently effective batches of ALG or ATG. However, it is difficult to justify the “control” arm of these studies. Such control patients should receive the same intensive inpatient care usually provided to patients undergoing ATG therapy or bone marrow transplantation, but third-party payers cannot be expected to bear the cost, and granting agencies have shied away from funding these very expensive clinical studies.

What is needed are reliable in vitro tests that would predict those patients who would respond to ATG therapy. Ascensao et al and Kagan et al described a patient with ASAA whose lymphocytes inhibited in vitro colony formation by normal bone marrow. This inhibition could be overcome by the addition of ATG, suggesting that the use of this immunosuppressive agent would be a rational approach to the therapy of ASAA. However, the initial enthusiasm was soon tempered by the realization that multiply transfused patients become sensitized to HLA antigens and that their lymphocytes, in vitro, then inhibit colony formation by marrow obtained from unrelated individuals. Studies of lymphocytes from untransfused patients and of lymphocytes from transfused patients using marrow from HLA-identical siblings showed that only a small fraction of patients with ASAA have some evidence suggesting an “autoimmune” mechanism against erythroid burst-forming units (BFU-E) or colony-forming units (CFU-C). The report by Torok-Storb et al describes a modest statistical correlation between in vitro tests and the clinical response to ATG therapy. As yet, the correlation is not strong enough to form a basis for clinical decisions and the two weeks required for the BFU-E assay may be too long for clinical usefulness. Improved in vitro tests are under investigation in several laboratories.

With regard to the pathogenesis of ASAA, an attractive hypothesis, which explains at least some of the confusing clinical and laboratory observations concerning ASAA, is as follows: A foreign agent, such as a virus or a drug, enters the body and attaches itself to the hemopoietic stem cell. The foreign substance then serves as a “hapten,” which initiates an autoimmune reaction so that the patient’s lymphocytes destroy most or all of the stem cells. Subsequently, the “autoimmune” process may continue or may terminate when there is no further antigenic stimulus. Spontaneous recovery in a small fraction of patients may take place with termination of the immune process and regeneration of the patient’s stem cell compartment, or the patient can recover following simple infusion of syngeneic marrow. If the immune process continues, immunosuppressive therapy in the form of ATG may be effective, or immunosuppressive therapy followed by marrow transplantation may be required. Documentation of such a hypothesis is made difficult by two major factors: First, presently available in vitro tests may be too insensitive to measure very low levels of autoimmune reactivity. Second, and perhaps most important, the active pathogenic mechanism may be of relatively brief duration and may well be over by the time the symptoms of pancytopenia make the patient aware that something is wrong. It is very difficult to study something that is no longer there.

Allogeneic marrow grafting after high-dose immunosuppression, usually with cyclophosphamide, has almost always involved an HLA-identical sibling as a donor. The early experience with patients who had failed “conventional” therapy resulted in a 45% cure rate. Failures were due principally to the complications of advanced illness, to graft rejection, or to complications of acute graft-versus-host disease (GVHD). With transplantation earlier in the course of the disease and with improved methods of preventing graft rejection, the long-term cure rate has improved to 70% to 80%. The longest survivors have now been followed for 13 years. “Cure” in this context means long-term survival with hematologic normalcy, but a small fraction, approximately 10%, of the long-term survivors have chronic GVHD that is not responsive to therapy. A recent report by Speck et al indicates a better survival (70%) in patients treated with ALG than in those treated with an HLA-identical sibling marrow graft (47%), but the difference is largely due to the relatively poor results in the marrow-grafted patients. Other marrow transplant teams are reporting long-term survivals of 62% to 83%.

It is important to keep in mind the advantages and disadvantages when comparing the results of ATG or marrow transplantation. Advantages of marrow transplantation are a high fraction of long-term survivors, on the order of 70% to 80%, and complete hemopoietic recovery with cure of the disease. Disadvantages are complications from chronic GVHD seen in some long-term survivors, the potential for late sequelae from the conditioning regimen (including malignant tumor
when the regimen has involved irradiation), and finally, the high initial cost of the transplant. Advantages of ATG therapy are fewer initial side effects and a lesser initial cost of the procedure. Disadvantages are a lower overall survival (on the order of 40% to 60%), frequent slow and incomplete hemopoietic recovery necessitating prolonged supportive care, and the possibility of later recurrences of ASAA. As many patients given ATG also receive androgens, there may be long-term side effects from androgen therapy.

In view of all the confusion surrounding pathogenesis and treatment, what should the practicing hematologist do when encountering a newly diagnosed patient with ASAA? Perhaps the most rational plan, based on patient age and donor availability, is as follows: If the patient has a normal identical twin, marrow transplantation should be carried out promptly, regardless of age. If recovery is not underway within three to four weeks, a second syngeneic transplant should be carried out following an immunosuppressive preparative regimen. If the patient is a potential candidate for an allogeneic bone marrow transplant, transfusion of blood products should be avoided if at all possible, and, in particular, transfusion of blood products from family members should not be given. For patients under the age of 40, marrow transplantation from an HLA-identical sibling is the treatment of choice. Thus, HLA typing of the family should be carried out promptly, and if the patient has an HLA-identical sibling, marrow transplantation should be performed as expeditiously as possible, preferably before transfusions have to be given. If the patient does not have an HLA-identical sibling, ATG therapy should be administered. If the patient does not respond to ATG therapy, then a search of the extended family or of the available panels of unrelated volunteer marrow donors may disclose a suitable marrow donor. For patients between the ages of 40 and 50, the results of marrow transplantation are not as good, primarily because of increasing problems with GVHD. The data available at the present time do not answer the question of which is the better treatment, marrow transplantation or ATG, and so the subject remains controversial. Current studies of in vitro treatment of donor marrow with monoclonal antibodies and complement or with immuno-toxins point the way to amelioration of the GVHD problems, but these studies are still experimental. Also, some patients who have been conditioned with cyclophosphamide and who reject their marrow grafts and return to the original state with ASAA may subsequently regenerate their own stem cell compartments and recover, or they may still be candidates for other therapeutic attempts. An alternative approach is to treat these patients with ATG and to reserve marrow transplantation for those patients who do not respond, recognizing the grave risk of death during the waiting period. Most marrow transplant teams do not perform transplants for patients over the age of 50. Thus, these patients should be treated with ATG.

It is evident that much progress has been made in the understanding and treatment of ASAA, but many problems remain. Fortunately, ASAA is not a very common disease. It seems prudent, therefore, to refer these patients as quickly as possible to one of the centers actively engaged in research on aplastic anemia. Perhaps, in another decade, someone can write a truly informative and definitive article on the subject of acquired severe aplastic anemia.

REFERENCES

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