EDITORIALS

A New Standard Immunosuppression Regimen in Severe Aplastic Anemia

Phillip Scheinberg, M.D., Ph.D.

Organ failure is a major cause of illness and death across medical conditions. In particular, primary failure of the bone marrow can result in various cytopenias. Aplastic anemia is the prototype of the bone marrow failure syndromes that are characterized by hypocellular marrow and pancytopenia, and severe aplastic anemia is fatal if untreated.[1]

Since the 1980s, clinical and experimental data have indicated an autoimmune cause in the majority of idiopathic cases of aplastic anemia.[1] In a minority of cases, genetic defects that are associated with inherited forms of aplastic anemia usually manifest with characteristic physical signs in childhood.[2] In immune aplastic anemia, activated T cells produce proinflammatory cytokines and proteins that are associated with a lack of immune regulation and that recognize and eliminate hematopoietic stem cells.[1,3]

The backbone of therapy in patients with severe aplastic anemia is antithymocyte globulin (ATG), which is composed of serum containing polyclonal xenogeneic antibodies obtained from animals that have been sensitized to human T cells. ATG is lymphocytotoxic and causes lymphodepletion in humans.[4] ATG plus cyclosporine became standard immunosuppressive therapy in 1991 after a randomized trial showed that this combination was superior to ATG alone.[5] The next 20 years were disappointing, given that several alternative regimens did not perform better than horse ATG plus cyclosporine, and the enthusiasm to investigate new immunosuppressive therapies was dampened.[3,4]

The results of a trial sponsored by the National Institutes of Health (NIH), published in the *Journal* in 2012,[6] showed that eltrombopag, a thrombopoietin-receptor agonist that was developed for the treatment of patients with chronic immune thrombocytopenia, was effective in 44% of patients with severe aplastic anemia who had not had a response to initial immunosuppression. Eltrombopag was hypothesized to stimulate the thrombopoietin receptors expressed in hematopoietic stem cells, contributing to an increase in the number of hematopoietic stem cells and progenitor cells.[7] In a subsequent single-group trial conducted at the NIH, responses among patients who received eltrombopag combined with front-line immunosuppressive therapy (horse ATG plus cyclosporine) were compared with those among patients in a historical cohort. Higher overall and complete response rates were observed among patients who received eltrombopag plus immunosuppressive therapy, especially when all three drugs were administered simultaneously on day 1 and cyclosporine and eltrombopag were continued for 6 months.[8]

In 2014, the European Society for Blood and Marrow Transplantation spearheaded RACE (Randomized, Multicenter Trial Comparing Horse ATG plus Cyclosporine with or without Eltrombopag as First-Line), an investigator-led, open-label, randomized superiority trial that compared standard horse ATG plus cyclosporine (Group A, 101 patients) with this immunosuppressive therapy plus eltrombopag (Group B, 96 patients). In this issue of the *Journal*, Peffault de Latour and colleagues[9] report the results of this trial involving 197 patients (≥15 years of age) who received treatment during the period from 2015 through 2019 at 24 European centers. El-

trombopag was initiated on day 14 at a dose of 150 mg per day, and treatment was continued through 6 months, or through 3 months in patients who had a complete response at 3 months.

The experimental therapy was superior to the standard therapy with respect to the primary end point, a hematologic complete response at 3 months (10% in Group A and 22% in Group B). At 6 months, 20% and 32%, respectively, had a complete response. The overall response was 31% in Group A and 59% in Group B at 3 months and 41% and 68%, respectively, at 6 months. Responses were more rapid in Group B than in Group A (3.0 months vs. 8.8 months). At 2 years, event-free survival was 34% in Group A and 46% in Group B. Similar benefits were observed when the NIH criteria for partial response were applied to the RACE data set.

At all landmark time points, the combination of horse ATG–cyclosporine plus eltrombopag was superior to standard therapy and produced a higher and more rapid complete and overall hematologic response, which translated into earlier transfusion independence, fewer complications from pancytopenia, and better quality of life. Among patients who had a response, these benefits were even more pronounced.

In the current trial, the smaller pool of patients who did not have a response to initial immunosuppression in Group B than in Group A is of great positive consequence, given that refractory severe aplastic anemia is a complex clinical scenario and often leads to death (usually from infection) if the persistent severe pancytopenia is not reversed. Hematopoietic stem-cell transplantation, which is often considered for these patients, is associated with increased risk, especially among adults and older patients. In addition, the use of less effective treatments for severe aplastic anemia or supportive care measures is unlikely to change the natural history of the disease.

Peffault de Latour and colleagues report on an exploratory analysis of somatic mutations by means of next-generation sequencing. This analysis is noteworthy because the presence of clones at baseline, their expansion, and the appearance of new clones in both groups were not predictive of a lack of response or other dire outcomes. This observation is important given a theoretical concern that eltrombopag could promote expansion of mutant clones, although this expansion has not been confirmed.[10] Thus, the data from this analysis should discourage physicians from overinterpreting the presence of mutant clones at diagnosis or after therapy in isolation, and the detection of these clones does not warrant high-risk procedures such as hematopoietic stem-cell transplantation.

An important unanswered question is whether the results of the current trial could have been better if, instead of starting eltrombopag on day 14, it was initiated on day 1 with immunosuppression. The latter regimen was associated with the best outcomes in the NIH trial.[8]

The European investigators conducted an important trial that supports horse ATG–cyclosporine plus eltrombopag as the new standard in severe aplastic anemia. Longer-term follow-up is under way to further elucidate, with direct internal control, events of relapse, high-risk clonal evolution, and death, which thus far have not differed between the groups in this trial. It is hoped that it will not take another 30 years before the next important advancement occurs in the medical management of severe aplastic anemia.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

From the Division of Hematology, Hospital A Beneficência Portuguesa, São Paulo, Brazil.

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