Recent Advances and Long-Term Results of Medical Treatment of Acquired Aplastic Anemia: Are Patients Cured?

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KEYWORDS

• Aplastic anemia • Eltrombopag • Immunosuppressive therapy
• Antithymocyte globulin • Cyclosporine • Bone marrow failure

KEY POINTS

- Horse antithymocyte globulin plus cyclosporine remains the current standard immunosuppressive regimen despite many efforts to improve beyond it.
- The thrombopoietin receptor agonist eltrombopag has shown significant activity as a single agent in treatment of refractory patients with hematologic response rates of 40% to 50%.
- When eltrombopag was combined with horse antithymocyte globulin plus cyclosporine in first line (3-drug regimen), overall and complete hematologic response rates were higher than what is observed with immunosuppression alone.
- Late events of relapse and clonal evolution thus far with the 3-drug regimen are in accordance with a vast long-term experience with horse antithymocyte globulin plus cyclosporine alone.
- Longer follow-up will be important to determine durability of response and possible cure rates following the novel regimen, which combines standard immunosuppression with eltrombopag.

INTRODUCTION

For most of the twentieth century, aplastic anemia (AA) was perceived as a disease caused by certain environmental exposures, chemicals (benzene), drugs (chloramphenicol, dipyrone), and/or toxins (pesticides).[1] Several early reports associated the onset of AA to these exposures, but many lacked strong scientific and statistical rigor. The first suggestion that the immune system might be implicated in AA pathogenesis

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derived from experimental models by Mole in 1964 wherein lymph node cells from C3H/H mice were infused into sublethally irradiated CBA/H mice, which died a few weeks later from pancytopenia.[2] This phenotype resembled AA and suggested that a similar phenomenon could be contributing in humans.

An immune pathogenesis in humans was later inferred in the 1970s when recovery of hematopoiesis was observed in patients who failed to engraft after hematopoietic stem cell transplantation (HSCT).[3] Therapies used in the conditioning, such as antithymocyte globulin (ATG), were credited for the recovery in bone marrow function. Several clinical protocols conducted in Europe, Asia, and the United States in the 1980s and 1990s confirmed the effectiveness of ATG as therapy in severe aplastic anemia (SAA). The addition of cyclosporine (CsA) further increased the hematologic response rate from 40% to 50% (with ATG alone) to 60% to 70% (with the combination of ATG plus CsA). The regimen most studied was based on horse antithymocyte globulin (h-ATG), which has been shown to be the most effective formulation.[4] This combined immunosuppressive therapy (IST) changed the natural history of SAA.

PATHOGENESIS

Immune System

Hematopoiesis is severely reduced in AA, as evidenced by bone marrow specimens, $CD34^+$ cell enumeration, imaging techniques (MRI), or progenitor colony assays. Clinical and laboratory studies suggest that most acquired AA is secondary to immunologically mediated destruction of hematopoietic cells by cytotoxic lymphocytes and their cytokine products, especially interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α).

Recognition of hematopoietic stem cells (HSCs) by immune effector cells has been considered to be responsible for the pathogenesis of AA.[5,6] T-helper 1 (Th1)- and Th17-associated inflammatory proteins such as IFN-γ and TNF-α have been shown to be increased and contribute to the destruction of early progenitor cells via a Fas-dependent pathway.[7–12] Skewing of the $CD8^+$ T-cell repertoire in SAA supports an antigen-driven expansion of a few oligoclones, which tends to become more normalized (Gaussian) after successful IST.[13] The target antigens however remain elusive. A reduction of regulatory T cells (Treg) and an increase in Th17-related T cells resulting in a high Th17/Treg ratio at diagnosis tends to normalize in patients responding to IST.[8,10] The genetic loss of one HLA haplotype on chromosome 6p suggests further pressure of the immune system and may provide an escape mechanism of $CD8^+$-mediated HSC destruction and clonal evolution, as seen in certain cases of leukemia relapse.[14,15] Several of these observations have been confirmed in murine models corroborating the important contribution of an aberrant immune system in AA pathogenesis.[1,16,17]

Genetics

Nearly 2 decades ago, shortening of leukocyte telomere lengths (TL) were described in patients with apparent acquired AA.[18,19] This biologic characteristic is recognized in children with the constitutional form of bone marrow failure, dyskeratosis congenita; short TL had not been described in adults without classical physical stigmata of an inherited disorder. Sequencing of genes related to the telomerase complex (*TERT*, *TERC*, *DKC1*, *RTEL1*, *TINF2*) were found to be mutated, inferring that in some cases a genetic defect associated with constitutional forms of AA could also be contributing to “acquired” AA pathogenesis.[20–23] Initially, TERC and TERT