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PLATELETS AND THROMBOPOIESIS

Comment on Cuker et al, page 1855

A conceptual framework for managing iTTP

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In this issue of *Blood*, Cuker et al propose revised outcome definitions for immune thrombotic thrombocytopenic purpura (iTTP) that incorporate mechanistic insights that will better inform treatment choices of existing and novel therapeutics.[1]

iTTP is a rare life-threatening autoimmune disease caused by antibodies targeting ADAMTS13, a plasma metalloprotease that cleaves ultralarge von Willebrand factor (VWF) multimers. Severely decreased plasma ADAMTS13 levels (<10% normal) allow ultralarge VWF multimers to circulate and bind platelets in areas of turbulent blood flow, leading to thrombosis in disseminated small blood vessels and widespread tissue ischemia. The classical signs of fever thrombocytopenia, microangiopathic hemolytic anemia, and ischemic organ damage (eg, renal, cerebral, and cardiac) ensue. Earlier empiric therapies (eg, therapeutic plasma exchange [TPE] with or without steroids, splenectomy, or vincristine) induced clinical response (defined as a platelet count of >150 × 10^9/L and lactate dehydrogenase <1.5 times the upper limit of normal) and prevented the majority of immediate fatalities. However, clinical refractoriness, exacerbations, and relapse remained common, resulting in significant late morbidity and mortality. The discovery of the role of ADAMTS13 protease and the clinical availability of assays for ADAMTS13 activity and antibodies improved diagnostic accuracy and therapeutic decisions. This mechanism also provided a logical therapeutic target. The anti-VWF nanoantibody caplacizumab has been approved by the US Food and Drug Administration (FDA) after evaluation in rigorous, appropriately powered multicenter clinical trials.[2,3] Other similar anti-VWF agents and recombinant ADAMTS13 are in development.[4,5]

Overview of definitions and therapeutic options

Clinical remission	Biological (ADAMTS13) remission
Definition Clinical response • Platelet count ≥150 × 10^9/L • LDH <1.5 times upper limit of normal • No new or progressive ischemic organ injury with either (1) no temporizing agents for 30 days, or (2) ADAMTS13 remission	Partial: ADAMTS13 activity ≥20% to <LLN Complete: ADAMTS13 activity ≥LLN
Therapeutics Temporizing agents for clinical response • Plasma exchange • Caplacizumab • Other anti-VWF therapeutics* • Recombinant ADAMTS13*	Disease-modifying agents for biological remission • Plasma exchange • Steroids • Rituximab • Other immunomodulating agents

LDH, lactate dehydrogenase; LLN, lower limit of normal.

*In development.

Using data from the TITAN and HERCULES studies of caplacizumab,[2,3] an international working group (IWG) that includes many investigators from the pivotal trials developed revised consensus outcome definitions that incorporates ADAMTS13 activity and anti-VWF therapy (see table). The group recommends updates to the 2017 consensus definitions of clinical response, remission, exacerbation, and relapse. The changes highlight the differences between clinical responses induced by temporizing agents, such as TPE and caplacizumab, and disease-modifying therapies that include steroids, TPE, and immunomodulatory agents. Temporizing agents prevent platelet consumption and ongoing microthrombosis to rapidly restore the platelet count to effect clinical response and prevent acute morbidity, but patients are likely to relapse. Disease-modulating therapies address the underlying autoimmune disorder and lead to biological (ADAMTS13) remission, allowing long-term clinical remission. TPE is both temporizing, as it restores plasma ADAMTS13 levels and removes abnormal VWF multimers, and disease modulating, as it removes ADAMTS13 antibodies.

Standardized definitions of response inform clinical decisions when choosing appropriate therapies, and future therapeutic options should the patient require them. Initial therapy should aim at both clinical response and biological (ADAMTS13) remission and generally involve the use of TPE and steroids with or without caplacizumab and/or rituximab.[6] Clinical response in the absence of biological remission suggests the patient is at risk of an exacerbation

or relapse and should be monitored carefully or treated with an immunomodulatory agent.

The combination of TPE, immunosuppressives, and anti-VWF therapy in the TITAN and HERCULES studies showed significant improvements in time to clinical remission and overall morbidity.[2,3] It is notable that only 1 TTP-related fatality among 108 patients was reported (after the treatment period) in the test arms of either study, while 5 of 112 patients died in the control arms. Nevertheless, there is still room for improvement, considering the risks of each therapeutic option. TPE is a complex procedure not available at smaller centers and has a high rate of venous access complications, and the use of plasma from multiple donors runs the risk of infectious disease transmission and hypersensitivity reactions. The use of recently FDA-approved pathogen-reduced cryoprecipitate reduced plasma[7] (with reduced ultralarge VWF multimers) or solvent detergent-treated plasma[5] may reduce the risks of plasma exposure. Recombinant ADAMTS13, which is in development, has been proposed to replace TPE,[5] and a case report described the successful use of caplacizumab without TPE.[8] Rituximab is associated with adverse events, including boxed warnings for fatal infusion-related reactions, severe mucocutaneous reactions, hepatitis B reactivation, and progressive multifocal leukoencephalopathy. Its use in TTP is off label. Caplacizumab is associated with a significant increase in mild to moderate bleeding events.[2,3] The addition of rituximab as primary therapy demonstrates a positive cost/benefit ratio,[9] whereas the cost/benefit ratio for caplacizumab was reported as strongly unfavorable in one study.[10] There is a need of safer and more cost-effective therapies and/or treatment regimens.

The definitions put forward by the IWG consensus panel provide a conceptual construct on which to base therapeutic protocols for primary treatment, as well as for the treatment of refractoriness, exacerbations, and relapses. These constitute a major step forward in reshaping our thinking about immune TTP and its treatment. These new definitions have not been prospectively validated. With that caveat, physicians are well served to understand the proposed definitions as they select between the growing number of therapeutic options that may be temporizing, disease modifying, or both.

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

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DOI 10.1182/blood.2021011007

CLINICAL TRIALS AND OBSERVATIONS

Comment on Ribera et al, page 1879

Has MRD graduated from its adolescence in ALL?

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In this issue of *Blood*, Ribera et al[1] demonstrate that in adolescent and young adult (AYA) patients with Philadelphia chromosome–negative acute lymphoblastic leukemia (Ph$^-$ ALL) who present with high-risk features, the depth of response to initial therapy, as measured by measurable residual disease (MRD), is a powerful and clinically relevant predictive tool. The authors show that even high-risk patients who achieve MRD negativity may be able to forego allogeneic hematopoietic transplantation without impairing their chances of long-term survival.

Despite the high probability of obtaining complete remission (CR) in Ph$^-$ ALL, treatment failure as a result of either relapse or toxicity remains a major obstacle. These challenges are even more striking in AYA or older patients with ALL, where the disease is inherently more resistant than in pediatric ALL, and where patients may be less resilient than children to the effects of prolonged intensive treatment.

Traditional tools for risk stratification and assignment of postremission therapy have, for many years, consisted of the classical clinical and laboratory features at initial diagnosis (age, white blood cell count, and cytogenetics) and, more recently, the Ph-like gene expression signature.

Although the recognition that allogeneic hematopoietic cell transplant (alloHCT) may cure a proportion of AYA patients with Ph$^-$ ALL, the precise identification of candidates who should undergo this procedure in first CR remains a conundrum. Clinical trials and meta-analyses derived from patients treated in the 1980s and 1990s suggested that alloHCT reduces