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PLATELETS AND THROMBOPOIESIS

Comment on Kizlik-Masson et al, page 2427

New IDEaS for HIT treatment, anyone?

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In this issue of *Blood*, Kizlik-Masson et al[1] show that a bacterial protease, immunoglobulin G (IgG)–degrading enzyme of *Streptococcus pyogenes* (IdeS), by cleaving heparin-induced thrombocytopenia (HIT) antibodies, can potentially serve as an effective treatment of HIT. HIT is a serious prothrombotic disorder characterized by antibodies to platelet factor 4 (PF4)–polyanion complexes. Despite the recognition of HIT decades ago, outcomes remain concerning. A recent large population-based study of ~100 000 HIT patients showed that HIT still inflicts significant morbidity and mortality.[2] Roughly one-third of HIT patients develop thrombosis, and 1 in 10 patients die during the HIT hospitalization. An additional, somewhat less recognized issue is that of bleeding associated with the use of non–heparin alternative anticoagulants[2-4] so much so that the American Society of Hematology 2018 guidelines for management of heparin-induced thrombocytopenia calls for research on "…development of novel therapeutics that target pathways in the pathogenesis of HIT proximal to coagulation that could be effective in reducing thrombosis without increasing the risk of hemorrhage."[5]

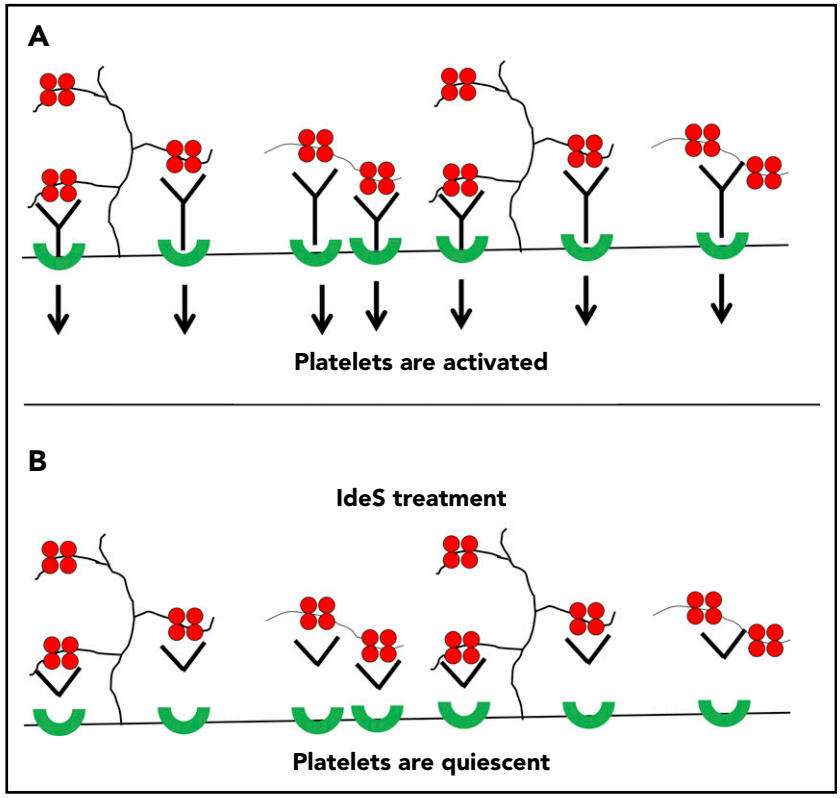
Recent work from our group and others has identified one such drug: IV immunoglobulin G (IVIg), which, by platelet IgG receptor, Fc gamma type 2 receptor A (FcγRIIA) blockade (in addition to other potential mechanisms), antagonizes HIT antibody-mediated platelet activation.[6] Although high doses of IVIg can be very effective in the challenging the setting of severe refractory HIT,[6] there is appropriate concern with routine use of IVIg due to its possible prothrombotic potential. Against this backdrop, Kizlik-Masson et al demonstrate the potential utility of another drug in treating HIT that acts upstream of coagulation. This drug, a cysteine protease called IdeS, identified previously in *S pyogenes*, has the ability to specifically cleave the heavy chain of IgG at the hinge region (see figure).

As expected, Kizlik-Masson et al found that IdeS cleaved 5B9, a monoclonal chimeric HIT IgG antibody developed by their group. Short incubation of IdeS with antibody resulted in single chain (sc) 5B9 (with only 1 of the heavy chains cleaved), whereas longer incubation periods resulted in cleavage of both heavy chains. sc5B9 demonstrated significantly reduced affinity for FcγRIIA as evidenced by lack of competitive binding inhibition of a monoclonal antibody to FcγRIIA. Binding of 5B9 $F(ab')_2$ to PF4/heparin complexes remained mostly unaltered after enzymatic digestion. Notably, IdeS-treated 5B9 was unable to activate platelets in functional assays such as the serotonin release assays. Similar to 5B9, IdeS also cleaved IgGs in samples obtained from HIT patients.

Using a microfluidic system, the authors demonstrated that leukocyte/platelet aggregates and fibrin formation induced by 5B9 was significantly decreased by IdeS treatment. Finally, IdeS-treated FcγRIIA-PF4 double transgenic mice injected with 5B9 and heparin were protected against thrombocytopenia, and levels of thrombin antithrombin complexes (TAT, used as an indicator of ongoing thrombin production) was significantly higher in IdeS-untreated mice in contrast to IdeS-treated animals where no increase in TAT levels was noted.

In a recent 25-patient landmark study, IdeS was successfully used to desensitize renal transplant recipients who were highly HLA sensitized,[7] a patient population that can be very challenging to transplant.[8] Adverse events noted in the study were limited and included infections (not surprising given complete loss of IgG after IdeS therapy) and myalgia (in 1 patient).[7] Management of HIT patients with severe refractory thrombosis and/or thrombocytopenia would be an obvious indication for the use of IdeS (the same setting in which IVIg has been most commonly used). Another clinical scenario is the emergent need for heparin use in a patient with acute HIT (eg, due to cardiac/other surgery performed with cardiopulmonary bypass support). In addition, although many HIT patients who present with isolated thrombocytopenia recover promptly after heparin cessation and initiation of alternative anticoagulation, several others go on to develop thrombotic sequelae despite optimal management. Thus, it is tempting to propose that IdeS may have utility as a therapeutic even in the routine "garden variety" HIT patient.

Studies suggest that most individuals have antibodies to IdeS, likely due to prior exposure to *S pyogenes*.[9] Although these antibodies do not appear to impact the ability of the enzyme to degrade IgGs with the initial infusion, a secondary immune response is observed 1 to 2 weeks later[10] that may limit any additional IdeS doses. Thus, if used, IdeS is likely to be given as a single dose as done in the setting of incompatible renal transplantation. Because of the short half-life of just a few hours, it will likely also be important for the HIT



Impact of IdeS treatment on HIT antibody-mediated platelet activation. (A) HIT antibodies cause platelet activation by binding to epitopes exposed on PF4 (red tetramers) complexed with heparin (black squiggle) or platelet surface glycosaminoglycans (black, shown branching from surface proteoglycans). Once bound, the constant portion of these antibodies (Fc) binds to and activates the platelet IgG receptor, FcγRIIA (in green), resulting in platelet activation. (B) IdeS-treated antibodies are able to maintain binding to their target via the $F(ab')_2$ portion, but given the lack of the Fc domain, are unable to bind to FcγRIIA and activate platelets.

patient to be placed on alternative anticoagulation or IVIg after IdeS therapy (the latter, to help avoid infectious complications resulting from plasma IgG cleavage, and to inhibit platelet activation induced by newly synthesized HIT antibodies). These important issues and questions should be investigated in the context of a prospective clinical trial.

Conflict-of-interest disclosure: A.P. has equity ownership in Retham Technologies; serves on the advisory board for Veralox Therapeutics; and receives royalties/patents from Versiti Blood Research Institute. ■

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RED CELLS, IRON, AND ERYTHROPOIESIS

Comment on Fields et al, page 2436

Brain O_2 reserve in sickle cell disease

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In this issue of *Blood*, Fields and colleagues demonstrate that patients with sickle cell disease (SCD) on hydroxyurea have lower cerebral oxygen extraction fraction (OEF) than similar patients not receiving disease-modifying therapy.[1] Although hydroxyurea has become the standard of care for young children with SCD, its ability to protect the white matter from silent strokes remains unknown. In the Créteil cohort, SCD patients had access to regular TCD screening since birth, and hydroxyurea was routinely administered to children with frequent vasoocclusive crises. Despite this, the prevalence of silent strokes was 37.4% by the age of 14 in this cohort.[2] With the increasing use of hydroxyurea, in lieu of transfusion therapy, for SCD patients with abnormal transcranial Doppler results,[3] there is appropriate anxiety about hydroxyurea's cerebral protection.