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Commentary

Heparin-Induced Thrombocytopenia

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COMMENTARY

The genesis of HIT involves the binding of platelet factor-4 (PF4), a chemokine, to a polyanion, causing a conformational change in PF-4 [1]. The structural change in PF-4 exposes epitopes that attract pathogenic immunoglobulin G (IgG) binding [1]. The complex of IgG-PF4-polyanion binds to platelets via their FcIIA receptor, activates them, and initiates a prothrombotic storm that may lead to venous and arterial thromboses [1].

The principal strategy for treating HIT has been to use factor II or X inhibitors to decrease the hypercoagulability present with HIT [3]. However, these anticoagulant therapies are not always successful in facilitating reversal of the thrombocytopenia that occurs in these patients, so it is critical to understand why these medications are ineffective and identify other effective therapies [4,5]. Some patients with severe HIT, now categorized as autoimmune HIT (aHIT), are among those who do not respond with platelet recovery when placed on anticoagulation therapy [4,5].

Autoimmune HIT is considered a subgroup of typical HIT. It has a similar pathogenesis to, and is difficult to distinguish from, typical HIT [4,5]. Their differences are summarized in Table 1. The main difference between the two is the etiologic polyanion. Typical HIT is most always associated with unfractionated heparin (UFH), but aHIT can be caused by other polyanions including bacterial lipopolysaccharides, chondroitin sulfate, nucleic acids, pentosan polysulfate, and polyphosphates [1,4-6], or even occur in the absence of a polyanion. Unlike typical HIT, patients with aHIT have platelet activation that occurs independently of UFH. The thrombocytopenia can persist for weeks [4,5]. Patients with aHIT are difficult to diagnose because the clinical picture is not always suggestive of HIT and laboratories do not consistently use buffer control when confirming HIT via functional assays (i.e. serotonin release assay (SRA)). In addition, the strong platelet activation causes a significant decrease and a persistently low platelet count. In addition, potentially fatal complications such as disseminated intravascular coagulation (DIC) and thromboses of the large venous and arterial vessels can occur.

Over the last 3 decades, nearly 40 publications document treating patients with suspected HIT with intravenous immunoglobulin (IVIG). Dougherty et al critically evaluated this literature to identify case reports of confirmed, or highly suspected, aHIT (n=24), and presented the demographic and pertinent clinical findings from these cases [7]. Table 2 summarizes these data, including response to IVIG. Overall, at least 75% of patients had platelet recovery after the administration of IVIG [7]. The question is, "How does IVIG benefit these patients?" In vitro research by Greinacher et al and Padmanabhan et al has shown that multiple commercial IVIG products can inhibit platelet activation in patients with HIT through blocking the platelet Fc receptor [8,9]. The Fc domain portion of IgG in IVIG is able to compete with pathogenic IgG HIT antibodies for the platelet receptor FcRIIa and interrupt platelet activation [8,9]. The platelet counts can recover from their low levels once the interruption of platelet activation occurs.

Greinacher et al and Padmanabhan et al also investigated the concentration of IgG that is necessary to inhibit in vitro platelet activation [9,10]. Greinacher et al found an in vitro IgG concentration of 20 mg/liter was optimal, and estimated that a dose of IVIG of 0.5-1 g/kg/day on 2 consecutive days would be needed to achieve this concentration for optimal in vivo activity [8]. Padmanabhan et al evaluated multiple IVIG doses (g/kg) and determined that an IVIG dose of 2 g/kg provided optimal inhibition of platelet activation by measuring P-selectin expression [9].

Data suggest that approximately 90% of patients with typical HIT who are administered a non-heparin anticoagulant have a platelet recovery [10]. Therefore, patients that have do not respond within 7 days after treatment of a non-heparin anticoagulant may have aHIT and must be considered for IVIG administration. Patients that have been diagnosed with aHIT using a functional assay (buffer control) can be considered for IVIG prior to 7 days based on platelet response. Prudent use of IVIG is critical because the administration of IVIG is not without risk. The drug can cause significant adverse events including infusion-related reactions of angioedema and anaphylactic shock, and it has been associated with thromboembolic events [11,12]. In addition, IVIG is obtained from human donor pools and is an expensive drug when hospitals have limited financial resources [13].

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The following clinical factors should be considered if IVIG administration is needed: platelet count < 20 x 109/liter, low platelet counts for an extended time, and lack of platelet count increase after initiation of a non-heparin anticoagulant [4,5]. Patients who are administered IVIG should be continued on a non-heparin anticoagulant to prevent or treat thrombotic events. Administration of IVIG for aHIT, as opposed to other HIT therapies, focuses treatment on the pathogenesis of this specific form of HIT by blocking the platelet Fc receptor, preventing platelet activation and allowing platelet recovery [4,5]. The most common dose from available literature is 1 g/kg/day x 2 consecutive days [7].

CONCLUSION

Enzymes have evolved to achieve remarkably efficient and specific chemical transformations. Yet atomic-level details of enzyme mechanisms remain elusive: the intermediates are transient and the chemistry that drives the transformation, such as changes in hybridization and protonation states, is difficult to characterize in functioning enzyme systems. NMR crystallography is poised to make a significant contribution to this understanding by the synergistic combination of solid-state NMR spectroscopy, X-ray crystallography, and computational chemistry. This fusion allows specific models of the chemical structure to be built upon the coarse X-ray framework and then tested by comparison of predicted and assigned chemical shifts. The result is a unique and chemically-rich view into functioning enzyme catalysis, which for the case of tryptophan synthase leads to a new acid-form hypothesis for the indoline quinonoid intermediate.

REFERENCES

1. Greinacher A. Heparin-induced thrombocytopenia. N Engl J Med. 2015;373:252-261.
2. Staibano P, Arnold DM, Bowdish DM, Nazy I. The unique immunological features of heparin-induced thrombocytopenia. Br J Haematol. 2017;177:198-207.
3. Cuker A, Arepally GM, Chong BH. American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia. Blood Adv. 2018;2:3360-3392.
4. Warkentin TE. High-dose intravenous immunoglobulin for the treatment and prevention of heparin-induced thrombocytopenia: a review. Expert Rev Hematol. 2019;12:685-698.
5. Greinacher A, Selleng K, Warkentin TE. Autoimmune heparin-induced thrombocytopenia. J Thromb Haemost. 2017;15:2099-2114.
6. Nguyen TH, Medvedev N, Delcea M, Greinacher A. Anti-platelet factor 4/polyanion antibodies mediate a new mechanism of autoimmunity. Nat Commun. 2017;8:14945.
7. Dougherty JA, Yarsley RL. Intravenous immune globulin (IVIG) for treatment of autoimmune heparin induced-thrombocytopenia: a systematic review. Ann Pharmacother 2020.
8. Greinacher A, Liebenhoff U, Kiefel V, Presek P, Mueller-Eckhardt C. Heparin-associated thrombocytopenia: the effects of various intravenous IgG preparations on antibody mediated platelet activation—A possible new indication for high dose i.v. IgG. Thromb Haemost. 1994;71:641-645.
9. Padmanabhan A, Jones CG, Pechauer SM. IVIg for treatment of severe refractory heparin-induced thrombocytopenia. Chest 2017;152:478–485.
10. Pon TK, Mahajan A, Rosenberg A. Platelet response to direct thrombin inhibitor or fondaparinux treatment in patients with suspected heparin-induced thrombocytopenia. J Thromb Thrombolysis 2018;45:536-542.
11. Barahona Afonso AF, João CM. The production processes and biological effects of intravenous immunoglobulin. Biomolecules. 2016;6:15.
12. Perez EE, Orange JS, Bonilla F. Update on the use of immunoglobulin in human disease: a review of evidence. J Allergy Clin Immunol. 2017;139:S1-46.
13. Ness S. Differentiating characteristics and evaluating intravenous and subcutaneous immunoglobulin. Am J Manag Care. 2019;25:S98-S104.