Agents for the Treatment of Heparin-Induced Thrombocytopenia

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KEYWORDS

• Heparin-induced thrombocytopenia • Coumarin necrosis
• Hirudin • Argatroban • Danaparoid • Fondaparinux

Heparin-induced thrombocytopenia (HIT) is an adverse drug reaction caused by platelet-activating immunoglobulin G (IgG) antibodies that recognize complexes of platelet factor 4 (PF4) bound to heparin. HIT is highly prothrombotic: at least 50% of affected patients develop thrombosis involving veins, arteries, or even the microcirculation.[1,2]

Even among patients without clinically evident thrombosis (“isolated HIT”), consensus conference guidelines[3,4] recommend therapy with a nonheparin anticoagulant, provided that the diagnosis of HIT is confirmed or strongly suspected on clinical grounds; this is because simple discontinuation of heparin, or substitution of heparin with warfarin, is associated with a subsequent risk for symptomatic thrombosis of between 35% and 50%, and for sudden fatal thrombosis of approximately 5%.[1,5]

A diagnosis of HIT usually signifies—rightly or wrongly—that all heparin preparations, including unfractionated heparin (UFH) and low-molecular-weight heparin

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(LMWH), are contraindicated. (Whether this is true or not is uncertain; in the author's experience, severe complications occur at least as often *after* stopping heparin as when its use is continued.) However, there is little doubt that initiating or maintaining warfarin therapy during HIT-associated hypercoagulability is an important risk factor for microvascular thrombosis, including the syndrome of warfarin-associated venous limb gangrene.[6] Thus, the ''contraindication'' status of UFH, LMWH, and warfarin during acute HIT necessarily means that novel anticoagulants have attained a prominent role in the management of HIT.

Three nonheparin anticoagulants—recombinant hirudin (r-hirudin), argatroban, and danaparoid—are approved in many jurisdictions for treatment of HIT[7–9] (an exception: danaparoid is neither approved for HIT nor available in the United States). Two other anticoagulants—fondaparinux and bivalirudin—are approved for non-HIT indications, but are used ''off-label'' for HIT.[10,11] These 5 anticoagulants can be divided into 2 groups: (1) long-acting, antithrombin 3 (AT3)-dependent, factor Xa inhibiting oligosaccharides (danaparoid, fondaparinux), and (2) short-acting, AT3-independent (ie, direct), thrombin inhibiting agents (r-hirudin, bivalirudin, argatroban), known as direct thrombin inhibitors (DTIs). The thesis of this review is that *for most patients with HIT the indirect factor Xa–inhibiting agents have the greatest therapeutic efficacy*.

HIT: A CLINICAL-PATHOLOGIC SYNDROME

HIT can be defined as any clinical event (or events) best explained by platelet-activating anti-PF4/heparin antibodies (''HIT antibodies,'' or HIT-Abs) in a patient who is receiving, or who has recently received, heparin.[12] Thrombocytopenia is the most common event in HIT, and is observed in at least 90% to 95% of patients, depending on how thrombocytopenia is defined.

HIT is a clinical-pathologic syndrome: thus, the diagnosis requires (1) one or more clinical events (eg, thrombocytopenia, thrombosis, disseminated intravascular coagulation [DIC], necrotizing skin lesions at heparin injection sites, post-intravenous heparin bolus anaphylactoid reaction) that bear a temporal association with a preceding immunizing heparin exposure; and (2) the presence of HIT-Abs (**Box 1**). Thus, a patient suspected to have HIT but in whom antibodies cannot be detected does not have this diagnosis. Rarely, patients develop a syndrome that mimics HIT on both clinical and serologic grounds but without a preceding exposure to heparin;[13–15] although named ''spontaneous HIT,'' affected patients usually have a preceding inflammatory event such as infection or surgery.

Laboratory Testing for HIT-Abs

Detectability of HIT-Abs is a key diagnostic criterion. Properly performed, platelet activation assays (using washed platelets) and PF4-dependent enzyme immunoassays (EIAs) are very sensitive for HIT, and thus a negative assay generally rules out the diagnosis.[16] Platelet activation assays (eg, serotonin-release assay [SRA]) detect HIT-Abs based on their characteristic ability to activate platelets at therapeutic (0.1–0.3 U/mL) but not supratherapeutic (10–100 IU/mL) concentrations of UFH. More commonly, commercial PF4-dependent EIAs, which use PF4 bound to heparin or polyvinylsulfonate or platelet lysate proteins, are used to support a diagnosis of HIT.[16] However, approximately 15% to 25% of patients tested yield positive results in an immunoassay and, of these, only one-third to one-half also have a positive test for platelet-activating antibodies[16–18]; thus, only approximately 7% to 10% of patients who undergo serologic investigation for HIT truly have this diagnosis. In general, the more abnormal