REVIEW ARTICLE ▮▮▮▮▮▮

THE PHARMACOTHERAPY OF HEPARIN-INDUCED THROMBOCYTOPENIA (HIT) : A REVIEW OF CONTEMPORARY THERAPEUTIC CHALLENGES IN CLINICAL PRACTICE

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Our objectives were to discuss a general overview on the description and recognition of heparin–induced thrombocytopenia (HIT) and present a critical review of the traditional and most recent advances in its pharmacotherapy. Computerized searches were done on MEDLINE and Iowa Drug Information Service (IDIS) databases from June 2001 until June 2007 and from May 2005 until May 2007, respectively. Search terms used included 'heparin-induced thrombocytopenia', 'heparin-associated thrombocytopenia', therapeutics, HIT, HAT. We largely selected publications within the timeframe above, but did not exclude commonly referenced and highly regarded older publications. The commonly referenced published articles were obtained through manual searches derived from bibliographic citations and retrievals from the authors' personal files. Pertinent literatures (89 key articles) that were thought to have substantially contributed new information to the therapeutics of HIT within the last 6 years were identified, reviewed and presented. The following limits were used for the MEDLINE and IDIS searches: 'human', drug therapy', 'review', 'meta-analysis', 'clinical trial', and case reports. The therapeutics of HIT is rapidly evolving and needs to consider an evidence – based approach. It is imperative that practitioners be aware of the associated risk and be up-to-date with the current advances in the management of this fatal clinical condition.

Key words : *heparin-induced thrombocytopenia, HIT, therapeutics, fondaparinux, bivalirudin, drotrecogin-alfa (activated), lepirudin, argatroban, danaparoid.*

Introduction

Heparin-induced thrombocytopenia (HIT) can be defined as any drop in platelets best explained by platelet factor 4 (PF4)/heparin-reactive antibodies ("HIT antibodies") in a patient who is receiving, or who has recently received heparin.[1] It is also one of the most common fatal adverse events encountered by clinicians in managing patients treated with heparins, either those who are on unfractionated heparin (UFH) or low-molecular weight heparins (LMWHs). The clinical importance of HIT primarily stems from its unique association with thrombosis.[2] Two types of HIT exist and they are considered two distinct clinical entities. Type I, which is non-immune mediated and does not involve heparin-dependent antibodies; and type II, which involves heparin-dependent antibodies and causes the immune-mediated syndrome (3-6). Some literature regard the type II as HIT but type I is just an isolated event of thrombocytopenia that occurs in heparin-treated patients and not considered as HIT(2, 5, 6). A more descriptive term for the type I is nonimmune heparin-associated thrombocytopenia (HAT).

HAT is a non-immune mediated thrombocytopenia, defined as a platelet count of 100 – 130 × 10³/mm³ that occurs 1-4 days after the start of heparin therapy (7). It is reported to occur in

approximately 25% of patients who receive heparin (3). In contrast, HIT is an immune-mediated complication in which platelet counts may decline below $100 \times 10^3/mm^3$ or to less than 50% of the baseline (7). It is usually observed 5-10 days after the start of heparin(3, 8).However, a rapid onset HIT with a very early platelet drop if subject has been exposed to heparin in the last 100 days has also been reported. The immune-mediated type is more fatal and is usually associated with undesirable sequelae, with 25-50% risk of thrombosis and 5% thrombotic death (1, 3).This latter situation is referred to as HIT with thrombosis (HITTS).

The frequency of HIT varies with the type of heparin product, the dose administered, the patient population, race, and gender (3, 8, 9).

Discontinuation of all heparin products should be the initial measure in patients with suspected or confirmed HIT. Appropriate non-heparin anticoagulants should be started in these patients immediately, even if they do not present with thrombosis. Some alternative anticoagulants have been approved for use in HIT and other marketed ones have also secured off-label use with variations in different regions of the world. Due to the global variations and new advances in therapeutics, here we present a mini-review on the contemporary challenges and evolution of therapeutic options for the management of HIT.

Epidemiology and risk groups

It has been reported that HIT can affect up to 5% of patients receiving unfractionated heparin (UFH) (10). It can affect all ages equally, however Caucasians were reported to have the highest proportion compared to other racial groups (11, 12). Females are at greater risk than males with an odd ratio of 2.37 (13, 14).The overall incidence of HIT is 0.2-0.5% and is higher in patients receiving therapeutic doses (0.79%) compared to those receiving prophylactic doses (<0.1%) (10, 15).The relative risk for thrombotic composite end point also decreased 2% for each 1-kg increase in body weight in HIT patients without thrombosis (adjusted hazard ratio, 0.98; 95% CI, 0.96 to 0.998, p = 0.029) (14). In patients undergoing cardiac surgeries and are planned to receive heparin during the surgery, HIT can be seen in up to 50% of them (10, 16, 17).In the ICU, thrombocytopenia secondary to heparin is much less prevalent (0.3-0.5%) than other sources of thrombocytopenia (30-50%) (18). Postsurgical patients who are on UFH are at higher risk than medical patients and who are on low molecular

weight heparin (LMWH) (18, 19). In hemodialysis patients the prevalence and incidence are approximately 0.26 and 0.32 per 100 patients, respectively. In subarachnoid hemorrhage (SAH) patients, the incidence was reported to reach up to 15% and such patients may experience fatal outcomes (20).In pediatrics, particularly newborns and infants whose age is under 4 years and undergoing cardiac surgery, the incidence is high (1-2%), otherwise the incidence is similar to the general population (21, 22).With the presence of malignancy alongside HIT, the prognosis will be worsening and higher rates of deep venous thrombosis and pulmonary embolism are expected (23).In general, patients who are elderly, females, Caucasians, undergoing cardiothoracic and orthopedic surgeries or procedures, post-surgical, having SAH , renal impairment or malignancy, and taking full dose of UFH are at a major risk of HIT.

Furthermore, subcutaneous heparin is often associated with less HIT than intravenous heparin (24), perhaps due to the size of the dose and availability. The incidence of HIT while using porcine UFH is 1.3–8% compared to 1.9–30.8% for bovine heparin (4). Due to the fact that most of the patients undergoing cardiac surgeries who are receiving bovine heparin are likely to develop functional heparin-PF4 antibodies, bovine heparin should be avoided or replaced by other alternatives (25). The weight of the heparin molecule can also contribute to the antigenic property of the drug. For instance, argatroban has a low molecular size and it is synthetic, resulting in a low antigenic potential (26, 27).

Pathophysiology

HIT is as a result of an immune response; the principal antigen being a complex of heparin and platelet factor 4 (PF4). PF4 is a small positively charged molecule normally found in the platelet α-granules. When platelets are activated, PF4 is released into the circulation and some of it binds to the platelet surface. Heparin and other structurally related compounds have a high affinity for the PF4 molecules and bind to them, exposing neoepitopes that act as immunogens leading to antibody production. Most notably, IgG is involved, but occasionally IgA and IgM. As a response, the platelets will be activated, releasing procoagulant properties and enhance thrombin generation (5, 28, 29).These antibodies can be detected by ELISA as long as four months following HIT or even longer (28).As a result of an excessive thrombin generation,

expression of tissue factor by monocytes and endothelial cells will be seen (8).Furthermore, levels of von Willebrand soluble thrombomodulin may rise and that could lead to endothelial cell damage as a major factor in the pathophysiology of heparin-induced thrombocytopenia (30).IgM and IgA do not increase the release of prothrombotic platelet microparticles expression and hence play only a minor role (31).

Clinical features

Most of the patients who develop anti-PF4/ heparin antibodies do not present with any symptoms, whereas a few patients may develop signs and symptoms of thrombotic complications (12).Consequently, it is prudent to perform duplex sonography for patients whom HIT is strongly suspected or confirmed regardless of the symptoms (32). When HIT is evident, a 50% reduction in platelet count is usually seen. A 30-50% reduction in the platelet count or even lower than that, accompanied by thromboembolic complications (TEC) is suggestive of HIT. Other signs and symptoms may include: skin lesions at the injection site, or acute inflammatory reactions (e.g., fever, chills) post intravenous bolus even without any decrease in the platelet count (12).Cardiopulmonary symptoms such as hypertension, tachycardia, dyspnea, chest pain, cardiorespiratory arrest, may appear 30 minutes following intravenous bolus heparin (33). One of the fatal events is thrombus formation in the adrenal vein that could lead to adrenal necrosis followed by hemorrhage (34).

Diagnostic Tips

HIT type I occurs commonly within the first 2 to 3 days of heparin therapy and the there is only mild drop of platelet count (not below $100 \times 10^3/mm^3$). Conversely, a patient is suspected to have HIT type II when the platelet count falls more than or equal to 50% of baseline (thrombocytopenia) occurring within a temporal fashion (between day 5 and 14 of therapy), sometimes followed by fatal paradoxical thrombotic event (4, 5).Up to 60% of patients will develop HIT-associated thrombosis at the same day of thrombocytopenia or earlier (12). However, some patients might develop HIT earlier or later than the mentioned duration if they have already been exposed to heparin therapy before (24). In case of the delayed pattern, the platelet may drop after 9 to 40 days following cessation of heparin. In any patient presenting with arterial or venous thromboembolism following heparin, delayed onset

HIT should be suspected (24).Attention should be paid to any patient who has been re-admitted due to thromboembolic complication after recent exposure to heparin, and should be routinely investigated for possible HIT (35, 36).One study on the timing of onset of thrombocytopenia associated with heparin therapy has come up with this temporal-aspect to help in diagnosing HIT (28). A study was conducted on 243 patients that were confirmed to have HIT through serologic examinations. Seventy percent of these patients had reduction of platelet count four or more days after heparin treatment began. This study suggested that patients who develop thrombocytopenia within hours after the exposure to heparin might already have the circulating heparin-dependent antibodies, which arose during a heparin treatment recently. The "Four T's" is a useful clinical scoring system to predict which thrombocytopenic patients have HIT (2). This is based upon assessment of *T*hrombocytopenia, *T*iming, *T*hrombosis, and the absence of o*T*her explanations for thrombocytopenia (1, 2, 37). The system evaluates the degree of thrombocytopenia currently being experienced by a patient; the timing of onset of platelet fall or other sequelae of HIT in relation to the initiation of heparin therapy; the presence or absence of proven new or recurrent thrombosis (or other sequelae); and presence of other differentials that could explain the occurrence of thrombocytopenia (other than heparin). Scores of 0 – 2 are allocated to each of the four categories with a cumulative maximum possible score of 8, as described elsewhere (37, 38).The pre-test probability using the 4T scoring system suggests that HIT antibodies are unlikely (< 5%) whenever the score obtained is low (0-3), very likely (> 80%) if the score obtained is high (6-8), and likely if the score is intermediate (4-5) (37, 38).

All these are diagnostic clues only, and they warrant laboratory confirmation using serological or functional assays. So far, no gold standard test is available and several assays exist. Platelet-activation or functional methods, antigen immunoassays, flow cytometry, monoclonal ELISA, and rapid antigen assay are common examples of available methods. Clinicians should be aware of false-positive and false-negative results associated with these investigations (24) and caution should be exercised in interpretation of such results.

The Pharmacotherapy of HIT : General Overview

The general principles of treating HIT in the presence or absence of thrombosis include

discontinuation of all heparin products (including low doses used to flush invasive catheters and LMWH); initiation of rapidly acting, non-heparin anticoagulant; discontinuation or avoidance of warfarin until thrombocytopenia is substantially resolved; and avoidance of prophylactic platelet transfusions (6, 39-41). Many clinicians discontinue heparin treatment in their patients when they suspect the patients are experiencing HIT. However, depending on the type (HIT vs. HAT) heparin cessation alone may not be adequate as patients are still at risk for new, progressive or recurrent TEC (42). The risk is even higher during the first few days after stopping heparin therapy (5). Patients with HAT usually do not experience thrombotic complications, and no specific treatment is necessary because platelet counts recover soon after heparin is discontinued (4, 7). In patients with HIT, heparin should be discontinued and appropriate therapy should be given immediately. Discontinuation may be warranted in patients who present with mixed clinical manifestations of both HAT and HIT, in the face of shortage of facilities to conduct serological investigations. The clinical index of suspicion for the association is considered high if there is a clear temporal relationship between an abrupt decline in platelet count and initiation of the suspected culprit (heparin), in the absence of any obvious alternative explanation. This fact may be strengthened by the application of adverse drug reaction probability scales such as Naranjo algorithm (43) as well as the clinical scoring system described by Warkentin (2).

An alternative non-heparin anticoagulant should be started upon discontinuation of heparin. This is due to the fact that patients are at high risk of developing thrombosis after heparin is stopped (2, 4-6, 29, 41). Current evidences suggest the use of direct thrombin inhibitors (lepirudin, argatroban, and bivalirudin), factor Xa inhibitors (fondaparinux, and danaparoid), as well as warfarin and dextran. There is a plethora of literature on the safety and efficacy of most of these therapeutic agents for the management of HIT. Some of the agents have been well-established and approved for this indication, while others have shown a great promise but still awaiting approval. Hitherto, the reputation of some therapeutic agents as alternatives has been disputed. Therefore, the pharmacotherapy in HIT patients with or without thrombosis continues to evolve (39).

LMWHs are generally suitable alternative anticoagulants to UFH in many cases. But they are generally considered contraindications for treatment of HIT because of concerns about cross-reactivity, a relatively high risk of triggering persistent or recurrent thrombocytopenia with associated thrombosis, and because other more effective treatment options are available (44, 45). In fact, LMWHs also induce HIT by less than 0.1%, though at lower rates but more in severity compared to UFH; so they are no better options (46).

Warfarin's role in the treatment of HIT has long been disputed. This is because of its relatively slow onset of action ($\geq$ 4days to achieve anticoagulation), multiple drug interactions, and association with the unusual syndrome of venous limb gangrene as well as skin necrosis (44-45). These are in addition to warfarin's ability to initially reduce protein C levels, and excessive effects early in therapy in the absence of a DTI, or platelet count recovery. Therefore, the use of warfarin in patients with HIT is not recommended, at least until the platelet count has recovered (4, 47). Since patients might need anticoagulation for long-term management of thrombotic diseases, some authors have made recommendations in administering warfarin to HIT patients (41, 47). However, it is recommended that the platelet level should have normalized or recovered to near normal levels, and loading dose of warfarin should be omitted.

Updates and Recent Advances in the Pharmacotherapy of HIT

FDA Approved Alternatives

There is resurgence of interest in the use of direct thrombin inhibitors (DTIs) for the treatment of HIT. Argatroban and lepirudin have been proven to be safe and effective as treatment options and have secured United States Food and Drug Administration's (FDA) approval for the treatment of HIT (8). Bivalirudin is also approved for use in patients with or at high risk for HIT or HITTS who are undergoing elective or primary percutaneous coronary intervention (PCI) (48). The American College of Chest Physicians (ACCP) at its 7th Conference on antithrombotic and thrombolytic therapy has given the highest level of recommendation to lepirudin (1C+), followed by argatroban (1C) and bivalirudin (2C) (8). The 1C+ grade of recommendation for lepirudin implies that the risk to benefit ratio is clear and strong recommendation can apply to most patients in most circumstances, whereas the 1C grade for argatroban has the implication of intermediate-strength recommendations that may change when stronger evidence is available. Bivalirudin with 2C grade has

an unclear benefit-risk ratio and very weak recommendation with other alternatives equally reasonable.

Here the DTIs that have secured the FDA's approval (argatroban, lepirudin, bivalirudin) would be briefly described. We will also discuss the Factor – Xa Inhibitor, danaparoid, a drug being approved for HIT in other parts of the world and conclude with agents that are under investigation or have great potential to be used in the treatment of HIT and its associated sequelae.

Argatroban

Argatroban, a direct thrombin inhibitor (DTI) used in the management of HIT, is an arginine-based synthetic anticoagulant (24). It has been used as an alternative to heparin in interventional cardiology procedures, acute myocardial infarction, unstable angina pectoris, cerebral thrombosis or ischemic stroke, peripheral obstructive arterial disease, vascular surgeries, extracorporeal circulation, hypoplastic left heart syndrome, ventricular assist device (VAD) and continuous veno-veno hemofiltration (CVVH) support (49-51). A major benefit of using argatroban is that it can be re-administered safely in patients who have recurrent HIT (52). The recommended initial dose is 2 mcg/kg/minute given intravenously and adjusted to achieve an aPTT of 1.5-3 times the baseline value (in patient with normal hepatic function) (53). In order to avoid unnecessary bleeding, clinicians are advocated to start with minimal doses of 1.2+/-0.9 mcg/kg/minute based on the basic aPTT and adjust them accordingly (54). Since argatroban follows a linear-kinetic fashion, the dose can be increased by 0.5 mcg/kg/minute in most of the patients whose liver function is normal and 0.25 mcg/kg/minute when liver impairment is present (55). In case of elevated aPTT due to antiphospholipid antibody syndrome (APS), weight-based, fixed-dosing schedule may be sufficient and necessitate no laboratory monitoring (56).

Literature has sufficiently reported that since argatroban is cleared by the liver, dose adjustment is not needed even when severe renal impairment is evident (CLcr < 30 ml/min) or those in need of renal replacement therapy (RRT) such as hemodialysis or continuous venovenous hemofiltration (CVVH) (57-60). Activated partial thromboplastin time, ACT, plasma argatroban concentrations, and systemic clearance are expected to be stable during RRT providing effective and safe anticoagulation therapy without the need for any dose modification (59).

Issue of dosage adjustment in renal failure is however an area of controversy, since there have been observations independent of clinical trials where lower doses were utilized. Due to the lack of sufficient clinical evidence, argatroban should be avoided whenever liver impairment (serum total bilirubin >1.5 mg/dL, or ALT and/or AST > 100 U/L) is detected, but if no more choices are readily available, consideration for reducing the initial dosing to 0.25-0.5 mcg/kg/minute is recommended (53, 55). This dose seems to be effective without adding a significant risk of major bleeding. Serum total bilirubin levels more than 1.5 mg/dL and/or concurrent hepatic and renal function are the main clinical endpoints that necessitate lower dosing scheme (61).

Generally, heparin is the agent of choice and should be used when possible during cardiac procedures. Heparin still can be utilized if the clinician is able to delay, ideally 12 weeks, the surgery until HIT is negative without unnecessary risks (62, 63). It is recommended, however, to avoid using heparin before and after the surgery in order to avoid and prevent formation of HIT antibodies (62). In cardiopulmonary bypass surgeries with the presence of other comorbidities such as end-stage renal failure, and ischemic cardiomyopathy with ventricular fibrillatory arrest, argatroban has been used successfully and the patient did not suffer any sequelae 6 weeks following the surgery. In patients undergoing Percutaneous Coronary Intervention (PCI), a dose of intravenous 350 mcg/kg initial bolus followed by maintenance dose 2.5 mcg/kg/minute adjusted to achieve an activated clotting time of 300-450 seconds may achieve good outcomes (64). If massive thrombus is formed during PCI, argatroban still can resolve it successfully (65). In cardiac surgeries, ecarin coagulation time (ECT), though not readily available at this time, is recommended to be used for monitoring instead of aPTT. In critically ill patients, however, extra frequent monitoring is required to avoid over anticoagulation and coagulopathies even under the recommended dosing or lower (63, 66). Bleeding can happen when excessive anticoagulation occurs, so argatroban should be withheld instantly and then resumed with low doses (67). Furthermore, ischemic stroke is a common occurrence amongst HIT patients and significantly increases mortality. In a retrospective study which included 960 patients, argatroban was able to significantly reduce new strokes and associated mortality without increasing the intracranial hemorrhages (68).

Further, the safety, efficacy, and pharmacokinetics of argatroban have not yet been extensively studied in pediatric patients. However, argatroban has been tested for the treatment of HIT, congenital cardiac surgeries, anticoagulation for ECMO post-cardiac surgery in pediatrics and in children who require extracorporeal life support (51, 69-72). A bolus dose of 200–250 mcg/kg can be given and maintenance dose of 7.5–10 mcg/kg/min and 3.0–7.5 mcg/kg/min can be given to children and newborn; respectively, to be adjusted accordingly. The published cases for pediatrics are very similar to the adults as regards to their success, though, very limited and yet strong evidence cannot be drawn. So far, only one case has been published showing unexplained resistance to argatroban, when a 6 year-old girl was treated with up to 18 mcg/kg/ minute for treatment of HIT and yet the aPTT was subtherapeutic. In such cases, argatroban may be substituted with other anticoagulants such as lepirudin (73).

Lepirudin

Lepirudin, a recombinant hirudin is a well-established agent in the treatment of serologically confirmed HIT complicated by thrombosis. It has been commercially available since May 1997 and March 1998 in the European Union and in the US for the treatment of HIT-associated thrombosis respectively (44). Lubenow and colleagues in a meta-analysis of 3 prospective studies involving 91 patients with acute isolated HIT concluded that the incidence of combined end-points of death, new thromboembolic complications and limb amputation were significantly lower in the lepirudin-treated patients (74). The recommended dose is 0.4 mg/kg as a bolus followed by 0.15 mg/kg/hour, adjusting the dose to achieve an aPTT of 1.5-3 times the baseline for HITTS and 0.1 mg/kg/hr for isolated HIT (75). Lepirudin use in children with HIT, though with tremendous success, is based on case reports, as summarized by Knoderer et al (40). Although guidelines exist suggesting the potential administration of lepirudin as treatment for children with HIT, further studies are needed to determine the safest yet most effective dosage for this population. Lepirudin should be used with caution to avoid potential bleeding complications (29).

Bivalirudin

Bivalirudin, another DTI, is approved for use in patients with HIT who must undergo PCI (7). No controlled or comparative trials for *bivalirudin* were available in a MEDLINE and IDIS search we conducted and this is supported by Seybert and colleagues (39). Evidence for the use of bivalirudin for the management of HIT in both cardiac surgery and medical patients is limited to open label trials and descriptive studies. One notable trial is the Anticoagulant Therapy with Bivalirudin to Assist in the Performance of PCI in Patients with HIT (ATBAT), which was a multi-center, open-label single arm study to evaluate the safety and efficacy of bivalirudin in the stated population (76). The results of ATBAT showed that clinical success, defined as absence of death, emergency bypass surgery, or Q-wave infarction was achieved in 96% of the patients. Whereas, procedural success (TIMI grade 3 flow and < 50% stenosis) was achieved in 98% of patients, and no patient had significant thrombocytopenia (platelet count $< 50 \times 10^9$/L) after treatment. Bivalirudin appeared safe and provided effective anticoagulation during PCI. These data, and extensive experience with bivalirudin in PCI, support its use as an anticoagulant in patients with HIT who require coronary intervention. Bivalirudin is an attractive modality due to its relatively short half-life, smaller dose requirements, easy monitoring via aPTT measurements, metabolism primarily via proteolytic degradation, which provides a greater margin of safety in patients with renal or hepatic dysfunction as compared to other direct thrombin inhibitors (6, 39). Dosing and monitoring recommendations for bivalirudin use in patients with HIT has not yet been established (24).

Non-FDA-Approved Alternatives and Potential Investigational Agents

Factor – Xa inhibitors have also found indications in the treatment of HIT. Danaparoid is one of such agents that is approved for the treatment and prevention of HIT-related thrombosis in many jurisdictions around the world, but not currently in the United States (3, 8, 9, 44). The most recent and promising advance in the pharmacotherapy of HIT based on our literature search and evaluation is another factor-Xa inhibitor, fondaparinux (7, 24, 77). This agent is neither approved for HIT in the US nor in other jurisdictions outside the US. Drotrecogin, a recombinant human activated protein C licensed for severe sepsis has been reported to be used successfully in a case of HITTS and may also be a promising option in future.

Danaparoid

Danaparoid is a mixture of 3

glycosaminoglycans (heparin sulphate, dermatan sulphate, and chondroitin sulphate) that exerts its anticoagulant effect by catalyzing the inactivation of factor Xa by anti-IIa (antithrombin) (anti-Xa: anti-IIa activity ratio > 28:1). Danaparoid was previously approved for HIT in the US, but withdrawn from the market in 2002. However, its popularity in the treatment of HIT is broadening. Approval to use it in the treatment of HIT has been secured in a few countries (New Zealand, Denmark, France, Germany, Luxemburg, Belgium, Portugal, Sweden, The Netherlands), although it is often administered in other countries for this indication where it is available for postoperative antithrombotic prophylaxis (44). One approach to dosing danaparoid for the treatment of HIT is to administer an intravenous bolus dose of 2500U followed by 400U/hour for 4 hours, then 300U/hour for 4 hours, and subsequently 200U/hour until anticoagulation is no longer required, adjusting the dose to maintain plasma anti-Xa level within 0.5-0.8 U/mL (78). However, there are several approaches to dosing this agent.

Fondaparinux

A newer agent, namely fondaparinux, which has lower cross-reactivity in vitro with heparin-dependent antibodies might also be effective for HIT (41, 79). Fondaparinux is a synthetic pentasaccharide and indirect-acting factor-Xa Inhibitor that has no significant cross-reactivity with heparin-platelet factor 4 antibodies and is administered subcutaneously. It has rapid onset of action, half-life of 17-21 hours and administered once daily (80). In vitro studies have demonstrated a lack of cross-reactivity between fondaparinux and HIT antibodies (81-83). It is approved for a wide range of indications including venous thromboembolism and acute coronary syndromes (80). Although fondaparinux is not approved for use in patients with HIT, a small body of clinical experience indicates its efficacy in the setting of immune-mediated thrombocytopenia (7). It is equally not an approved agent for HIT outside the US. The cost of therapy, solely by intravenous/infusion route with lepirudin and argatroban are extremely exorbitant. As such, there are compelling needs for therapeutic alternatives. Fondaparinux is one such promising alternative agent in the treatment and prophylaxis of HIT. As it is administered subcutaneously, fondaparinux is an appealing alternative to the DTIs, which are administered by continuous infusions and require close monitoring (7). Successful treatment of acute

and subacute HIT with fondaparinux has been reported in 35 patients (77), and more evidences continue to evolve. The optimal dosage of fondaparinux is unclear (24), but the dosage in published studies ranges from 2.5-10 mg/day (84-86). The ACCP states that minimal data supporting the efficacy of fondaparinux in HIT and other thrombocytopenic situations precludes them from making any recommendations (8). In a review by Spinler Sarah, it was stated that "while several reports have described the treatment and prophylaxis of thrombosis in patients with HIT using fondaparinux, clinical trials should be conducted and reported before fondaparinux becomes a therapy of choice for HIT" (77). Warkentin and colleagues have described a 48-year-old woman in whom a syndrome resembling HIT developed after bilateral knee replacement while she was receiving fondaparinux (Arixta ®). They raised an important hypothesis regarding a potential mechanism of delayed HIT in association with fondaparinux (87).

Role of Drotrecogin alfa (activated) in the Treatment of HIT

Drotrecogin alfa (activated) is the recombinant form of human activated protein C, a naturally occurring protein C with antithrombotic, anti-inflammatory, and profibrinolytic activities (88). Drotrecogin is licensed in North America for severe sepsis following a trial in which it was compared with a placebo in 1,690 subjects with severe sepsis (88). Inhibition of propagation of coagulation using recombinant human activated protein C offers a promising therapeutic target for antithrombosis. HIT associated thrombosis may undoubtedly benefit from this. Rubeiz GJ and colleagues have reported the successful use of this agent in a patient with HIT and thrombotic complications (89). In this case, a 96-hour course of drotrecogin alfa (activated) 24 mcg/kg/hr was initially started in addition to the standard of care for the treatment of a presumed severe sepsis with shock. The clinical course of the patient was complicated by HIT and thrombosis. After HIT became apparent, all heparin products/sources were discontinued and drotrecogin alfa (activated) was continued as a sole antithrombotic agent. The patient survived with reasonable outcomes and salvage of her limbs (89). To our knowledge, this was the first reported case of HIT with thrombosis that was treated with recombinant human activated protein C. Even though this case serves as a pointer to the potential role of drotrecogin alfa (activated) in the

management of HIT with thrombosis especially when an alternative to direct thrombin inhibitor is desired, yet well-designed clinical studies to evaluate its safety and efficacy in this situation are warranted. To date, there are no randomized trials or systematic evaluations of efficacy of drotrecogin alfa (activated) in HIT setting.

Conclusion

The different presentations which characterize the 2 distinct entities (HIT and HAT) may intercalate or mimic each other, making it highly challenging even to the astute clinician to make a decision. Hence, there are serious concerns in decision making due to the conflicting views, myths and misconceptions in the diagnosis and management of HIT. To date, lepirudin and argatroban are the agents of mainstay in the therapeutics of HIT, and bivalirudin is recommended in PCI setting. Danaparoid, though not FDA-approved, has gained approval in many countries. Yet, the pharmacotherapy of HIT is rapidly evolving and novel agents have shown a great promise. Fondaparinux and drotrecogin are 2 such examples. Nevertheless, due to limited clinical experiences with the use of these agents, well-designed clinical trials are most needed before they become alternatives that should be used for HIT. We strongly recommend that practitioners should come up with a consensus or guideline on diagnosis of HIT/HAT, algorithm on treatment and when or when not to discontinue heparin therapy, based on evidence. It should also highlight the best evidences on alternative pharmacotherapeutics and management of HIT/HAT.

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