

Editorial Focus

Fondaparinux versus direct thrombin inhibitor therapy for the management of heparin-induced thrombocytopenia (HIT) – Bridging the River Coumarin

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Fondaparinux is a synthetic antithrombin-binding "penta-saccharide" anticoagulant with proven antithrombotic efficacy in a variety of prophylactic and therapeutic settings (1). Although its use is associated with formation of anti-platelet factor 4 (PF4)/heparin antibodies at a frequency similar to that observed with low-molecular-weight heparin (LMWH), fondaparinux is less likely to produce immune thrombocytopenia, probably because it (unlike LMWH) forms poorly with PF4 the antigens recognized by HIT antibodies (2, 3). To date, a syndrome resembling HIT seems rare with fondaparinux (3).

Fondaparinux is increasingly viewed as an attractive candidate anticoagulant to manage HIT (1, 4). Many of its properties – subcutaneous administration, long half-life, lack of international normalized ratio (INR) prolongation, specific factor Xa inhibition – differ from those of the direct thrombin inhibitors (DTI), lepirudin and argatroban, approved to treat HIT. These pharmacologic differences may be useful. For example, DTI-coumarin (warfarin) overlap poses risk of precipitating microvascular thrombosis, particularly venous limb gangrene, in some patients with HIT (5, 6). Warfarin use during the acute (thrombocytopenic) phase of HIT is inimical because it does not inhibit HIT hypercoagulability, and it predisposes to depletion of the natural anticoagulant, protein C. In theory, fondaparinux-coumarin overlap should have lower risk of such complications.

In this issue of *Thrombosis and Haemostasis*, Lobo et al. (7) report the results of an open-label prospective pilot study of fondaparinux in seven patients with a diagnosis of HIT treated with fondaparinux (with warfarin overlap). Unlike previous studies of fondaparinux for HIT, they also evaluated a comparator group, consisting of ten historical controls managed at the same hospital with DTI (lepirudin, n=6; argatroban, n=4) and warfarin. Dosing of fondaparinux was the same as for non-HIT indications, i.e. 7.5 mg for patients (of body weight between 50 and

100 kg) with thrombosis, and 2.5 mg for patients without thrombosis. All patients had HIT "confirmed" by a positive anti-PF4/heparin enzyme-immunoassay (EIA). The primary objective was an evaluation of platelet count recovery. Secondary objectives included comparisons of various complications (death, amputation, new thrombosis, major bleeding), as well as the frequency of achieving "successful bridging" with warfarin, defined as reaching an INR of 2.0 to 3.0 for two consecutive days while receiving fondaparinux, or after stopping the DTI.

The investigators found that the frequencies and extents of platelet count recovery did not differ significantly between the fondaparinux and DTI treatment groups, and that no new thrombotic events occurred in either group. However, successful bridging to warfarin therapy was seen in just two of six (33%) fondaparinux-treated patients, and in none of the eight DTI-treated patients who received warfarin. Of note, the low frequency of successful bridging in the fondaparinux-treated patients appeared to reflect in part investigator inattention to the study protocol since in two patients the fondaparinux was stopped on the first day that the INR reached the therapeutic range, even though the protocol called for *two* days of overlap within the INR therapeutic range. For the other two bridging failures, one resulted from deliberate interruption in coumarin therapy (to permit amputation), whereas the other occurred because the INR abruptly rose to 4.0 during overlap, i.e. a true bridging failure. For the 10 DTI-treated patients, four developed venous limb gangrene, although in two patients this complication was associated with warfarin use prior to initiation of DTI therapy. However, for another patient, limb necrosis may have developed (or worsened) during attempts at DTI-warfarin bridging characterized by several episodes of stopping and restarting the DTI.

Why is DTI-coumarin overlap an at-risk period for warfarin-induced venous limb gangrene? Factors include the prolongation

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of INR by DTI (8), especially argatroban (with potential for physicians to conclude prematurely that the patient is adequately anticoagulated with warfarin), the prolongation of the partial thromboplastin time by warfarin (leading to DTI underdosing) (6), and the short half-lives of DTI (with potential for abrupt "rebound" of thrombin action if the DTI is stopped when HIT is still active).

In contrast, fondaparinux use could minimize such risk during bridging to warfarin. First, the physician has the option to discharge the patient on continuing subcutaneous fondaparinux therapy, thereby avoiding or postponing warfarin (although this approach was not studied by Lobo et al.). In addition, the subcutaneous dosing and long half-life of fondaparinux probably reduce risk of severe thrombin "rebound" if it is stopped prematurely. Further, fondaparinux does not prolong the INR, and so fondaparinux-warfarin overlap should be no more complex to manage than similar bridging to warfarin performed during LMWH or danaparoid therapy.

What are the limitations of this study by Lobo et al.? First, the authors relied on a positive anti-PF4/heparin EIA to diagnose HIT; however, a positive EIA does not always "rule in" this diagnosis (9). Many patient sera that test EIA-positive lack platelet-activating antibodies. The overall "weak" EIA reactivity in the fondaparinux-treated patients (the median EIA optical density [od] was only 0.70 units) raises doubt as to whether all the patients suffered from HIT. (Indeed, one patient with an od of only 0.50 units, no thrombosis, and preceding abciximab therapy may well have had delayed-onset of thrombocytopenia induced by this glycoprotein IIb/IIIa antagonist.) Given growing acceptance of the key role of heparin-dependent platelet-activating anti-

bodies in the pathogenesis of HIT, the demonstration of such antibodies (using sensitive platelet activation assays) in future studies of fondaparinux therapy is recommended.

Second, the primary study endpoint – platelet count recovery – does not reliably indicate therapeutic benefit. After all, platelet counts recover as quickly in HIT patients managed with warfarin or anrod – two discredited HIT therapies (10).

Third, the study of Lobo et al. was small, with only seven fondaparinux- and 10 DTI-treated patients. Many patients evaluated for inclusion within the prospective cohort study or its historical controls were excluded for reasons of renal dysfunction and failure to follow the DTI protocol, respectively. The small study size does not allow for definitive conclusions as to whether severe HIT-associated hypercoagulability can be reliably controlled with fondaparinux.

In summary, fondaparinux has the likely advantage (vs. DTI) of improving bridging to warfarin, but (unlike DTI) its efficacy as a primary non-heparin anticoagulant for severe HIT-associated hypercoagulability is not established. How can physicians deal with this therapeutic conundrum? One possibility – not yet described in the literature, but theoretically attractive – is to utilize a DTI during the thrombocytopenic phase of HIT; however, once the platelet count has substantially recovered, rather than performing DTI-warfarin bridging, a DTI-fondaparinux transition can be performed. In this way, one circumvents the "off-label" use of fondaparinux as the primary treatment of HIT, while at the same time avoiding the complexity (and risk) of DTI-warfarin overlap. This study by Lobo et al. provides lots of ideas for the management of HIT.

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