Fondaparinux for the treatment of patients with acute heparin-induced thrombocytopenia

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Summary

Heparin-induced thrombocytopenia (HIT) is a life-threatening immune response to heparin that is associated with a high risk of thromboembolic complications. We prospectively treated seven subjects with acute HIT with fondaparinux and compared the results to a similar historical control population from the same hospital. Six of the seven fondaparinux-treated subjects were transitioned to warfarin, beginning after platelet count recovery occurred. Ten historical controls were treated with a direct thrombin inhibitor (DTI), eight of which were transitioned to warfarin. The primary study outcome was platelet count recovery which was defined as an increase from baseline by at least 30% of nadir to greater than 100,000/mm^3 by day seven. Seven subjects were prospectively treated with fondaparinux for a median of eight days. Six of the seven had HIT with thrombosis at the time of enrollment. All fondaparinux treated subjects had a complete platelet count recovery, and none experienced a new thromboembolic complication, major bleeding or death by week four. One subject underwent limb amputation. Ten historical controls were treated with a DTI for a median duration of eleven days. Platelet count recovery occurred in eight of the ten historical controls. No new thromboembolic complications or major bleeds occurred but limb gangrene occurred in four controls. The development of limb gangrene in the historical controls may have been a result of delayed recognition of HIT and/or inappropriately early institution of warfarin in the historical controls. This pilot study suggests that fondaparinux may be useful in patients with acute HIT.

Keywords

Coagulation inhibitors, deep vein thrombosis, heparins, thrombocytopenia, fondaparinux

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Introduction

Heparin-induced thrombocytopenia (HIT) is a life-threatening immune response to heparin that occurs in up to 5% of patients treated with unfractionated heparin (1–3). Venous or arterial thromboembolic complications will develop in 30–75% of patients with HIT unless they are treated with an alternative anticoagulant (4–7). Current guidelines recommend the use of either direct thrombin inhibitors (DTI) or heparinoids (danaparoid) for patients with suspected or confirmed HIT (1). The DTI lack cross-sensitivity to heparin and have become a standard therapy for patients with HIT in the USA (1, 8–12). These agents include lepirudin (Refludan® – Berlex), bivalirudin (Angiomax®-The Medicines Company) and argatroban (GlaxoSmithKline) (13–15). Unfortunately, the usefulness of these agents is limited by the need for continuous intravenous infusions, frequent aPTT monitoring, and prolongation of the international normalized ratio (INR), which complicates transitioning patients to warfarin (16–17).

Fondaparinux is a selective factor Xa inhibitor that is administered once daily by the subcutaneous route for the prophylaxis and treatment of patients with arterial or venous thrombosis (18, 19). Unlike danaparoid, in-vitro data with fondaparinux shows a lack of cross reactivity with HIT antibodies (8–12). Published data on fondaparinux in HIT is limited to abstracts, case reports, retrospective case series and a letter describing a small case series (20–25). The purpose of our open-label, prospective pilot study was to assess the feasibility of administering fondaparinux as an alternative anticoagulant to patients with acute HIT. Comparisons were made with historical control patients who were treated with a DTI.

Methods and materials

This study was conducted at Methodist University Hospital, Memphis, TN, USA, between October, 2005 and July, 2006. The institutional review board approved the study protocol and in-

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formed consent document. All prospectively treated subjects gave informed consent prior to enrollment. The study was conducted in accordance with the 1975 Declaration of Helsinki.

Subjects

In order to be considered for inclusion into the study, all subjects were required to be at least 18 years of age with a diagnosis of heparin-induced thrombocytopenia (HIT). The diagnosis of HIT was made when patients experienced an otherwise unexplained 50% or more decrease in platelet count from baseline (pre-heparin) during or within two weeks after heparin exposure and/or any new thromboembolic complication during or within two weeks after heparin exposure. In addition, all patients were required to have a positive heparin PF4 antibody test or serotonin release assay.

Thromboembolic complications occurring prior to or after study enrollment of either prospectively treated or historical controls were confirmed as follows: in patients with signs and symptoms consistent with deep vein thrombosis, arterial thrombosis or pulmonary embolism, diagnosis was confirmed with duplex ultrasonography, ventilation-perfusion scanning or high-resolution computerized tomography. Subjects were excluded if they met any of the following criteria: creatinine clearance less than 30 ml/min (estimated by Cockroft Gault equation); pregnant or lactating; active blood dyscrasia other than HIT, recent or planned surgery of CNS, eye or other procedure involving large open surfaces or high bleeding risk; planned lumbar puncture; active bleeding of GI, GU, respiratory tract or CNS; malignant hypertension; pericarditis; pericardial effusion; endocarditis; eclampsia; inadequate support system at home; alcoholism, drug abuse, psychosis or dementia; hypersensitivity or contraindication to fondaparinux or warfarin.

Study design

Fondaparinux treated subjects

This pilot study prospectively treated patients with a diagnosis of HIT with fondaparinux and compared their outcomes to a similar population of historical controls from the same hospital. Prospectively treated subjects were identified and screened following laboratory support of the diagnosis of HIT. Patients who were already being treated with a direct thrombin inhibitor (DTI) could be enrolled as long as the duration of DTI treatment was less than one day. If arterial or venous thrombosis was present at the time of enrollment, subjects were assigned to the following weight-based fondaparinux regimen given subcutaneously once daily: 5 mg if body weight less than 50 kg; 7.5 mg if body weight was between 50–100 kg, or 10 mg if body weight greater than 100 kg. Subjects without thrombosis at the time of enrollment received 2.5 mg subcutaneously once every 24 hours. Subjects who did not have thrombosis and who weighed less than 50 kg were excluded from the study.

The study protocol called for fondaparinux to be administered for at least seven days or until the INR was in the therapeutic range (2–3) and stable for at least two consecutive days. Warfarin use and dosing decisions were left to the discretion of the attending physician.

Daily measurements and assessments during fondaparinux treatment included the following: platelet counts; Hg; warfarin dose; presence of bleeding; transfusions; new thromboembolic complications; peripheral pulses; observation of skin for color and presence of ischemic complications including skin necrosis or venous limb gangrene; amputations; other surgical procedures and deaths. Venous limb gangrene was defined as acral necrosis that developed despite palpable or Doppler-identifiable pulses. Patients or caregivers were contacted each week for four weeks following the discontinuation of fondaparinux in order to identify any new complications such as bleeding, thrombosis, amputations or death.

Historical controls (DTI treated subjects)

Historical controls were identified using a list of patients with positive heparin antibody results from April 2003 until October 2005. Data on the historical controls was obtained through computerized and manual chart review. All historical controls were required to meet the same inclusion and exclusion criteria as the prospectively treated group. Furthermore, all historical controls must have been treated with a standardized direct thrombin inhibitor (DTI) protocol. The DTI protocol allowed the physician to select either lepirudin or argatroban, with a dosing and monitoring algorithm consistent with the manufacturer's FDA-approved labeling. The reason for requiring the standard DTI protocol was to reduce the potential for errors in dosing and monitoring and to reduce the variability in how the historical controls were treated.

Study objectives

The primary objective of the study was to compare platelet count recovery in fondaparinux treated subjects to a historical control group who received "standard" therapy with a DTI. Since thrombocytopenia (platelet count < 150,000/mm^3) occurs in most, but not all patients with HIT, and because platelets may begin to recover prior to initiation of treatment, we had two definitions of platelet count recovery. Platelet count recovery in patients with thrombocytopenia at baseline (one day prior to treatment) was defined as an increase in the platelet count from baseline by at least 30% of nadir to greater than 100,000/mm^3 by day seven. In patients without thrombocytopenia at baseline (one day prior to treatment), platelet count recovery was defined as a platelet count greater than 100,000/mm^3 on days three and seven of treatment.

There were two secondary objectives of the study: 1) comparison of complication rates between fondaparinux treated subjects and historical controls and 2) successful bridging in those treated with fondaparinux versus historical controls. Complications were defined as death, limb amputation, new thromboembolic complications, venous limb gangrene or major bleeding. Patients receiving fondaparinux were monitored for possible complications by phone for four weeks after discontinuation. Major bleeding was defined as overt bleeding associated with a hemoglobin decrease of 2g/dl or fatal, life-threatening, intracranial, or any overt bleeding requiring transfusion of at least 2 units of blood while receiving HIT treatment.

Successful bridging in subjects treated with warfarin was defined as an INR of 2–3 for two consecutive days while not receiving a DTI. This definition was necessary for DTI treated subjects because these agents may prolong the INR, resulting in the need

Table 1: Baseline characteristics.

Characteristic	Fondaparinux (N=7)	Historical control (N=10)
Age (years)	65	65
Male (%)	57	70
Race (% White)	43	40
Race (% African-American)	57	60
Mean Pre-Heparin Platelet Count (X 1000/mm^3)	241	261
Mean Platelet Count Nadir (X 1000/mm^3)	66	85
Mean Baseline (pre-treatment) Platelet Count (X 1000/ mm^3)	73	155
Subjects having HIT with thrombosis (N)		8
– DVT only (N)	6	3
– PE with/without DVT (N)	1	2
– Arterial (N)	3	1
– Arterial and Venous (N)	2	2
Mean time to begin HIT treatment after 50% decrease in platelet count (days)	2.3	5.2
Median Optical Density	0.7	1.7

to discontinue the DTI and recheck the INR while on warfarin monotherapy.

Discrete variables, including baseline data, platelet count recovery, complications and successful bridging were compared using the Fisher's Exact test (GraphPad Software, Inc). The level of significance was defined as 0.05 (two tailed).

Results

Subjects

Of the 20 subjects screened for prospective treatment with fondaparinux, seven met eligibility requirements and were enrolled. The most common reason for excluding potential study subjects was having an estimated creatinine clearance < 30 ml/min (N=11). Other reasons for exclusion were active bleeding (N=1) and expected life expectancy of less than one month (N=1). Four subjects developed HIT while receiving heparin or enoxaparin postoperatively, while three were exposed to heparin during hospitalization for acute medical illness. Six of the seven had acute thrombosis at the time of HIT diagnosis and received full treatment doses of fondaparinux; one subject was without thrombosis and therefore received 2.5 mg once daily.

There were three fondaparinux treated subjects who were treated initially with a DTI (two argatroban, one lepirudin) for less than 24 hours prior to being enrolled in the study. Only one of the fondaparinux treated subjects was receiving another drug that is commonly associated with thrombocytopenia. This subject (#3) had undergone cardiac catheterization with abciximab. None of the remaining subjects had other drugs (besides heparin) that required discontinuation when thrombocytopenia was recognized. Furthermore, six of seven fondaparinux treated subjects had a "high" pretest probability of HIT using the 4 T's scoring system (26). The heparin –PF4 ELISA optical densities of each subject are displayed in Table 2.

Of 51 subjects with HIT who were screened to serve as historical controls, 31 were excluded because they had not been treated with the standardized DTI protocol. Other reasons for exclusion from the historical control group included having an estimated creatinine clearance less than 30 ml/min (N=8) and total body weight less than 50 kg (N=2). Seven subjects developed HIT postoperatively, while three were exposed during their hospitalization for acute medical illnesses. Six of the historical controls were treated with lepirudin and four with argatroban.

Baseline characteristics of the study subjects are shown in Table 1. Six of seven prospectively treated subjects and eight of ten historical controls had experienced a thromboembolic complication of HIT prior to beginning treatment with fondaparinux or the DTI protocol. Fondaparinux treated subjects had average baseline (pre-treatment) platelet counts that were significantly lower compared to the average baseline platelet count in the historical controls (73 versus 155; two-tailed P value equals 0.0131; CI: –145.35 to –20.03).

Efficacy

All fondaparinux treated subjects experienced platelet count recovery as defined in the protocol (Table 3). The average percentage increase in platelet count from nadir to day 7 was 525% (range: 53–1900%).

Platelet count recovery occurred in most (8/10) historically treated subjects (Table 4). The average percentage increase of 245% (range: 5–600%), was not significantly different from the fondaparinux treated subjects (two-tailed P value equals 0.2466). Two historical controls died (Subjects #4 and #7) during the data collection period, and data on platelet count recovery are therefore incomplete on these subjects.

Table 2: PF4-heparin ELISA optical densities.

Fondaparinux subjects									
Subject #1	Subject #2	Subject #3	Subject #4	Subject #5	Subject #6	Subject #7			
0.7	1.8	0.5	0.82	0.44	>3	0.6			
Historical controls									
Subject #1	Subject #2	Subject #3	Subject #4	Subject #5	Subject #6	Subject #7	Subject #8	Subject #9	Subject #10
1.3	1.25	1.8	2.32	>3	0.8	1.9	1.6	2.6	0.44

Table 3: Platelet count response in fondaparinux treated subjects.

Subject Number	Platelet Nadir	Baseline Platelet Count	Platelets on Day 3	Platelets on Day 7	Percent increase (from nadir) at Day 7
01	139	139	249	476	242
02	20	20	68	196	880
03	11	29	101	220	1900
04	37	52	79	120	224
05	91	91	168	281	208
06	67	80	168	182	171
07	98	98	139	150	53

Table 4: Platelet count response in historical controls.

Subject Number	Platelet Nadir	Baseline Platelet Count	Platelets on Day 3	Platelets on Day 7	Percent increase at (from nadir) Day 7
01	118	144	180	207	75
02	53	53	160	371(day 10)	600
03	108	108	239	583	440
04	20	153			
05	89	90	164	282	216
06	82	188	150	86 (day 8)	5
07	91	127	94	199	118
08	51	246	191	185	263
09	89	165	354	468 (day 6)	426 (day 6)
10	147	280	384	234	59

Complication rates

Fondaparinux treated subjects

No new thromboembolic complications, major bleeding events or deaths had occurred in any of the fondaparinux treated subjects during the study period or upon follow-up at four weeks. However, subject #6, who presented with acute popliteal artery thrombosis approximately one week following knee replacement, was enrolled after unsuccessful thrombectomy and later underwent lower limb amputation after seven days of fondaparinux.

Bleeding complications were minor, and no patient met criteria for major bleeding. There were three fondaparinux treated subjects 43% (3/7) who experienced a 2 g/dl or greater decrease in Hg that was not associated with bleeding while on treatment. Four fondaparinux treated subjects 57% (4/7) were transfused. Since none of the transfused patients had clinically overt bleeding, their bleeding was classified as minor. Minor bleeding not requiring transfusion was observed in 43% (3/7) of fondaparinux treated subjects.

Historical controls

No new thromboembolic complications or major bleeding events were noted in the historical controls while they were being treated with a DTI, although venous limb gangrene was seen in four of the ten subjects. Subject #2 developed gangrenous necrosis of a single digit of the same limb affected by DVT prior to treatment with DTI and while he was receiving warfarin. Subject #4 developed gangrenous necrosis of the left hand which required amputation. As with subject #2, this occurred prior to DTI treatment and while the patient was receiving warfarin. He also had gangrenous necrosis of both lower extremities and died on the same day that a DTI was initiated. Patient #6, who had a right lower extremity DVT, experienced an area of focal necrosis of the right lower extremity that was consistent with gangrenous necrosis. This subject did not require surgery or amputation. Subject #10, who had severe peripheral arterial disease and bilateral femoral-popliteal artery bypass grafts, developed gangrenous necrosis of the left lower extremity requiring amputation 12 days after initiating a DTI. This subject had been treated with a DTI and warfarin for eight days prior to the left above the knee amputation. Of note, the DTI had been stopped and started several times while warfarin was being titrated into the therapeutic range.

Rates of bleeding complications in the historical controls were similar to the fondaparinux group. One-half (5/10) experienced a 2 g/dl or greater decrease in Hg while on DTI treatment; tranfusions were performed in 40% (4/10). Clinically overt but minor bleeding not requiring transfusion was noted in one subject (10%). No patient met the criteria for major bleeding.

Successful bridging to warfarin

Of the six fondaparinux treated subjects who were transitioned to warfarin due to thromboembolic complications, 33% (2/6) were successfully bridged, i.e. stable in the therapeutic range (INR=2–3) for two consecutive days prior to discontinuation of fondaparinux. The other four subjects did not meet our strict criteria for successful bridging for different reasons. One of the subjects had to prematurely discontinue warfarin in order to have her lower limb amputation. She was not continued on the study after the amputation (although she continued to receive fondaparinux post-op off-protocol). One subject overshot the therapeutic range (INR went from 3.0 to 4.1) and the fondaparinux was simply discontinued because it was felt that the patient was adequately anticoagulated. In two of the subjects, fondaparinux was discontinued on the day that the therapeutic range was reached. They did not meet our definition of successful bridging although they were deemed to be stable and in the therapeutic range one day after fondaparinux discontinuation. Although warfarin was initiated in 8/10 of the historical controls, none were successfully bridged during the study period despite long courses of warfarin overlapping with DTI therapy. Significantly more aPTTs were measured in the DTI treated subjects (Table 5).

Discussion

We report the first prospective, clinical trial of fondaparinux in patients with suspected acute HIT. All of our subjects met our pre-specified criteria for acute HIT when they began treatment with fondaparinux and all experienced a complete platelet count recovery with clinical outcomes that were at least as good as a historical control population treated with a DTI. None of the historical controls or fondaparinux treated subjects developed a new thromboembolic event during treatment or within one month following treatment. However, progression of existing thrombosis leading to amputation may have occurred in one fondaparinux treated subject and one of the historical controls.

The basis for studying fondaparinux in patients with HIT rests upon the well established lack of cross-sensitivity between heparin and fondaparinux in the sera of patients with HIT (8–12). Several case reports have described the use of fondaparinux in patients with acute HIT (20–22). A prospective case series of six patients with a history of HIT who received fondaparinux for thromboprophylaxis showed no adverse events during treatment (23). Kuo et al. administered 7.5 mg fondaparinux daily to five patients with HIT (24). Platelet counts recovered in all patients between days two and nine and no new thromboses reportedly developed. Bradner and colleagues conducted a retrospective review of 20 patients who had a diagnosis of HIT and who received fondaparinux (25). Most patients had received fondaparinux within two weeks of the diagnosis of HIT. No new thromboses occurred during or after fondaparinux use. Furthermore, D'Angelo reported that the anti-PF4-heparin antibody became negative in a patient with HIT treated with fondaparinux over 29 days (27).

Despite the case reports and lack of cross-reactivity *in vitro* between heparin and fondaparinux in the sera of patients with HIT, there are reasons for caution regarding the use of this drug in patients with HIT. It has been demonstrated that fondaparinux is as likely as enoxaparin to generate anti-PF4 heparin antibodies in humans receiving the drug for thromboprophylaxis after orthopedic surgery (12). This suggests that fondaparinux is just as likely to sensitize patients, and therefore place them at risk for HIT if they are subsequently exposed to heparin or LMWH. However, since the antibodies generated in fondaparinux treated subjects reacted *in vitro* to PF4/heparin and PF4/enoxaparin rather than PF4/fondaparinux, it has been postulated that it is unlikely that fondaparinux itself causes HIT. Moreover, the small size and numbers of fondaparinux induced PF4/fondaparinux antibody complexes are believed to be insufficient to cross link platelet Fc receptors *in vitro* thus unlikely to induce platelet activation (28). Since fondaparinux was marketed globally in 2001, only one published case of fondaparinux associated HIT has been reported (29). This suggests that if HIT does occur with fondaparinux, it is extremely rare.

In contrast to previous reports, we prospectively treated patients with suspected acute HIT, most of whom had thromboembolic complications, and compared our results to a population of similar patients who were treated with a DTI. The baseline clinical characteristics between the two groups were similar in terms of platelet count nadir following heparin exposure and baseline thromboembolic complications resulting from HIT. However, fondaparinux-treated subjects began treatment earlier than controls, and more often in the absence of preceding warfarin monotherapy during the acute phase of HIT. In fact, some historical controls had already experienced platelet count recovery when the DTI was initiated, whereas the prospectively treated subjects were still thrombocytopenic upon treatment initiation. It is possible that the apparent delay in recognition and treatment of HIT in the historical controls accounts for the two deaths seen in this group.

It should be mentioned that one of the fondaparinux treated subjects may have had abciximab-induced, rather than heparin-induced thrombocytopenia. It is in fact possible that some of our patients did not have acute HIT, since we did not perform serotonin-release assays to confirm the presence of heparin-dependent platelet-activating antibodies. Furthermore, the heparin-PF4

Table 5: Fondaparinux versus historical control: treatment characteristics.

Treatment	Median days of HIT treatment (range)	Median days of warfarin overlap until HIT treatment discontinued (range)	Mean # aPTTs per patient* (range)	Median # INRs per patient (range)	Median # CBCs per patient (range)	Median # units transfused (range)
Fondaparinux	8 (7–19)	5 (3–8)	1.3 (0–6)	7 (0–7)	9 (8–22)	2 (0–6)
DTI	11 (1–38)	8 (5–16)	21 (2–59)	9 (1–28)	13 (2–50)	0 (0–14)

ELISA optical densities were higher in the historical controls. Published data suggest that HIT patients without thrombosis and OD scores > 1.0 are at a nearly 6-fold increased risk of subsequent thrombosis than those < 1.0 (30). However, it is important to point out that six of our seven prospectively treated subjects did actually develop thrombosis during or after heparin exposure, making their relatively lower OD scores less pertinent. It is known that HIT with thrombosis occurs across a spectrum of OD scores, and that the value of OD scores is largely related to predicting the likelihood of future thrombosis. Unfortunately, we did not "confirm" the presence of heparin-dependent platelet-activating antibodies by serotonin-release assay, a test that could have added further weight to the diagnosis of acute HIT.

An intriguing finding in our study was that venous limb gangrene in the limb affected by a DVT occurred in three of the historical controls, but in none of the fondaparinux treated subjects. A fourth case of limb gangrene also occurred in a historical control with arterial and venous thrombosis as well as a fondaparinux-treated subject who had arterial thrombosis. It has been reported that the DTI-warfarin overlap is a high risk period for warfarin-associated venous limb gangrene (31, 32). This is believed to be related to the failure of warfarin to control thrombin generation early in therapy, when there are decreased levels of the natural anticoagulants protein C and S (33). Thus, patients with HIT must be very carefully transitioned to warfarin after thrombocytopenia has resolved and while maintaining adequate anticoagulation with a DTI (34). Moreover, during DTI-warfarin overlap, the DTI should not be stopped until a minimum five-day overlap period has taken place, the INR is stably in the therapeutic range for at least the last two days of overlap, and the platelet count has recovered to a stable plateau. It is certainly conceivable that because of the long half-life of fondaparinux, more consistent anticoagulation is maintained during this transition than with DTIs. Also, since DTIs commonly prolong the INR, clinicians sometimes prematurely interrupt DTI therapy leading to unopposed warfarin. The possibility that fondaparinux might have an advantage of reduced risk for venous limb gangrene is a hypothesis that should be tested.

One subject (#6) in the fondaparinux group did undergo lower limb amputation after unsuccessful thrombectomy of an acute popliteal artery thrombosis. This subject underwent total knee replacement and received enoxaparin for two weeks, then experienced acute, severe popliteal artery thrombosis requiring thrombectomy. At this time it was noted that her platelet count had declined from 222,000 to 67,000/mm^3, leading to suspicion of HIT and initiation of argatroban for approximately 12 hours. Upon confirmation of heparin antibody positivity, (OD > 3), she was enrolled in the study. She had no manually detectable arterial pulses in her right foot prior to enrollment and until the day of amputation. Her platelet counts increased from 80,000/mm^3 (baseline) to 168,000/mm^3 after three days of fondaparinux. Despite an appropriate platelet count response, she was taken back to surgery due to persistently absent pulses in the affected limb. The surgeon noted "extensive white clot in the distal popliteal artery," some of which was removed. After eight days the limb was deemed to be unsalvageable (insensate, paralyzed, bluish with multiple bullae) and was amputated. Of note, she had received a 2.5 mg dose of warfarin the day after beginning fondaparinux when her platelet count was not completely recovered (118,000/mm^3 K). Early introduction of warfarin in this subject theoretically could have exacerbated the pre-existing ischemic damage leading to the development of gangrenous necrosis and the need for amputation. However, the patient's INR did not increase after this low warfarin dose, and we do not believe that the warfarin contributed to her gangrene.

Because DTIs often cause prolongation of the INR, overlapping with warfarin therapy is more complicated than when overlapping heparin and warfarin. Although warfarin was initiated in 80% of the historical controls and therapy was overlapped for a median duration of eight days, none of the controls had a stable, therapeutic INR when the DTI was discontinued. Fondaparinux was overlapped with warfarin for a median duration of five days, and 33% had a stable, therapeutic INR at the time fondaparinux was discontinued. This suggests that fondaparinux may simplify the process of bridging to warfarin.

There are several reasons why fondaparinux may be an attractive alternative to DTI. These include subcutaneous dosing without the need for aPTT or INR monitoring, simplified transition to warfarin, and significantly lower acquisition cost when compared to DTIs. The current average wholesale price (AWP) for lepirudin and argatroban ranges from $1,093.76 to $1,212.96 per day (35). In contrast, the AWP for fondaparinux is $43.50 to $107.55 per day, depending on the dose.

Danaparoid is an effective alternative to DTIs and shares a number of properties with fondaparinux. However, danaparoid is less selective for factor Xa and is associated with a significant degree of cross-reactivity. While it is no longer available in the U.S., it is licensed for marketing in Canada, Australia, New Zealand and much of Europe. A recent review of clinical outcomes in 1,478 patients treated with danaparoid suggests that outcomes are comparable to those seen with DTIs, particularly when standard treatment doses are used in those with isolated HIT (36). Our study protocol employed a prophylactic dose of fondaparinux in subjects without thrombosis. The subject (subject #3) who received a prophylactic dose was not transitioned to warfarin because she was receiving aspirin and clopidogrel following coronary stent placement. While she did not experience a recurrence of her coronary artery thrombosis, we did not adequately test the hypothesis that a prophylactic dose of fondaparinux may be useful in the prevention of thrombosis in patients with HIT. In view of the experience with danaparoid, we would suggest that full treatment doses be employed even for patients without thrombosis.

Our study is clearly limited by the small number of patients treated and the possibility that some of these patients did not have HIT. However, it should add a measure of confidence that fondaparinux may be safely administered to patients with a history of HIT. More research is needed in order to define the role of fondaparinux in patients with acute HIT. Fortunately, there are several emerging antithrombotics, including oral factor Xa inhibitors and direct thrombin inhibitors, some of which are likely to play an important role in the management of patients with HIT (37).

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