Once-daily fondaparinux monotherapy without warfarin for long-term treatment of venous thromboembolism

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Dear Sir,

Warfarin is usually prescribed for long-term anticoagulation of venous thromboembolism (VTE). However, some patients are unable to tolerate warfarin or to be safely or effectively anticoagulated. These patients are usually managed with once or twice-daily low-molecular-weight heparin (LMWH). Fondaparinux is a synthetic, anti-thrombotic agent with specific anti-factor Xa activity which allows for a simple, weight-based, once daily subcutaneous injections without the need for laboratory monitoring (1). In this pilot study [NCT00413504], we followed patients with deep vein thrombosis (DVT) and/or pulmonary embolism (PE) unable to tolerate or be managed adequately on warfarin to determine the feasibility of fondaparinux monotherapy as a long-term (90 days) option for the treatment of VTE.

Methods

From July 2006 to February 2007, patients more than 18 years old with objectively confirmed DVT or PE who required long-term (at least 90 days) anticoagulation were screened. Patients included in the study had to be unable to take warfarin therapy for one of the following reasons: VTE despite therapeutic anticoagulation with warfarin, bleeding complications due to warfarin, inability to achieve the target international normalized ratio (INR) on warfarin within at least 30 days prior to enrollment, non-bleeding side effects of warfarin such as hair loss, fatigue, or purple toe syndrome, or patients requiring parenteral monotherapy for VTE. Patients were excluded if they were pregnant, had known hypersensitivity to fondaparinux, had renal insufficiency with a creatinine > 1.5 mg/dl, or if anticoagulation was deemed unsafe due to bleeding risk based on the investigator's clinical judgment. The Human Research Committee of Partners HealthCare approved the protocol, and all patients provided written, informed consent.

This was an investigator-initiated, prospective, cohort study. Fondaparinux was provided in prefilled syringes and given subcutaneously once every 24 hours based on the patient's weight: 5 mg for patients < 50 kg, 7.5 mg for patients > 50 kg and < 100 kg, and 10 mg for patients > 100 kg. Laboratory testing for hematocrit, platelet count, renal function, and transaminase levels as well as clinical evaluations were performed at three study visits (day 0, day 45, and day 90).

The primary endpoints were symptomatic recurrent VTE confirmed by venous compression ultrasonography or chest computed tomography (CT) and major hemorrhagic events. Hemorrhagic events were defined as bleeding that caused a decrease in hemoglobin levels of > 2 g/dl, transfusion of > 2 units of packed red blood cells, intracranial hemorrhage, cardiac tamponade, hemorrhage that required major surgical intervention, or death due to bleeding. Secondary endpoints included changes in the values of hematocrit, platelet count, renal function, and transaminase level when comparing days 0, 45, and 90.

Hematocrit, platelets, blood urea nitrogen, creatinine, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were tested for time trends using a general linear model (GLM) procedure. Because multiple comparisons of laboratory

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values were performed, a Bonferroni adjustment [significance level of 0.00083 (0.05/6)] was used to achieve an overall significance of 0.05 (2). Analyses were performed using SAS version 9.1 (SAS Institute; Cary, NC, USA).

Results

Thirty patients were enrolled, and 26 completed the 90-day protocol to receive once-daily fondaparinux monotherapy. Table 1 shows baseline characteristics and the principal reasons for enrollment. All patients self-injected without difficulty and without reported injection site bruising or hematomas. During the 90 days of treatment, there were no symptomatic recurrent VTE events or major bleeding complications.

A minor bleeding complication was noted in one patient, at the 45-day follow-up visit, who developed ecchymotic changes to the lower extremities. The patient was taking concomitant aspirin and non-steroidal antiinflammatory drugs (NSAIDs). After discontinuation of both aspirin and NSAIDs, the ecchymoses resolved.

The deaths of two patients during the study – after review by the patients' primary care physicians and oncologists – were attributed to progression of underlying advanced malignancy. Autopsies, however, were not performed. A third patient withdrew from the study prior to the first injection of fondaparinux. A fourth patient did not return for the final visit but was contacted by phone and reported no recurrent thromboembolic or bleeding complications.

There were no significant differences in hematocrit, platelets, blood urea nitrogen (BUN), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) at day 0, day 45, and day 90, and there were no significant side effects associated with fondaparinux.

Tab. 1: Baseline Characteristics

Baseline characteristics	Fondaparinux monotherapy
Age (years)* ± SD	50.2 ± 13.7
Men [n (%)]	12 (40%)
Weight (kg)* ± SD	84.1 ± 27.2
Principal reason for warfarin intolerance [n (%)]	
Recurrent VTE despite therapeutic INR	13 (43.3%)
Inability to reach target INR**	13 (43.3%)
Parenteral monotherapy due to malignancy	2 (6.7 %)
Parenteral monotherapy for other reason^	1 (3.3%)
Non-bleeding side effect of warfarin[&]	1 (3.3%)
VTE history [n (%)]	
History of recurrent VTE	16 (53.3%)
Patients with DVT	20 (67.7%)
Patients with proximal DVT	18 (90.0%)
Idiopathic VTE	11 (36.7%)
Hypercoagulable state[$]	13 (43.3%)
Transient risk factors for VTE[#]	3 (10%)
Cancer	3 (10%)
Primary endpoints [n (%)]	
Recurrent VTE	0 (0)
Major bleeding complications	0 (0)
Significant differences in secondary endpoints[##]	None

*Mean, **Inability to reach target INR within at least the last 30 days prior to enrollment. ^Parenteral monotherapy per orthopedic surgeon request, [&]Profound fatigue, [$]Antiphospholipid antibody syndrome, factor V Leiden, hyperhomocysteinemia, protein C deficiency, or prothrombin gene mutation. [#]Recent orthopedic surgery, motor vehicle accident, or oral contraceptive use. ##Comparison of hematocrit, platelets, blood urea nitrogen, creatinine, aspartate aminotransferase, and alanine aminotransferase at days 0, 45, and 90 using a general linear model using a Bonferroni adjusted significance level of 0.0083 (0.05/6). DVT = deep vein thrombosis; INR = international normalized ratio; IQR = interquartile range; kg = kilograms, mg = milligrams; PE = pulmonary embolism; SD = standard deviation; VTE = venous thromboembolism.

Discussion

Fondaparinux monotherapy appears to be a feasible option for the long-term treatment of VTE in patients who cannot tolerate warfarin. There were no symptomatic, recurrent VTE events or major bleeding complications and no significant changes in hematological measurements, renal function, or hepatic function over the 90 day study period. Our results raise the possibility of using fondaparinux in patients who have had recurrent VTE despite therapeutic anticoagulation with warfarin, patients with difficult to control INRs, or patients requiring parenteral monotherapy for other reasons.

Parenteral anticoagulant monotherapy without warfarin for long-term treatment of VTE has been previously evaluated. Beckman et al. showed that enoxaparin monotherapy at 1 mg/kg twice daily without oral anticoagulation was as safe and effective as standard therapy with enoxaparin as a "bridge" to warfarin in the treatment of acute symptomatic PE (3). Kucher et al. subsequently showed that enoxaparin monotherapy at 1.5 mg/kg once daily was comparable to standard therapy with warfarin for treating acute PE for a period of 90 days (4). Hull et al. recently compared LMWH (tinzaparin) to vitamin K antagonists in a randomized open label trial for the management of proximal DVT for a three-month period and showed that tinzaparin was non-inferior to vitamin K antagonists (5).

The MATISSE Investigators demonstrated that fondaparinux once daily was non-inferior to enoxaparin twice daily as a "bridge" to warfarin for initial treatment of acute symptomatic DVT and PE (6, 7). The two MATISSE trials led to the FDA approval of fondaparinux in the treatment of acute symptomatic DVT and PE as a "bridge" to warfarin.

A further indication for fondaparinux monotherapy may include anticoagulation in patients with hypercoagulable states who have a high rate of recurrent VTE. Wittkowsky et al. showed that patients with antiphospholipid antibody (APA) syndrome had higher rates of thromboembolic complications and more frequently required emergency department visits and hospital admissions to manage warfarin-related adverse events than non-APA patients (8). Our study included a high percentage of patients with hypercoagulable states (43%) and shows that fondaparinux may be an important option in these difficult to manage patients.

Limitations of our study include the small sample size. The cohort design does not allow for comparisons between treatment groups. The trial was not randomized or blinded. Patient enrollment was at the discretion of the study investigators. This meth-

odology may have introduced bias into the results. Routine follow up scans to investigate clinically silent events were not performed.

Our trial provides a simple, weight-based, once daily regimen with consistent anticoagulant response. It allows home treatment with self-administration for patients with VTE. Until now, no studies have investigated the use of fondaparinux for more than 26 days for the treatment of PE and more than 10 days for the treatment of DVT (9).

Our study suggests that fondaparinux provides a feasible option for patients receiving long-term anticoagulation for prevention of recurrent VTE. The ability to treat patients with one of three weight-based dosing regimens and the once daily dosing give fondaparinux a distinct advantage over LMWH. Fondaparinux is also a potential treatment option in patients who have had recurrent thrombotic events despite therapeutic anticoagulation with warfarin and in patients unable to tolerate or maintain therapeutic warfarin therapy.

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