Received: 13 November 2021 | Revised: 23 May 2022 | Accepted: 19 June 2022

DOI: 10.1002/rth2.12773

rpth research & practice in thrombosis & haemostasis

CASE REPORT

Recurrent thrombosis rescued by fondaparinux in high-risk patients: A case series

Mégane Tanguay MD[1] | Chantal Séguin MD[2]

[1]Department of Medicine, McGill University, Montreal, Quebec, Canada

[2]Division of Hematology, Department of Medicine, McGill University, Montreal, Quebec, Canada

Correspondence
Chantal Séguin, McGill University Health Center, 1001 Décarie Boul, Montreal, QC H4A 3J1, Canada.
Email: chantal.seguin2@mcgill.ca

Handling Editor: Dr Suzanne Cannegieter

Abstract

Background: Recurrent thrombosis treatment options are limited when anticoagulation with dose escalation of low molecular weight heparin or unfractionated heparin fail. Fondaparinux is a pure, synthetic pentasaccharide that consists of heparin's essential five-sugar chain that binds antithrombin to inactivate factor Xa. There is scarce data regarding fondaparinux's use in recurrent thrombosis.

Key Clinical Question: We aim to explore fondaparinux's role in recurrent thrombosis when other standard anticoagulation treatments fail.

Clinical Approach: We report a case series of six high thrombotic risk patients successfully treated with fondaparinux after thrombosis progression while on suprathérapeutic low molecular weight heparin or unfractionated heparin. Of our six patients, two were previously diagnosed with a high-risk thrombophilia: triple positive antiphospholipid syndrome, and homozygous factor V Leiden. The other four had an underlying malignancy.

Conclusion: With fondaparinux, no thrombosis progression was observed, and no bleeding complications occurred.

KEYWORDS
antiphospholipid syndrome, cancer, factor V Leiden, fondaparinux, thrombophilia, thrombosis

Essentials

- Recurrent thrombosis occurring despite anticoagulation is challenging to treat.
- We present six patients with anticoagulant-refractory thrombosis treated with fondaparinux.
- No thrombus progression or bleeding complications occurred with fondaparinux treatment.
- When dose escalation of anticoagulation fails, fondaparinux should be considered.

1 | INTRODUCTION

Fondaparinux is a synthetic analogue composed of heparin's pentasaccharide sequence. Fondaparinux binds to antithrombin with high affinity to induce a conformational change that expedites the neutralization rate of factor Xa. The inhibition of factor Xa prevents thrombin activation, thereby halting clot formation (Figure 1). Compared with heparin that tends to bind to plasma proteins, fondaparinux binds specifically to antithrombin and has complete bioavailability after administration, therefore exerting a predictable

anticoagulation response. The half-life of the molecule is 17 h, which allows for daily dosing. It is excreted, unchanged, by the kidney.[1–3]

Fondaparinux has made its way in clinical practice for deep vein thrombosis (DVT) and pulmonary embolism (PE) treatment, for prophylaxis of thromboembolic events following orthopedic surgery and is part of the therapeutic arsenal for heparin-induced thrombocytopenia (HIT) among other indications.[4–7]

Thrombosis progression occurring despite anticoagulation is challenging to treat. Therapeutic options are limited when dose escalation of low molecular weight heparin (LMWH) or unfractionated heparin (UFH) fail. We aim to explore fondaparinux's potential role in recurrent thrombosis.

2 | CASE SERIES

Six patients received fondaparinux after thrombosis progression at the McGill University Health Center between 2016 and 2021. After ethics approval, their clinical data were retrieved and analyzed. Patients' characteristics are outlined in Table 1. HIT was ruled out in all cases.

2.1 | Case 1

We first present a woman in her 20s, 64 kg, with triple positive antiphospholipid syndrome (APS): positive lupus anticoagulant (Dilute Russell's viper venom time method), anticardiolipin IgG antibodies (>120 U/ml), and beta-2 glycoprotein IgG antibodies (>160 U/ml). She experienced different thrombotic events such as an ischemic toe that prompted warfarin initiation and PE while on warfarin treatment. Her first pregnancy, while on therapeutic dalteparin and aspirin, was complicated by placental abruption at 28 weeks and postpartum hemolysis, elevated liver enzymes, and low platelets syndrome. At the 33rd week of her second pregnancy, she developed a transient ischemic attack while on aspirin and weight-adjusted dalteparin (200 units/kg), prompting a dose increase of 20% (240 units/kg). Her anti-Xa level was within therapeutic range at 0.99 U/mL (expected range, 0.5-1.5). Two days after her elective delivery, the patient developed several cerebral microinfarcts, which resulted in an additional 20% increase of her dalteparin dose (total 40% increase at 280 units/kg). Four days postpartum, she experienced worsening neurological symptoms and was found to have a large mitral valve thrombus (21 × 9 mm) on transesophageal

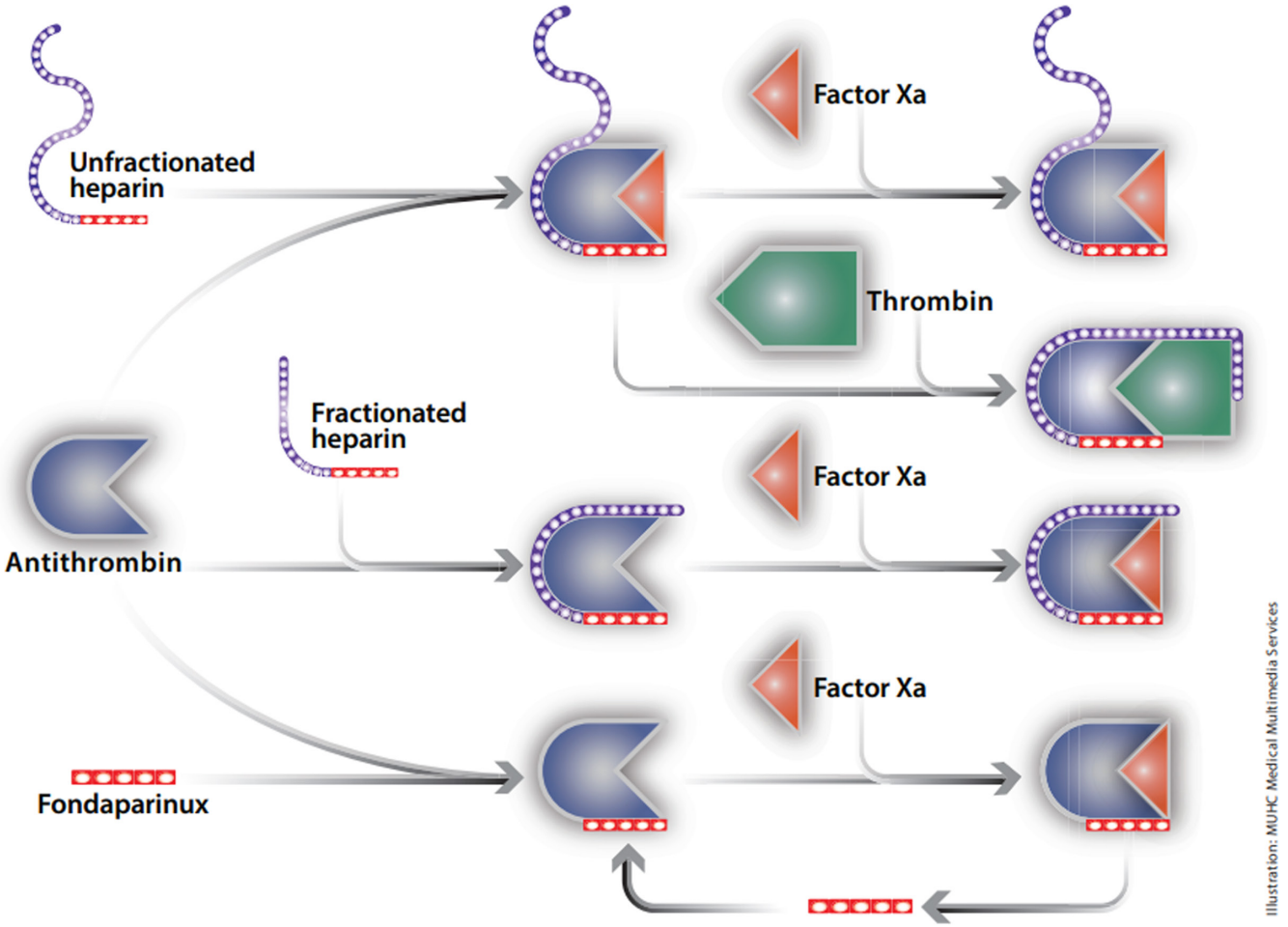

FIGURE 1 Mechanism of action of unfractionated heparin, low molecular weight heparin, and fondaparinux

TABLE 1 Patient characteristics

Patient (sex, age, weight)	High thrombotic risk condition	Thrombotic disease and treatment	Evolution
Case 1 Female, age 20s, weight: 64 kg	Triple positive APS	At 33 weeks of second pregnancy: developed a TIA while on dalteparin (200 units/kg) and aspirin - dalteparin dose increased 20% (240 units/kg) Elective delivery at 36 weeks 2 days postpartum: developed several cerebral microinfarcts - another 20% dalteparin increase (total 40%, 280 units/kg) 4 days pos-partum: found to have a large mitral valve thrombus (21 × 9 mm) and worsening neurological symptoms - fondaparinux 10 mg × 1, then 7.5 mg daily × 25 days (with warfarin bridging)	1 month after fondaparinux initiation: reduction in thrombus size to 3.4 mm, no further embolic events No bleeding events
Case 2 Female, age 30s, weight: 92 kg	Homozygous factor V Leiden and May-Thurner syndrome diagnosed after postpartum DVT: left common iliac vein stent was inserted	In-stent left common iliac vein thrombosis while on therapeutic warfarin (4 months after insertion) - switched to dalteparin 200 units/kg 30 days later: Left leg DVT progression - dalteparin increased 25% (250 units/kg) 7 days later: right common femoral DVT - fondaparinux 10 mg daily × 14 months, followed by warfarin	Duplex 5 months after: patent right leg veins, partial DVT regression on the left No bleeding events
Case 3 Male, age 50s, weight: 65 kg	Testicular metastatic germ cell tumor	Bilateral above-knee DVTs - started on dalteparin 15% above weight-adjusted dose (230 units/kg) 7 months later: acute bilateral above-knee DVTs - fondaparinux 7.5 mg daily × 5 months, followed by apixaban	Duplex 5 months post: bilateral partial recanalization, post-thrombotic changes No bleeding events
Case 4 Male, age 50s, weight: 57 kg	Stage IV pancreatic cancer	Right above-knee DVT – started on dalteparin 200 units/kg 3 weeks later: acute left above-knee DVT - dalteparin increased 30% (260 units/kg) 2 months later: bilateral PEs - fondaparinux 7.5 mg daily × 40 days (then died from cancer)	Duplex 1 month after: partial recanalization of bilateral DVTs No bleeding events
Case 5 Female, age 60s, weight: 63 kg	Hodgkin lymphoma	Catheter-related subclavian DVT - started on UFH (about 40,000 units/24 h for therapeutic PTT) After 3 days of UFH: extension in axillary vein - fondaparinux 7.5 mg daily × 8 months	Duplex 2 months later: partial recanalization No bleeding events
Case 6 Male, age 70s, weight: 75 kg	Multiple myeloma	Right above-knee DVT and PEs – started on dalteparin 200 units/kg 10 months later: spontaneous thigh hematoma requiring transfusion, duplex showed acute right above-knee DVT - IVC filter insertion and anticoagulation stopped 2 weeks later: left above-knee DVT - started on UFH (about 28,000 units/24 h for therapeutic PTT) After 4 days of UFH: worsening bilateral limb-threatening DVTs - fondaparinux 7.5 mg daily × 16 months, followed by apixaban	1 week after: near resolution of D-dimers Duplex 3 months after: bilateral partial recanalization No bleeding events

Abbreviations: APS, antiphospholipid syndrome; DVT, deep vein thrombosis; PE, pulmonary emboli; PTT, partial thromboplastin time; TIA, transient ischemic attack; UFH, unfractionated heparin.

echocardiogram. According to the patient's weight of 64 kg, fondaparinux was initiated with a loading dose of 10 mg because of the extensive thrombosis burden and was pursued at 7.5 mg daily for a total of 25 days with warfarin bridging. The daily recommended therapeutic fondaparinux dose is 10 mg for >100 kg, 7.5 mg for 50 to 100 kg, and 5 mg for <50 kg. One month after fondaparinux initiation, the thrombus size was reduced to 3.4 mm and the valve was thrombus-free at 5 months. There was no recurrence and no bleeding complications during a 2-year follow-up.

2.2 | Case 2

This woman in her 30s, 92 kg, with homozygous factor V Leiden and possible May-Thurner syndrome developed an extensive postpartum proximal DVT requiring a left common iliac vein stent insertion followed by warfarin treatment. Four months after intervention, while on therapeutic warfarin, she developed an intrastent thrombosis and dalteparin 200 units/kg was initiated. Despite anticoagulation, her left DVT showed progression on venous duplex 30 days later, prompting a 25% dalteparin dose increase to 250 units/kg. Seven days later, she developed a right common femoral DVT. Her anticoagulation was changed to fondaparinux 10 mg daily given impressive clot burden and the patient's higher weight. She was kept on fondaparinux 10 mg daily for 14 months before transitioning back to warfarin with higher international normalized ratio target. Her symptoms gradually resolved and a Doppler scan done 5 months after fondaparinux initiation showed patent right leg veins with partial DVT regression on the left. There was no thrombosis recurrence and no bleeding events during a 4-year follow-up.

2.3 | Case 3

This man in his 50s, 65 kg, with metastatic testicular germ cell tumor was diagnosed with bilateral proximal DVTs initially treated with dalteparin 230 units/kg (15% above weight-adjusted dose). Seven months later, he was found to have acute bilateral above-knee DVTs while on anticoagulation. Because he was already on suprathera-peutic LMWH, he was treated with fondaparinux 7.5 mg daily for 5 months. A venous duplex 5 months after fondaparinux initiation showed bilateral partial recanalization with postthrombotic changes; there was no thrombosis recurrence nor bleeding events during a 3-year follow-up.

2.4 | Case 4

This man in his 50s, 57 kg, with stage IV pancreatic cancer undergoing chemotherapy, was diagnosed with a right above-knee DVT, which prompted weight-adjusted 200 units/kg dalteparin initiation. Three weeks later, he developed an acute left above-knee DVT while on anticoagulation. His dalteparin dose was increased by 30% at 260 units/kg. Two months after his dose increase, he developed bilateral PEs. He was then switched to fondaparinux 7.5 mg daily. A venous duplex 1 month after fondaparinux initiation revealed partial recanalization of lower extremities. After 40 days of fondaparinux without thrombosis progression or bleeding complications, the patient died from his cancer.

2.5 | Case 5

This woman in her 60s, 63 kg, with Hodgkin lymphoma undergoing treatment presented with a catheter-related subclavian DVT. She was started on UFH. She required about 40,000 units/24 h to achieve therapeutic partial thromboplastin time. Her left arm edema and pain significantly worsened and, after 3 days of UFH, a venous duplex revealed thrombus extension in the axillary vein. She was switched to fondaparinux 7.5 mg daily. Two months later, a repeat Doppler scan showed partial recanalization of DVT. She was kept on fondaparinux for 8 months without thrombosis recurrence and without bleeding events during a 4-year follow-up.

2.6 | Case 6

This man in his 70s, 75 kg, with multiple myeloma undergoing chemotherapy was treated with dalteparin 200 units/kg for a right proximal lower extremity DVT and PEs. Ten months later, he developed a spontaneous thigh hematoma requiring blood transfusion, and a venous duplex showed an acute right above-knee DVT despite anticoagulation. His anticoagulation was stopped, and an inferior vena cava filter was inserted. Two weeks later, he presented with an extensive left above-knee DVT and he was started on UFH. About 28,000 units/24 h were required to achieve therapeutic partial thromboplastin time. After 4 days of UFH, he had worsening bilateral limb-threatening DVTs. He was switched to fondaparinux 7.5 mg daily for 16 months. One week after fondaparinux initiation, he achieved near resolution of D-dimers and a venous duplex 3 months after showed bilateral partial recanalization. His subsequent Doppler scans showed chronic changes and he remained free of thrombosis recurrence, without bleeding complications, at 4-year follow-up.

3 | DISCUSSION

We have presented six cases in which fondaparinux was effective in treating thrombosis progression without resulting in bleeding complications. Dose escalation of heparin has been suggested to overcome thrombosis progression[8–10]; however, this approach was not sufficient to prevent thrombosis recurrence in our patients. Also, further dose escalation can result in a higher bleeding risk.

Our six patients had an underlying hypercoagulable state, increasing their risk of developing thrombosis. With our first two cases, we highlight the potential role of fondaparinux for patient with refractory thrombosis in the setting of APS and factor V Leiden. Little is known about the use of anticoagulants other than LMWH, UFH, and warfarin for patients with APS, and direct oral anticoagulants (DOACs) are not recommended for triple positive APS patients.[11] To date, only a few case reports support the successful use of fondaparinux in APS with refractory thrombosis other than in the setting of HIT.[12–14] Additionally, homozygous factor V Leiden is a high-risk thrombophilia, and we are not aware of other cases in the literature reporting the use of fondaparinux in refractory thrombosis in this patient population.

We also highlight fondaparinux's potential use in cancer-associated thrombosis refractory to LMWH and UFH. The available literature on the subject appears to be limited.[15,16] We acknowledge that our cases were treated before the widespread use of DOACs in cancer-associated thrombosis. However, LMWH and UFH still remain commonly used in different cancer thrombosis situations such as in high clot burden circumstances, thrombocytopenia, chemotherapy interactions with DOACs, and thrombosis progression occurring on DOACs. When anticoagulation failure occurs on LMWH or UFH, options are limited, and fondaparinux could be considered because it was effective in four of our patients with malignancies.

The pathophysiology explaining fondaparinux's success in our case series remains unclear. UFH has a length of at least 18 saccharide units, required to bridge antithrombin to thrombin. A total of 50% to 75% of LMWH chains are shorter than 18 saccharide units in length, meaning that most cannot bridge antithrombin to thrombin.[17] In contrast, fondaparinux is a small molecule consisting simply of heparin's pentasaccharide. After subcutaneous injection, fondaparinux has a bioavailability of 100%. The pentasaccharide binds with high affinity to antithrombin and enhances its anti-Xa activity by 300-fold. Because of its specificity to antithrombin, fondaparinux does not bind to thrombin or other nontarget plasma proteins, which potentially results in a more predictable anticoagulation effect. Once the antithrombin molecules are saturated, additional fondaparinux will not exert more anticoagulation effect.[2,18]

In conclusion, fondaparinux was a limb-saving and possibly life-saving option when other standard methods of anticoagulation failed in six patients. Our findings may provide clinicians facing a clinical dilemma with a potentially safe treatment option. Larger studies are needed to validate our findings.

RELATIONSHIP DISCLOSURE

The authors declare that they have no conflicts of interest.

AUTHOR CONTIBUTIONS

C. Séguin found the patients of interest and was responsible for the critical revision of the manuscript. M. Tanguay retrieved the patient's data and wrote the manuscript. Both authors reviewed the literature, revised, and accepted the final manuscript.

ORCID

Mégane Tanguay https://orcid.org/0000-0001-9498-0609
Chantal Séguin https://orcid.org/0000-0003-2865-3671

REFERENCES

1. Nutescu EA, Burnett A, Fanikos J, Spinler S, Wittkowsky A. Erratum to: pharmacology of anticoagulants used in the treatment of venous thromboembolism. *J Thromb Thrombolysis*. 2016;42(2):296-311.
2. Samama M-M, Gerotziafas GT. Evaluation of the pharmacological properties and clinical results of the synthetic pentasaccharide (fondaparinux). *Thromb Res*. 2003;109(1):1-11.
3. Zhang Y, Zhang M, Tan L, Pan N, Zhang L. The clinical use of fondaparinux: a synthetic heparin pentasaccharide. *Prog Mol Biol Transl Sci*. 2019;163:41-53.
4. Büller HR, Davidson BL, Decousus H, et al. Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. *Ann Intern Med*. 2004;140(11):867-873.
5. Büller HR, Davidson BL, Decousus H, et al. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. *N Engl J Med*. 2003;349(18):1695-1702.
6. Turpie AGG, Bauer KA, Eriksson BI, Lassen MR, Steering Committees of the Pentasaccharide Orthopedic Prophylaxix Studies. Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery: a meta-analysis of 4 randomized double-blind studies. *Arch Intern Med*. 2002;162(16):1833-1840.
7. Warkentin TE. HIT paradigms and paradoxes. *J Thromb Haemost*. 2011;9(Suppl 1):105-117.
8. Carrier M, Le Gal G, Cho R, Tierney S, Rodger M, Lee AY. Dose escalation of low molecular weight heparin to manage recurrent venous thromboembolic events despite systemic anticoagulation in cancer patients. *J Thromb Haemost*. 2009;7(5):760-765.
9. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest*. 2016;149(2):315-352.
10. Lyman GH, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2013;31(17):2189-2204.
11. Pengo V, Denas G, Zoppellaro G, et al. Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. *Blood*. 2018;132(13):1365-1371.
12. Baron BW, Baron JM. Four-year follow-up of two patients on maintenance therapy with fondaparinux and mycophenolate mofetil for microthrombotic antiphospholipid syndrome. *Lupus*. 2019;28(8):1003-1006.
13. Sayar Z, Burke S, Cohen H. The use of fondaparinux for recurrent thrombotic events [abstract]. *Res Pract Thromb Haemost*. 2020;4(suppl 1):Abstract PB2410.
14. Hussain H, Tarantino MD, McCrae KR, Chaturvedi S, Roberts JC. Eculizumab for refractory thrombosis in antiphospholipid syndrome. *Blood*. 2020;136(Suppl 1):10-11.
15. Ramasubbaiah R, Kiel PJ, Mehta R, Greist A, Jones KL. Fondaparinux for the treatment of recurrent venous thromboembolism during low molecular weight heparin therapy: a retrospective case series. *Blood*. 2009;114(22):4179.

16. Dush AD, Ray L, Li Q, Yucebay F, Kraut EH. Management of recurrent venous thromboembolism in patients with cancer. *J Thromb Thrombolysis*. 2013;35(3):415.
17. Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2, Supplement):e24S-e43S.
18. DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. McGraw-Hill; 2005.

How to cite this article: Tanguay M, Séguin C. Recurrent thrombosis rescued by fondaparinux in high-risk patients: A case series. *Res Pract Thromb Haemost*. 2022;6:e12773. doi: 10.1002/rth2.12773