Can rivaroxaban be a drug of choice for treating heparin-induced thrombocytopenia in a patient with pulmonary thromboembolism?

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Introduction

Heparin-induced thrombocytopenia (HIT) is an adverse effect of heparin therapy (1). There are two types of HIT: non-immunomediated (HIT-I) and immunomediated (HIT-II) disorders. HIT-II is characterized by the formation of IgG antibodies against the heparin-PLT factor 4 complex (PF4) (1, 2). Bounded with heparin, this factor creates a neoantigen and stimulates the production of antibodies (2). Activated PLTs, along with the heparin/PF4 antibody complex attached to their surface, undergo aggregation and premature removal from the circulation, leading to thrombocytopenia and additionally to a procoagulant state with high potential for thrombus formation and thromboembolic events (3). The incidence of HIT-II is 0.1%–1% in low-molecular-weight heparins (LMWH) and 3%–5% in un-fractionated heparin (UHF)-treated patients (3). In HIT-II, the PLT count drop can be seen 3–4 days after exposure in patients with pre-existing heparin-PF4 antibodies from a previous exposure to heparin, whereas in those exposed for the first time, the PLT count drops 5–10 days after heparin administration (3). It has been confirmed that new oral anticoagulants (NOACs) offer advantages regarding this side effect (4), and this case report aims to share our first positive experience in relation to the previously mentioned.

Case Report

A 35-year-old patient presented with shortness of breath and tachycardia that had worsened in the last 4 days following phlegmon treatment on the left leg. Besides immobility, obesity was a significant risk factor (body mass index, 32.4 kg/m²). ECG revealed sinus tachycardia, right axis deviation, and an S_{1}Q_{3}T_{3} pattern typical of pulmonary thromboembolism (PTE) (Fig. 1). He was hospitalized and suspicion of PTE was confirmed using D-dimer test (8700 ng/mL), color Doppler ultrasound (non-obstructive thrombus in the left femoral superficial vein), echocardiography [large thrombus in the right atrium (RA), dilated right ventricle (RV) with reduced systolic function, McConnell’s sign, tricuspid regurgitation, and dilated truncus pulmonary (TP)], and computed tomography (CT) [RV/LV ratio, >1; thrombi in RA; saddle thrombus in TP; and subocclusive thrombi in the main pulmonary arteries] (Fig. 2). Anticoagulant therapy with
UFH was initiated. During the follow-up hemograms and hemo-
stasis, although the therapeutic UFH effect was confirmed by
prothrombin and activated partial thromboplastin times, which
were within the therapeutic range, a significant drop in the PLT
count was observed ([initial 278x10^9 L to 11x10^9 L] on day five.
Suspicion of HIT was confirmed with increased heparin-PF4
antibodies [positive ELISA test (reactivity, >40% and heparin in-
hibition, >50%)]. A very low PLT count, accompanied with epi-
staxis and hemoptysis, was an indication for PLT concentrate
transfusion. UFH was replaced with LMWH. After an initial rise
of the PLT count (108x10^9 L), a significant drop (>50% [52x10^9
L]) was again observed after 5 days. At that point rivaroxaban
was initiated (15 mg twice daily). Rivaroxaban led to a progres-
sive rise in the PLT count (262x10^9 L), which remained stable,
simultaneously with a significant thrombotic material resolu-
tion, leading to normalization of RV function seen at 2-weeks’
ehocardiography control and on CT scans performed after 10
days and 1 month (RV/LV ratio, <1; lysis of the thrombi in RA;
saddle thrombus; and the one in the left PA) (Fig. 2, Video 1).

Discussion

This case draws attention to the importance of close follow-
up of patients receiving heparin therapy in order to recognize the
ey early signs of HIT. Diagnosis is typically made on clinical grounds,
with laboratory tests playing a supportive role (significant PLT
drop, ≥50% of the baseline value or <150x10^9/L) (2). Four T’s have
been recommended for clinical use: thrombocytopenia, timing of
PLT count drop, thrombosis and other sequelae, and other non-
evident causes of thrombocytopenia (5, 6). Treatment should be
initiated as soon as HIT diagnosis is suspected. Exposure to all
forms of heparin should be discontinued, and according to the
current guidelines, alternative anticoagulants such as the di-
rect thrombin inhibitors (DTIs) lepirudin, bivalirudin, argatroban,
fondaparinux, and danaparoid should be initiated (6). DTIs do not
react with HIT antibodies but are associated with a higher bleed-
ing risk and are available only in parenteral forms, making them
unsuitable for outpatient treatment. Vitamin K antagonists do
not interact with HIT antibodies but can cause venous limb gan-
grene and skin necrosis during the hypercoagulable stage of HIT
and are difficult to maintain within their therapeutic range (4).
Rivaroxaban, as all NOACs, might be a potential candidate for HIT
treatment because of the direct antithrombin/anti FXa activity as
opposed to heparins, a feature that makes NOACs particularly
suitable in patients with HIT (7, 8). A study by Walenga confirms
that rivaroxaban does not cause PLT activation or aggregation
with any of the HIT antibodies (7).

Conclusion

Rivaroxaban appears to be effective in the treatment of HIT
patients. This conclusion applies to all NOACs, although specific
guidelines on their use in HIT treatment—an underdiagnosed
complication of heparin treatment—are still unavailable.

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