Rivaroxaban Treatment for Left Ventricular Thrombus

Jayesh Changela and Maria Anwar

INTRODUCTION

Rivaroxaban, a direct oral anticoagulant (DOAC), is a factor Xa inhibitor indicated for treatment and prevention of deep vein thrombosis and pulmonary embolism, as well as for prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.[1] No large randomized controlled trials have been performed to formally study the use of rivaroxaban for treatment of left ventricular (LV) thrombus, and there is limited information available about the efficacy and safety of any DOAC for managing LV clots. Currently, the recommended pharmacological treatment for LV thrombus in patients who have experienced transient ischemic attacks (TIAs) or stroke is vitamin K antagonist therapy.[2] We report a case in which rivaroxaban was prescribed for LV thrombus in a patient with heart failure secondary to systemic lupus erythematosus and history of TIA.

CASE REPORT

A 40-year-old patient presented to the emergency department on October 8, 2014, with dysarthria lasting 2 min and left-sided facial numbness lasting 1 h; the diagnosis was TIA.* The medical history was significant for remote alcohol abuse (> 15 years previous) and systemic lupus erythematosus, diagnosed 3 years previous. Pre-admission medications for the latter diagnosis included prednisone, hydroxychloroquine, azathioprine, and methotrexate. The patient was an active smoker, but did not have hypertension, dyslipidemia, or a family history of premature coronary artery disease.

*Informed consent could not be obtained from the patient or family. Potentially identifying details not pertinent to the patient's diagnosis and treatment course have been omitted from this report.

The patient had experienced a similar TIA episode 1 month before (on day –35, in relation to the date of index presentation to the emergency department), presenting with dysarthria, left-arm weakness, and facial paralysis lasting 5 min. Magnetic resonance imaging (MRI) of the brain at that time revealed punctate watershed infarcts in the right frontal lobe; acetylsalicylic acid (ASA) 81 mg daily was initiated. Transthoracic echocardiography was performed 3 weeks later (on day –14) to investigate the possibility of cardioembolic stroke. The imaging showed moderate to severe eccentric LV hypertrophy and systolic dysfunction, with 31% LV ejection fraction and LV apical dyskinesia, which together suggested the presence of an LV thrombus. The patient was subsequently referred to a cardiologist, and anticoagulation therapy, consisting of warfarin overlapped with low-molecular-weight heparin (LMWH), was recommended. However, the patient did not wish to receive injections or to undertake regular testing of international normalized ratio and therefore declined this therapy.

The risks of forgoing the recommended therapy, including the increased risk of further embolic events, were explained by the cardiologist, with support from a cardiology pharmacist. The patient continued to decline the preferred treatment option, so non-indicated options for treating LV thrombosis were considered. The patient appeared to understand the information provided about these options and elected to proceed with off-label use of rivaroxaban 15 mg twice daily for 21 days, followed by 20 mg daily, with the therapy starting on day –10. Repeat transthoracic echocardiography was planned for 3 months after initiation of rivaroxaban, to allow reassessment of the need for continuing therapy on the basis of LV function and resolution of the LV thrombus.

At the time of this case (in 2014), evidence regarding the use of any DOAC for treatment of LV thrombus was very limited,

and there was no compelling evidence favouring one DOAC over another. The patient had no prior history of major bleeding, and the hemoglobin level and platelet count were within normal ranges. Given the availability of provincial drug benefit coverage for DOAC therapy and the absence of evidence for any specific DOAC in this setting, rivaroxaban was chosen. The dosing strategy selected was similar to what would be used for treatment of deep vein thrombosis with the goal of mimicking, to the extent possible, the most comparable indication-specific dosing available. Cardiac MRI performed 4 days after the start of rivaroxaban therapy (on day –6) confirmed the presence of the LV thrombus; repeat outpatient imaging was planned for 3–6 months later, to check for thrombus resolution.

Less than a week later, and 1 day before a planned hospital admission for renal biopsy, the patient presented to the emergency department (day 0 of this case report) with new TIA symptoms. The biopsy had been scheduled on short notice to investigate ongoing microscopic hematuria and possible lupus nephritis. At the time of this presentation, ASA had been held since day –6 and rivaroxaban since day –1, as part of the plan for periprocedural management, to minimize the risk of bleeding during the biopsy (such that ASA and rivaroxaban would be held for a total of 7 days and 48 h, respectively, before the biopsy, which was planned for day +1). Computed tomography angiography of the head and neck, performed on day 0, ruled out intracranial hemorrhage. It was suspected that the TIA was secondary to emboli from the previously documented LV thrombus, so treatment with heparin by IV infusion was initiated, and all other antithrombotic medications remained on hold. The planned renal biopsy was postponed to day +2, but on that date, while awaiting the procedure, the patient experienced worsening left-arm weakness and speech difficulties. Repeat MRI of the brain revealed new acute right hemispheric infarcts. The left renal biopsy was performed anyway (on day +2), with the heparin infusion held just before the procedure. The partial thromboplastin time was 29.8 s at the time of the procedure, which indicated that the anticoagulant effects of IV heparin were no longer present. Upon consultation, the hematology service speculated that the TIA symptoms were likely hemodynamically related; as a result, the patient's antihypertensive medications were held. The following day (day +3), the treatment-dose heparin infusion was resumed, and clopidogrel was started with a 300-mg loading dose, followed by 75 mg daily.

The patient's hospital stay was further complicated by progressively worsening abdominal pain, as well as decreases in blood pressure, respiratory rate, and responsiveness. The patient's hemoglobin decreased progressively, from 133 g/L at the time of the biopsy (on day +2) to 79 g/L (on day +6). The patient was eventually intubated and transferred to the intensive care unit, where cardiac arrest occurred (on day +6). Ultimately, resuscitation was unsuccessful, and the final autopsy report declared retroperitoneal hemorrhage, accounting for about 2000 mL of clotted blood, as the cause of death.

DISCUSSION

The usual treatment for LV thrombus in patients with TIA who have normal sinus rhythm is anticoagulant therapy with a vitamin K antagonist for 3 months or longer.[2,3] In patients with TIA complicated by LV thrombosis and LV ejection fraction less than 40%, and in the setting of myocardial infarction, treatment with LMWH, dabigatran, rivaroxaban, or apixaban for 3 months may be considered as an alternative to vitamin K antagonist therapy for prevention of recurrent stroke or TIA.[2]

Since the original presentation to the emergency department of the patient described in this case report (in late 2014), new literature has emerged regarding the use of DOAC for treatment of LV thrombus. In a recent review, Ghaffarpasand and others[4] identified 31 cases in which rivaroxaban was used to treat intracardiac thrombi, 16 of which were LV thrombi. The dosing regimens varied and included 10 mg daily (1 patient), 10 mg twice daily (1 patient), 15 mg daily (5 patients), 15 mg twice daily (1 patient), 20 mg daily (6 patients), and a combination of 15 mg twice daily followed by 20 mg daily (2 patients). The duration of anticoagulation ranged from 7 to 436 days. In 15 of the patients with LV thrombi, echocardiography after completion of anticoagulation treatment showed that the thrombus had resolved; 1 patient was lost to follow-up. None of the 15 patients with follow-up experienced a thromboembolic event; however, bleeding events were not reported.

Determining the ideal rivaroxaban dosage and duration of treatment is difficult, given the large variation in regimens described in the review by Ghaffarpasand and others.[4] For the patient described here, MRI of the left ventricle showed no resolution of the thrombus after 4 days of treatment with rivaroxaban 15 mg twice daily, and no repeat imaging was done (because the patient died). Whether extended therapy might have resulted in dissolution of the thrombus is difficult to determine; however, the information compiled by Ghaffarpasand and others[4] indicates that longer therapy is likely required to achieve this outcome, given that patients whose thrombi resolved generally had longer treatment duration.

According to the bleeding risk stratification based on type of operation presented in the guidelines of the American College of Chest Physicians,[5] renal biopsy is considered to pose a high risk of bleeding. Thrombosis Canada recommends that rivaroxaban should be held for at least 2 days before a major procedure, such as a renal biopsy.[6] In the case reported here, the patient's rivaroxaban therapy conformed with the Thrombosis Canada recommendation and with guidelines of the American Heart Association[7] and thus appeared to be appropriately managed to minimize the risk of bleeding in association with the renal biopsy. The last dose of rivaroxaban was taken on October 7, about 72 h before the biopsy was done (on day +2). Given the patient's estimated creatinine clearance at the time (109 mL/min, as calculated by the Cockcroft–Gault equation) and the half-life of

rivaroxaban in non-elderly patients (reported as 7–11 h[1]), a period of more than 5 drug half-lives had passed between the patient's last dose and the biopsy, and adequate clearance of rivaroxaban would therefore have been expected. In addition, given that the patient's partial thromboplastin time was normal at the time of biopsy (29.8 s), it can be concluded that the anticoagulant effects of heparin therapy had also worn off.

The contribution of the pharmacodynamic interaction between ASA and rivaroxaban to bleeding outcomes in this patient is difficult to quantify. The patient had most recently received rivaroxaban 24 h before and ASA 6 days before presentation to the emergency department. Thus, we assumed that 75%–87.5% of the rivaroxaban had been eliminated (with passage of 2–3 drug half-lives) and that for most platelets, inhibition of aggregation was unaffected by ASA (given that the normal lifespan of a platelet is 8–9 days).[8] Both the American Heart Association[7] and Thrombosis Canada[9] recommend holding ASA before a major procedure unless the patient has high cardiovascular risk, in which case the cardiovascular risk must be weighed against the risk of bleeding and the continuation of ASA may be appropriate. There are no explicit guidelines for the perioperative management of antiplatelet agents in patients with increased cerebrovascular risk. However, the guidelines of the American College of Chest Physicians suggest that in patients with moderate to high risk of a cardiovascular event, ASA should be continued around the time of the procedure.[5]

In the patient described here, the comparative risk of cerebrovascular attack and risk of bleeding was not documented. Detailed consult service notes were not available, as the hospital patient chart was unobtainable, which is a limitation of our report. The patient's course was further complicated by recurrent TIAs 2 days after admission. Whether continuing ASA in the lead-up to renal biopsy would have prevented these ischemic attacks is unknown. Other confounders included the administration of therapeutic heparin and clopidogrel for the management of recurrent TIA starting 1 day after the renal biopsy, which likely increased the risk of bleeding.

The complexity of this case warrants further examination. Specifically, should clinicians be more hesitant to apply therapies for off-label use in patients with complex comorbidities? What other patient- and drug-specific factors may play a role in adverse events? Balancing a patient's preferences with evidence-based practice can lead to challenging clinical conundrums. In this case, patient preference was the defining determinant for the use of off-label therapy. However, when considering the use of any medication for off-label indications, patient preferences, potential risks, and anticipated benefits must be carefully weighed, and any decisions must be made on a case-by-case basis. We propose the following framework, based on our clinical experiences, to help clinicians determine the appropriateness of off-label use of DOACs for LV thrombus:

1) Identify preferred therapeutic alternatives with more robust evidence for treatment of LV thrombus.
2) Identify the patient's preference in favour of or against these preferred alternatives.
3) If considering off-label anticoagulation therapy for treatment of LV thrombus, identify patient-specific risks of bleeding.
4) Determine whether the patient is taking other medications that might increase the risk of bleeding.
5) Discuss with the patient the advantages, disadvantages, and unknowns associated with off-label use of anticoagulants.

CONCLUSION

We have described a patient with presumed LV thrombus who preferred not to use warfarin bridged with LMWH injections and was treated instead with rivaroxaban 15 mg twice daily. The LV thrombus was confirmed by imaging 4 days after initiation of rivaroxaban. Renal biopsy to investigate other symptoms was performed several days later, despite the presence of multiple complicating factors (including additional medications known to increase the risk of bleeding); the patient experienced fatal bleeding shortly afterward. Because of the patient's complicated course, no imaging was done beyond the fourth day of rivaroxaban therapy, and it is therefore unclear whether the prolonged therapy had any effect on dissolution of the thrombus. Given the lack of robust evidence for the use of rivaroxaban to manage LV thrombus, vitamin K antagonists continue to be the therapy of choice. The efficacy and appropriate dosing strategy for off-label use of rivaroxaban in the treatment of LV thrombus are unknown, and this off-label use may increase the risk of bleeding. Further studies are warranted to confirm the efficacy and safety of rivaroxaban in this specific patient population.

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Jayesh Changela, BSP, ACPR, is a Clinical Pharmacist with Royal University Hospital, Saskatchewan Health Authority, Saskatoon, Saskatchewan.

Maria Anwar, BScPharm, ACPR, is Pharmacy Clinical Practice Leader, South Health Campus, Alberta Health Services, Calgary, Alberta.

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Address correspondence to:
Maria Anwar
Alberta Health Services, South Health Campus
4448 Front Street SE
Calgary AB T3M 1M4

e-mail: maria.anwar@ahs.ca

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