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CASE REPORT

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Dosing considerations in the use of the direct oral anticoagulants in the antiphospholipid syndrome

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Summary

What is known and objectives: At least four prospective trials have been initiated investigating the direct oral anticoagulants in the antiphospholipid syndrome. Preliminary reports have supported their use in patients with a history of venous thrombosis and a target INR of 2-3, but there have also been reports of failure of these agents in the antiphospholipid syndrome. The objective is to present a case report that illustrates there may be important dosing issues when considering the use of these agents in patients with the antiphospholipid syndrome.

Case summary: A 50-year-old woman with the antiphospholipid syndrome, manifesting clinically with recurrent pyoderma gangrenosum-like leg ulcers, was treated with apixaban, resulting in improved ulcer healing. For insurance purposes, she was switched to rivaroxaban with worsening of the ulcers which again improved when apixaban was resumed.

What is new and conclusion: Despite a similar half-life, pharmacokinetics and pharmacodynamics, the manufacturer-recommended maintenance dosing of apixaban is twice daily and rivaroxaban once daily. We believe this difference in recommended dose accounts for the differential clinical response noted in the present case report and that twice daily dosing and a larger daily dose of these agents may be more efficacious in potent hypercoagulable disorders, such as the antiphospholipid syndrome.

KEYWORDS
anticoagulation, clinical pharmacokinetics

1 | WHAT IS KNOWN AND OBJECTIVE

The antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterized by the persistent presence of antiphospholipid antibodies and an increased risk of arterial, venous and small vessel thrombosis. Many APS patients are treated with long-term anticoagulation and the approval of the direct oral anticoagulants (DOACs) – which have several advantages over older agents – has been of interest to those who treat APS. At least four prospective trials have been initiated worldwide investigating these agents in different APS populations, and preliminary reports have supported their use in APS patients with a history of venous thrombosis and a target INR of 2-3.[1,2] However, there have also been reports of failure of these agents in APS resulting in some hesitation in their use.[3,4] We present a case report and discussion proposing that there may be important dosing issues related to the use of DOACs in potent hypercoagulable disorders such as APS.

2 | CASE SUMMARY

A 50-year-old woman with a six-year history of recurrent episodes of bilateral pyoderma gangrenosum-like leg ulcers tested persistently positive for several antiphospholipid antibodies (aPL) after biopsy of one of the ulcers revealed evidence for microthrombus formation with associated tissue necrosis. Anticardiolipin IgM and beta 2 glycoprotein I IgM antibodies were present in moderate titre on three occasions over the 6 months following the abnormal skin biopsy. She also

tested positive for antiphosphatidylserine–prothrombin IgM and antiphosphatidylserine IgG antibodies. Thus, she met the 2006 revised Sapporo criteria for a diagnosis of definite antiphospholipid syndrome (APS) due to persistent aPL positivity and documented microthrombosis. Of interest, APS has been shown to be the most frequent cause for a misdiagnosis of pyoderma gangrenosum.[5]

The patient had been treated with cyclosporine and prednisone previously without ulcer healing, and the addition of aspirin provided no benefit. Given positive aPL, she was given a trial of apixaban at a dose of 5 mg twice daily and within 3 weeks, she noted progressive ulcer healing. In addition, she quickly noted that her long-standing daily headaches began to decrease in frequency and severity, and by 3 weeks, they had almost completely resolved. Improvement or even resolution of headaches, memory loss and other symptoms has previously been reported in patients with aPL treated with anticoagulation,[6,7] suggesting these symptoms may occur by a microthrombotic mechanism in this context.[8,9]

Due to a change in insurance status, the patient was changed from apixaban 5 mg twice daily to rivaroxaban 20 mg daily. Within 1-2 days of this therapeutic change, her headaches began to increase in frequency and severity, and within one week of the change, her ulcers began to worsen. She was switched back to apixaban at the previous dose with rapid improvement in ulcer healing and resolution of her migraines.

The DOACs apixaban and rivaroxaban act similarly to heparin by inhibiting activated factor X. Of note, both heparin and the DOACs have been demonstrated to inhibit complement activation, which may be important in APS. Heparin has been used effectively for many years in APS patients, including those that have failed warfarin, and the similar mechanism of action of the oral factor Xa inhibitors predicts they might also be efficacious in patients with APS.

Apixaban and rivaroxaban are both metabolized primarily by cytochrome P450 3A4 enzymes, have the same limited drug interactions and have predictable pharmacokinetics that do not require routine monitoring. Both agents have been approved for stroke prevention in non-valvular atrial fibrillation, VTE prophylaxis, and for the treatment of acute venous thromboembolism (VTE). Although higher doses are used for the first 1-3 weeks of acute VTE therapy, the manufacturer-recommended maintenance dose for rivaroxaban is 20 mg once daily and for apixaban is 5 mg twice daily (with an option for 2.5 mg twice daily for extended therapy after the first 6 months). Apixaban is thought to be less reliant on renal function for its routine metabolism and may be preferred over rivaroxaban in patients with renal insufficiency, but these agents are generally otherwise considered comparable.

Rivaroxaban is attractive for its once daily dosing. However, it should be noted that the half-life of apixaban and rivaroxaban is similar (approximately 8 hours), they have similar pharmacokinetics and their pharmacodynamic effects correlate closely with their plasma concentration.[10,11] Thus, the different dosing recommendations for these agents do not appear to have been based on pharmacological differences. Human dosing trials of apixaban and rivaroxaban have found that once daily dosing of these agents results in a significantly higher peak level and a significantly lower trough level as expected.[10,11] The difference in the dosing curves between once and twice daily apixaban is similar to that seen with the low molecular weight heparin agent enoxaparin dosed once versus twice daily. It was previously demonstrated by the Enoxaparin Clinical Trial Group that the VTE recurrence rate for the once daily dosing of enoxaparin was double that seen with the twice daily dosing in the subset of patients with cancer-associated thrombosis.[12] This finding was not surprising given the prolonged trough period seen with once daily dosing and the potent nature of malignancy-associated thrombosis. There was no report of aPL status in this study, but like cancer-associated thrombosis, APS is widely recognized to be a particularly potent hypercoagulable disorder and many providers choose to dose enoxaparin twice daily in APS patients as for cancer patients. A similar concern has been raised recently for the DOACs by Moore who suggested that the high, early peaks of rivaroxaban dosed once daily could increase the risk of bleeding and the low troughs could result in inadequate anticoagulation.[13]

Although as noted, there are several case reports in the literature of rivaroxaban failure in APS patients when administered at the recommended maintenance dose of 20 mg once daily, we are not aware of any reports of apixaban failure in APS, although rivaroxaban was first to market and has presumably been used more than apixaban. The present case report as well as the cited pharmacologic data and experience with enoxaparin suggests that these reported failures may have been due to the once daily dosing recommendation for rivaroxaban rather than a failure of the drug class *per se*.

3 | WHAT IS NEW AND CONCLUSION

For now, warfarin and low molecular weight heparin remain the first-line anticoagulants in patients with APS, but DOACs may be considered due to warfarin failure, severely labile INR, patient preference or other reason. The present case report illustrates the importance of understanding dosing issues when considering the use of DOACs in patients with APS. It also supports the emerging trend in tailoring the use of DOACs to the individual patient, taking into account bleeding and clotting history and risk, patient compliance, comorbidities and other factors.[14] For the heterogeneous disease APS, this might include extended therapy with low-dose apixaban (2.5 mg twice daily) in a patient with a low thrombotic risk antibody profile who had a provoked deep vein thrombosis; on the other hand, the long-term use of the doses recommended during the first weeks of an acute venous thromboembolism (rivaroxaban 15 mg twice daily or apixaban 10 mg twice daily) might be more appropriate in an APS patient with recurrent venous thrombosis, arterial events, those requiring an INR >3 when treated with warfarin, those with a high-risk antibody profile and/or those with comorbidities that increase thrombotic risk. These issues should also be considered when interpreting the ongoing trials of these agents in APS, as most are using rivaroxaban dosed once daily and the ASTRO-APS trial began with low-dose apixaban (2.5 mg twice daily) for all patients, including those with a history of arterial thrombosis.[15]

CONFLICTS OF INTEREST

The authors have no affiliations with or financial interest in any company or organization that could conflict with the views expressed in this manuscript.

REFERENCES

1. Sciascia A, Lopez-Pedrera C, Cecchi I, Pecoraro I, Roccatello D, Cuadrado MJ. Non-vitamin K antagonist oral anticoagulants and antiphospholipid syndrome. *Rheum*. 2016;55:1726-1735.
2. Cohen H, Hunt BJ, Efthymiou M, et al., RAPS trial investigators. Rivaroxaban versus warfarin to treat patients with thrombotic antiphospholipid syndrome, with or without systemic lupus erythematosus (RAPS): a randomised, controlled, open-label, phase 2/3, non-inferiority trial. *Lancet Haematol* 2016;3:e426-e436.
3. Signorelli F, Nogueira F, Domingues V, Mariz HA, Levy RA. Thrombotic events in patients with antiphospholipid syndrome treated with rivaroxaban: a series of eight cases. *Clin Rheumatol*. 2016;35:801-805.
4. Win K, Rodgers GM. New oral anticoagulants may not be effective to prevent venous thromboembolism in patients with antiphospholipid syndrome. *Am J Hematol*. 2014;89:1017.
5. Weenig RH, Davis MDP, Dahl PR, Su D. Skin ulcers misdiagnosed as pyoderma gangrenosum. *N Engl J Med*. 2002;347:1412-1418.
6. Asherson R, Gaimpaulo D, Singh S, Sulman L. Dramatic response of severe headaches to anticoagulation in a patient with antiphospholipid syndrome. *J Clin Rheumatol*. 2007;13:173-174.
7. Hughes GRV, Cuadrado MJ, Khamastha MA, Sanna G. Headache and memory loss: rapid response to heparin in the antiphospholipid syndrome. *Lupus*. 2001;10:778.
8. Hughes GRV. Heparin, antiphospholipid antibodies and the brain. *Lupus*. 2012;21:1039-1040.
9. Ziporen L, Polak-Charcon S, Korczyn DA, et al. Neurological dysfunction associated with antiphospholipid syndrome: histopathological brain findings of thrombotic changes in a mouse model. *Clin Dev Immunol*. 2004;11:67-75.
10. Frost C, Song Y, Barrett YC, et al. A randomized direct comparison of the pharmacokinetics and pharmacodynamics of apixaban and rivaroxaban. *Clin Pharmacol*. 2014;6:179-187.
11. Frost C, Nepal S, Wang J, et al. Safety, pharmacokinetics and pharmacodynamics of multiple oral doses of apixaban, a factor Xa inhibitor, in healthy subjects. *Br J Clin Pharmacol*. 2013;76:776-786.
12. Merli G, Spiro TE, Olsson C, et al. Subcutaneous enoxaparin once or twice daily compared with intravenous unfractionated heparin for treatment of venous thromboembolic disease. *Ann Intern Med*. 2001;134:191-202.
13. Moore TJ. Optimal dosing of rivaroxaban is undefined. *BMJ*. 2016;355:i5549.
14. Raschi R, Bianchin M, De Ponti R, De Ponti F, Ageno F. Emerging therapeutic uses of direct-acting oral anticoagulants: an evidence-based perspective. *Pharmacol Res*. 2017;120:206-218.
15. Woller SC, Stevens SM, Kaplan DA, et al. Apixaban for the Secondary Prevention of Thrombosis Among Patients with Antiphospholipid Syndrome: Study Rationale and Design (ASTRO-APS). *Clin Appl Thromb Hemost*. 2016 Apr;22:239-247.

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