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Rivaroxaban – a safe therapeutic option in patients with antiphospholipid syndrome? Our experience in 23 cases

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Abstract

In the therapeutic approach to patients with antiphospholipid syndrome (APS) with thrombotic manifestations, oral vitamin K antagonists (VKA) remain the standard of care. However, the use of VKA is very often associated with inability to achieve a therapeutic dose even in patients maintaining nutritional and therapeutic restrictions. The non-vitamin-K oral anticoagulants (NOAC) have a lot of advantages, but their efficacy and safety in APS have not been proven. We present 23 patients with APS treated with rivaroxaban in our department. Recurrence of thrombosis was observed only in 1 patient. No major or minor bleeding occurred. It proves the efficacy of treatment with rivaroxaban, but our observations require further prospective, randomized studies.

Key words: antiphospholipid syndrome, rivaroxaban, warfarin, thrombosis.

Introduction

The antiphospholipid syndrome (APS) is an autoimmune disorder characterized by venous and arterial thrombosis and/or recurrent fetal losses in the persistent presence of antiphospholipid antibodies (aPL) [1]. Antiphospholipid antibodies presence can be confirmed as persistent when anticardiolipin (aCL) or anti-β_2 glycoprotein I (aβ_2GPI) antibodies of IgM or IgG class or lupus anticoagulant (LA) are detected twice in an interval of 12 weeks.

The current standard of care in APS with thrombotic events is warfarin. This allows one to avoid future recurrences of thrombotic and/or obstetric complications [2]. The anticoagulant effect needs to be monitored on the basis of the international normalized ratio (INR) and remain within the therapeutic range. In some APS patients INR is labile due to variable responses of prothrombin time reagents in the presence of lupus anticoagulant [1]. Non-vitamin-K oral anticoagulants (NOAC) are deprived of this interaction. Thus NOAC can become an important alternative to warfarin in the routine care of patients with APS. At the moment no clinical data from randomized clinical trials confirming the efficacy and safety of NOAC exist.

Case series

Twenty-three patients with diagnosed APS receiving rivaroxaban (non-vitamin-K oral anticoagulant) between September 2013 and February 2016 were observed in our department for the presence of thrombotic recurrence or bleeding events. All patients were women – 17 with primary APS, and 6 with accompanying systemic lupus erythematosus (SLE). All patients fulfilled the classification criteria from Sydney for APS before starting the therapy. Introduction of rivaroxaban was preceded by taking patients' history, clinical examination, laboratory testing and confirmation of the APS diagnosis. All patients were treated with hydroxychloroquine. Reasons for rivaroxaban introduction were: INR lability/therapeutic simplification (n = 7), patient's choice (n = 8), recurrent thrombosis (n = 6) and pulmonary embolism (n = 2).

Twenty patients had been previously treated with VKA, while for the others it was the first anticoagulant. In the previous history arterial thrombotic events occurred in 8 patients, only venous in 9 and both in 5 patients. The risk of thrombosis according to aPL status was variable – 4 patients had a triple positive, 8 a double positive, and 11 a single positive aPL profile. One pa-

Table I. Characteristics of patients

	SLE	Arterial thrombosis	Venous thrombosis	aCL	LAC	aβ$_2$GPI
1						
2						
3						
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SLE – systemic lupus erythematosus, aCL – anticardiolipin antibodies, LAC – lupus anticoagulant, aβ_2GPI – anti-β_2-glycoprotein I antibodies

**The patient at the time of diagnosis had fulfilled the classification criteria for APS from Sydney, although at the screening before treatment with rivaroxaban the patient was aPL negative.*

tient did not reveal aPL during the study, although the diagnosis was made on high level positive anticardiolipin antibodies with splenic vein thrombosis. Patients' characteristics including diagnosis, type of thrombosis and aPL profile are presented in Table 1. None of the patients suffered from inherited thrombophilia, or renal or liver insufficiency. Patients reported regular rivaroxaban intake during follow-up. After a median follow-up of 20 months, one relapse of arterial thrombosis was reported (pulmonary embolism) – the therapy was discontinued in this patient and enoxaparin 1 mg/kg was introduced [2–20]. No major or minor bleeding occurred.

Discussion

The current standard of care after a thrombotic event is a bridge therapy for at least five days with unfractionated or low molecular weight heparin followed by long-term anticoagulation with a VKA such as warfarin, with the recommended INR target of 2.5. In APS patients with previous thrombotic events anticoagulation must be continuous, but its intensity is still being debated [2, 3].

Narrow therapeutic range, slow onset/offset of action, variable response and numerous interactions with food, drugs and alcohol are the main disadvantages of VKA treatment. It requires frequent INR monitoring and strict patient adherence [2, 3]. Due to the variable response of thromboplastin reagents to LA (and also to other aPL, although smaller), the anticoagulation effect may be difficult to estimate [3]. It is possible that in up to 10% of APS patients INR testing may produce falsely elevated results [4]. This can cause another problem – instability of the INR, requiring frequent anticoagulant monitoring with the attendant inconvenience to the patient and the costs.

The NOAC are a relatively new group of drugs. Prospective and randomized controlled trials of NOAC for

thromboembolism treatment have shown their efficacy and safety [5–7]. It is probable that among patients included in the phase III clinical trials of rivaroxaban versus VKA in patients with venous thromboembolism (VTE), 9.5% have aPL [8]. The efficacy of NOAC in APS patients was not reported specifically – at the moment 2 randomized clinical trials (RAPS and TRAPS) are underway [9, 10], and some brief reports are promising [11–13]. However, some investigators have already proposed using NOAC in APS patients [14].

The 14th International Congress on Antiphospholipid Antibodies Task Force (ICAATF) recommended that warfarin remain the mainstay in treatment of APS and newer oral direct inhibitors should be considered only when there is a known allergy/intolerance or poor control with warfarin due to lack of adequate data [15]. Other strategies include increasing the target therapeutic INR range, the addition of low-dose aspirin, or substitution of oral VKA by subcutaneous therapeutic dose low molecular weight heparin (LMWH) [16].

A fixed dose with predictable anticoagulant effect, no interactions with dietary constituents or alcohol, few reported drug interactions that affect anticoagulant intensity, and finally no need of monitoring anticoagulant intensity are the advantages of NOAC. The therapeutic dose in clinical trials of NOAC versus warfarin have used warfarin at a target INR of 2.5 (i.e. range 2.0–3.0) as the comparator [7]. Meanwhile it should be stated that the optimal intensity of anticoagulation in APS patients with recurrent thrombosis and those with arterial thrombosis is not established, although a target INR of > 3.0 was proposed by a number of experts [17].

Any anticoagulation is a risk factor for bleeding. According to the phase III clinical trials such as the ROCKET-AF (rivaroxaban) trial, the risk of major bleeding complications with rivaroxaban at a therapeutic dose are slightly lower compared to warfarin. But unfortunately it is not an easy choice for non-compliant patients, because the half lives of NOAC are in the range of 5–17 hours for the various new agents versus 40 hours for warfarin, which might increase the thrombotic risk in case of poor adherence to treatment. Moreover, in pregnancy and lactation periods VKA or NOAC cannot be prescribed. VKA are contraindicated during organogenesis, while for NOAC no data are currently available in this field.

So far, all the data on NOAC in APS have brought inconsistent results. Schafer et al. [16], Signorelli et al. [13], and Win and Rogers [18] reported failure of treatment with NOAC. All patients in these series can be counted as high-risk (recurrent thrombosis, arterial thrombosis, triple antibody positivity). In contrast, Sciascia et al. [12] reported in a series of 35 patients with previous VTE and poor anticoagulant control with VKA successful treatment with rivaroxaban. However, in this group patients with previous arterial thrombosis were excluded.

The study of Noel et al. [19] – the most similar to our observations – included 26 patients with various indications for NOAC. In this case series, as in our group, thrombosis recurrence was observed in only one patient. The prevalence and therapeutic approaches to APS without the classic (included in the criteria) antibodies or otherwise known as the "seronegative" form of APS require a separate discussion. However, it exceeds the scope of this report [20].

Summary

NOAC as an off-label indication can be considered in patients with APS and in our opinion can become a rational alternative in the therapeutic approach, in the light of the observation that thrombosis still occurs in 5% to 20% of APS patients despite adequate use of VKA [13]. Hopefully the results of randomized, prospective studies will soon evaluate the efficacy and safety profile of NOAC.

The authors declare no conflict of interest.

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