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-β2-glycoprotein I (anti-β2GPI) 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-
The patient 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.

**Table I. Characteristics of patients**

|     | SLE | Arterial thrombosis | Venous thrombosis | aCL | LAC | αβ2GPI |
|-----|-----|----------------------|--------------------|-----|-----|--------|
| 1   |     |                      |                    |     |     |        |
| 2   |     |                      |                    |     |     |        |
| 3   |     |                      |                    |     |     |        |
| 4*  |     |                      |                    |     |     |        |
| 5   |     |                      |                    |     |     |        |
| 6   |     |                      |                    |     |     |        |
| 7   |     |                      |                    |     |     |        |
| 8   |     |                      |                    |     |     |        |
| 9   |     |                      |                    |     |     |        |
| 10  |     |                      |                    |     |     |        |
| 11  |     |                      |                    |     |     |        |
| 12  |     |                      |                    |     |     |        |
| 13  |     |                      |                    |     |     |        |
| 14  |     |                      |                    |     |     |        |
| 15  |     |                      |                    |     |     |        |
| 16  |     |                      |                    |     |     |        |
| 17  |     |                      |                    |     |     |        |
| 18  |     |                      |                    |     |     |        |
| 19  |     |                      |                    |     |     |        |
| 20  |     |                      |                    |     |     |        |
| 21  |     |                      |                    |     |     |        |
| 22  |     |                      |                    |     |     |        |
| 23  |     |                      |                    |     |     |        |

SLE – systemic lupus erythematosus, aCL – anticardiolipin antibodies, LAC – lupus anticoagulant, αβ2GPI – anti-β2-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.

**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 (VTE), 9.5% have aPL [8]. The efficacy of NOAC in APS versus VKA in patients with venous thromboembolism included in the phase III clinical trials of rivaroxaban and safety [5–7]. It is probable that among patients treatment have shown their efficacy – according to the phase III clinical trials such as the ROCK-ET-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.

**References**

1. Della Valle P, Crippa L, Safa O, et al. Potential failure of the International Normalized Ratio (INR) system in the monitoring of oral anticoagulation in patients with lupus anticoagulants. Ann Med Interne 1996; 147 (Suppl. 1): 10-14.
2. Chighizola CB, Moia M, Meroni PL. New oral anticoagulants in thrombotic antiphospholipid syndrome. Lupus 2014; 23: 1279-1282.
3. Erkan D, Aguiar Cl, Andrade D, et al. 14th International Congress on Antiphospholipid Antibodies: task force report on antiphospholipid syndrome treatment trends. Autoimmun Rev 2014; 13: 685-696.
4. Cohen H, Machin SJ. Antithrombotic treatment failures in antiphospholipid syndrome: the new anticoagulants? Lupus 2010; 19: 486-491.
5. Signorelli F, Nogueira F, Domingues V, et al. Thrombotic events in patients with antiphospholipid syndrome treated with rivaroxaban: a series of eight cases. Clin Rheumatol 2016; 35: 801-805.
6. Bauersachs R, Berkowitz SD, Brenner B, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010; 363: 2499-2510.
7. The EINSTEIN-PE Investigators. Bülker HR, Prins MH, Lensin AW, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012; 366: 1287-1297.
8. Connolly SJ, Ezekowitz MD, Yusuf S, et al. RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361: 1139-1151.
9. Pengo V, Banzato A, Bison E, et al. Efficacy and safety of rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome: Rationale and design of the Trial on Rivaroxaban in AntiPhospholipid Syndrome (TRAPS) trial. Lupus 2016; 25: 301-306.
10. Cohen H, Doré CJ, Clawson S, et al.; RAPS Trial Protocol Collaborators. Rivaroxaban in antiphospholipid syndrome (RAPS) protocol: a prospective, randomized controlled phase II/III clinical trial of rivaroxaban versus warfarin in patients with thrombotic antiphospholipid syndrome, with or without SLE. Lupus 2015; 24: 1087-1094.
11. Son M, Wypasek E, Celinska-Lowenhoff M, Undas A. The use of rivaroxaban in patients with antiphospholipid syndrome: A series of 12 cases. Thromb Res 2015; 135: 1035-1036.
12. Sciascia S, Breen K, Hunt BJ. Rivaroxaban use in patients with antiphospholipid syndrome and previous venous thromboembolism. Blood Coagul Fibrinolysis 2015; 26: 476-477. Erratum in: Blood Coagul Fibrinolysis 2015; 26: 597.
13. Signorelli F, Nogueira F, Domingues V, et al. Thrombotic events in patients with antiphospholipid syndrome treated with rivaroxaban: a series of eight cases. Clin Rheumatol 2016; 35: 801-805.
14. Agnelli G, Becattini C, Franco L. New oral anticoagulants for the treatment of venous thromboembolism. Best Pract Res Clin Haematol 2013; 26: 151-161.
15. Erkan D, Aguilar CL, Andrade D, et al. 14th international congress antiphospholipid antibodies task force report on antiphospholipid syndrome treatment trends. Autoimmun Rev 2014; 13: 685-696.
16. Schaefer JK, McBane RD, Black DF, et al. Failure of dabigatran and rivaroxaban to prevent thromboembolism in antiphospholipid syndrome: a case series of three patients. Thromb Haemost 2014; 112: 947-950.
17. Ruiz-Irastorza G, Crowther M, Branch W, Khamashta MA. Antiphospholipid syndrome. Lancet 2010; 376: 1498-1509.
18. 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.
19. Noel N, Dutasta F, Costedoat-Chalumeau N, et al. Safety and efficacy of oral direct inhibitors of thrombin and factor Xa in antiphospholipid syndrome. Autoimmun Rev 2015; 14: 680-685.
20. Peterson LK, Willis R, Harris EN, et al. Antibodies to Phosphatidylerine/Prothrombin Complex in Antiphospholipid Syndrome: Analytical and Clinical Perspectives. Adv Clin Chem 2016; 73: 1-28.