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Failure of rivaroxaban to prevent thrombosis in four patients with anti-phospholipid syndrome

Rheumatology key message

- Rivaroxaban does not seem to be efficient and safe in all APS patients.

Sir, APS is an acquired autoimmune disorder characterized by the association of vascular thrombosis or pregnancy morbidity and the presence of persistent aPL [1]. Current management of thrombosis in APS is based on long-term vitamin K antagonists (VKAs) to prevent recurrences. Recently, direct oral anticoagulants have been shown to be non-inferior to VKAs for the secondary prevention of venous thromboembolism [2]. Small case series have indicated either a good safety and efficacy profile or thrombosis recurrence in APS patients on rivaroxaban [3, 4]. Here we report four new cases of recurrent thrombosis in APS patients treated with rivaroxaban.

The first patient was a 33-year-old man who presented with unprovoked superficial vein thrombosis of the right great saphenous vein who was treated with a therapeutic dose of s.c. low molecular weight heparin over 3 weeks and then switched to rivaroxaban 20 mg/day. A few days after the switch, he experienced dyspnoea leading to the diagnosis of pulmonary embolism. Laboratory testing revealed a high-risk aPL profile (triple positivity [5]: the presence of LA, aCL and anti-β_2-glycoprotein I antibodies). The patient improved after switching rivaroxaban to heparin and a VKA. One year later the patient was asymptomatic.

The second patient was a 21-year-old female diagnosed with SLE-associated APS based on skin involvement, arthritis, deep vein thrombosis (DVT) and triple aPL positivity. She was treated with acenocoumarol before switching to rivaroxaban for patient preference. Three months later she developed a lupus flare together with purpuric and necrotic skin lesions on the upper and lower limbs. The lupus flare was diagnosed based on arthritis associated with thrombocytopenia, antinuclear and dsDNA antibodies and decreased complement. A skin biopsy confirmed small vessel thromboses without any lupus vasculitis. Clinical and laboratory abnormalities disappeared rapidly after the introduction of low molecular weight heparin, aspirin, HCQ and i.v. pulse steroids. Thereafter, heparin was bridged to warfarin and there was no thrombotic recurrence for the next 2 years.

The third patient was a 26-year-old man diagnosed with a primary thrombotic APS (recurrent unprovoked distal DVT with triple positivity) treated with rivaroxaban. Nine months later, despite the anticoagulant treatment, an unprovoked bilateral proximal pulmonary embolism was diagnosed without DVT. However the patient confirmed suboptimal compliance to anticoagulant treatment with rivaroxaban.

The last case was a 58-year-old female diagnosed with SLE-associated APS (history of venous, arterial and small vessel thrombosis before the diagnosis of APS and triple positivity). Rivaroxaban was started in October 2015 for a second DVT of her right leg. Rivaroxaban was then stopped and warfarin was initiated because of the worsening of skin lesions 3 months after starting rivaroxaban. The patient did not experience any further thrombotic recurrence after 5 months.

Recently, Cohen *et al.* [6] reported the impact of rivaroxaban on thrombin generation in APS patients [Rivaroxaban in Anti-phospholipid Syndrome (RAPS) study]. APS patients included were at low risk, with at least one venous thrombosis during no or subtherapeutic anticoagulant therapy. Indeed, patients with previous arterial thrombosis or recurrent venous thromboembolism (VTE) while on a therapeutic dose of warfarin were not included. Overall, patients treated with rivaroxaban had a significant 2-fold increased thrombin potential, suggesting a higher thrombotic risk, compared with warfarin users. However, the authors concluded that rivaroxaban was a safe alternative to warfarin in APS patients since no clinical event occurred during the follow-up (210 days).

Our case reports illustrate four cases of rivaroxaban failure for preventing secondary thrombosis in APS patients (Table 1). In accordance with the RAPS study, our patients had a previous VTE. Only one had a history of arterial and small vessel thrombosis as well, which is considered a higher risk for thrombosis. Furthermore, all patients in this report have a high-risk aPL profile (triple positivity). In the RAPS study, a lower frequency of persistent triple-positive patients was included (12% in the rivaroxaban group). Differences in the patients' characteristics in terms of history of arterial thrombosis or aPL profile may have produced a higher rate of thrombosis recurrence in our patients.

The third case illustrates the drawback of the absence of biological monitoring, which does not allow an objective compliance assessment. Long-term VKA can be difficult for some patients, because the treatment requires repeated monitoring, but this can also be an advantage in APS patients. Thanks to their long half-life, the risk of thrombotic recurrence in case of a missed treatment dose may be lower than in patients on rivaroxaban, which has a shorter half-life, especially in patients with a high thrombotic risk [5].

In conclusion, rivaroxaban does not seem to be efficient and safe in all APS patients, especially those with a history of arterial thrombosis or triple positivity [7]. Therefore, it is urgent to perform randomized controlled trials to clarify in which subgroups rivaroxaban is a safe alternative to warfarin [8].

TABLE 1 Baseline characteristics of personal case series and RAPS study

Characteristics	Personal case series (*n* = 4)	RAPS study (*n* = 57)
Age, mean (S.D.), years	34.5 (16.4)	47 (17)
Gender, *n*/*N* (%)		
Women	2/4 (50)	42/57 (74)
Male	2/4 (50)	15/57 (26)
Number of criteria for definite APS, mean (S.D.)	1.5 (1)	NR
History of clinical manifestations, *n*/*N* (%)		
Venous thrombosis	4/4 (100)	57/57 (100)
Arterial thrombosis	1/4 (25)	0/57 (0)
Small vessel thrombosis	1/4 (25)	NR
Obstetrical morbidity	0/4 (0)	NR
aPL profile, *n*/*N* (%)		
Double positivity	0/4 (0)	16/57 (28)
Triple positivity[a]	4/4 (100)	7/57 (12)
Underlying autoimmune disease, *n*/*N* (%)		
Primary APS	2/4 (50)	NR
Associated APS	2/4 (50)	NR
SLE	2/4 (50)	11/57 (19)

[a]Triple positivity: LA and aCL antibodies and anti-β_2-GPI antibodies. *N*: total number of patients in the study; *n*: patients fulfilling the characteristic; NR: not reported.

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Virginie Dufrost[1], Jessie Risse[1,2], Stéphane Kirchner[3], Stéphane Zuily[1,2] and Denis Wahl[1,2]

[1]*CHRU de Nancy, Vascular Medicine Division and Regional Competence Center for Rare Vascular and Systemic Autoimmune Diseases,* [2]*Inserm UMR_S 1116 School of Medicine, Lorraine University and* [3]*Department of Pathology, Pathology Center Emile Gallé, Nancy, France*
Revised version accepted 1 March 2017
Correspondence to: Denis Wahl, CHRU de Nancy, Service de Médecine Vasculaire et Centre de Compétence Régional des Maladies Rares Vasculaires, Systémiques et Auto-Immunes, Institut Lorrain du cœur et des vaisseaux Louis-Mathieu, rue du Morvan, 54511 Vandoeuvre-Lès-Nancy Cedex, France.
E-mail: d.wahl@chru-nancy.fr

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Comment on: Increased inflammation and disease activity among current cigarette smokers with rheumatoid arthritis: a cross-sectional analysis of US veterans

SIR, I read the study by Sokolove and colleagues [1] with interest. The authors demonstrated both increased disease activity measured by Disease Activity Score 28