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Superior efficacy of warfarin based anticoagulation in the treatment of antiphospholipid syndrome

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Abstract

APS is an autoimmune disorder characterized by recurrent venous or arterial thrombosis in the presence of aPL autoantibodies. The treatment of APS has been a very challenging issue due to recurrent thrombotic episodes despite seemingly optimum anticoagulation. The mainstay of treatment in such patients has been oral anticoagulation with VKA usually in the form of warfarin. Recently DOACs are also being considered in this regard. However, there are no uniformly agreed management guidelines for the choice of anticoagulant. Here we present a case of APS in a young male who developed extensive pulmonary emboli as well as evidence of TMA while taking rivaroxaban.

Keywords

Antiphospholipid syndrome; Venous thromboembolism; Triple positivity; Rivaroxaban; Warfarin.

Abbreviations

APS: Antiphospholipid syndrome; aPL: antiphospholipid; VKA: Vitamin K antagonists; DOACs: Direct oral anticoagulants; TMA: Thrombotic microangiopathy; VTE: Venous thromboembolism; PA: Pulmonary artery; RVSP: Right ventricular systolic pressure; PVR: Pulmonary vascular resistance; TOE: Transesophageal echocardiography; RAPS: Rivaroxaban in Antiphospholipid Syndrome; ETP: Endogenous thrombin potential; TRAPS: Trial for Rivaroxaban in Antiphospholipid Syndrome; MHRA: Medicines and Healthcare products Regulatory Agency; ASTRO-APS: Apixaban for secondary prevention of thromboembolism among patients with antiphospholipid syndrome; LA: Lupus anticoagulant; EULAR: European League Against Rheumatism; ESC: European Society of Cardiology.

Introduction

APS is an autoimmune disease characterized by recurrent thromboembolic phenomena and pregnancy loss in the presence of aPL antibodies. Although the prevalence of the aPL antibodies in the

general population ranges between 1-5%, only a minority of such individuals develop the disease [1]. The antigenic targets are generally thought to be phospholipid-binding cofactor proteins. It is not clearly known as to how aPL antibodies arise in patients with this syndrome. It is believed that genetic factors might play a role although there is not a direct transmission from parent to offspring [2]. There are also reports of its association with viral infections such as HCV, HIV-1, CMV, VZV and EBV [3]. This has led to the hypothesis that infections may trigger the production of aPL antibodies in certain predisposed individuals. However, the exact cause of this susceptibility in such cases is not yet known. These antibodies are generally transient and disappear within 2-3 months but in sometimes, they might persist lifelong.

APS is a significant cause of morbidity and mortality. The principle of its management mainly focuses on diminishing the hypercoagulable state in addition to minimizing the potential risks associated with the anticoagulation therapy. The current therapeutic recommendation is lifelong anticoagulation therapy that is to be initiated after the first APS related thrombotic event which is usually with a VKA such as warfarin. DOACs which are direct inhibitors of factor Xa have also been tried mitigating the need for the ongoing monitoring and dose modifications as with VKA usage. However, there is lack of conclusive evidence to establish whether they are equally effective as VKA in the treatment and secondary prevention of thrombosis in these high-risk patients.

Case Presentation

A 34 year old male patient presented with a history of ongoing shortness of breath following an inpatient episode where he was being treated for atypical pneumonia. CT thorax was undertaken which revealed bilateral filling defects in the lower lobe pulmonary arterial branches consistent with pulmonary emboli. Echocardiogram at this point showed no evidence of pulmonary hypertension. Warfarin therapy was commenced immediately and discontinued after 6 months.

Approximately 2 years later, he was admitted again due to shortness of breath together with severe pain and swelling of his left calf. USG Doppler revealed an acute thrombus in the popliteal vein extending into the femoral vein. He was immediately commenced on rivaroxaban 15 mg BD for 21 days followed by 20 mg OD lifelong thereafter due to recurrent VTE. Thrombophilia testing of the patient however was not undertaken at this time.

On continued follow up over approximately 15 months, the patient complained of progressive dyspnea on exertion. He was therefore referred for investigation of possible pulmonary hypertension and was found to be at WHO Functional class 3 with worsening fatigue and breathlessness on limited exertion. Investigations revealed echocardiogram showing moderate pulmonary hypertension with RVSP estimated at 60 mm Hg and at right heart catheterization there was severe pulmonary hypertension with a mean PA pressure 60 mm Hg but preserved cardiac output giving a PVR of 970 dynes/sec/cm^{-5}. His VQ scan revealed multiple unmatched perfusion defects and CT angiography confirmed multiple stenoses. A diagnosis of chronic thromboembolic pulmonary hypertension was made. As a consequence, he was referred and underwent pulmonary endarterectomy from which he made a good recovery with improved exercise tolerance. He continued on rivaroxaban during this period of time.

A few months later he was referred to the nephrology department in view of his deteriorating kidney function and development of proteinuria (Figures 1,2,3). Clinical assessment revealed presence of livedo reticularis that had affected his lower limbs and a non-healing ulcer over his right lateral aspect of lower shin. USG KUB was unremarkable. In view of this gentleman's past medical history and clinical findings, a full renal immunology screen was requested in addition to routine hematology/biochemistry. The test results were as follows.

Tests	Test values	Normal values
IgG anti-β-2 glycoprotein I antibodies	37.6	0-6 U/mL
IgG anti-cardiolipin antibodies	65	<10 GPL-U/mL
IgM anti-β-2 glycoprotein I antibodies	4.1	0-6 U/mL
IgM anti-cardiolipin antibodies	4.2	0-7 MPL U/mL
Anti-ds DNA antibodies	<15	0-15 IU/mL
C3	1.35	0.68-1.80 g/L
C4	0.21	0.18-0.60 g/L
APTT	89.6	25-36.5 sec
PT	16.1	9.4-12.5 sec
Fibrinogen	5.1	2-3.9 g/L

LA could not be tested due to ongoing anticoagulation by rivaroxaban. TOE showed myxomatous mitral valve prolapse thought to be secondary to Libman Sacks vegetations. Based on clinical history, examination and investigations a diagnosis of primary APS was made. The likely renal diagnosis was of secondary focal segmental glomerulosclerosis secondary to TMA. Renal biopsy was not undertaken due to potential risks around anticoagulation need. Rivaroxaban was changed to warfarin based lifelong anticoagulation with a target INR of 2.5-3.5.

Following his change to warfarin based anticoagulation, his renal function has improved as has his level of proteinuria together (Figures 1,2,3) with the healing of his skin ulcer. His blood pressure is better controlled and he has commented that his breathing has subjectively much improved. Follow up TOE at 3 months showed some improvement in the size of the myxomatous changes of the mitral valve.

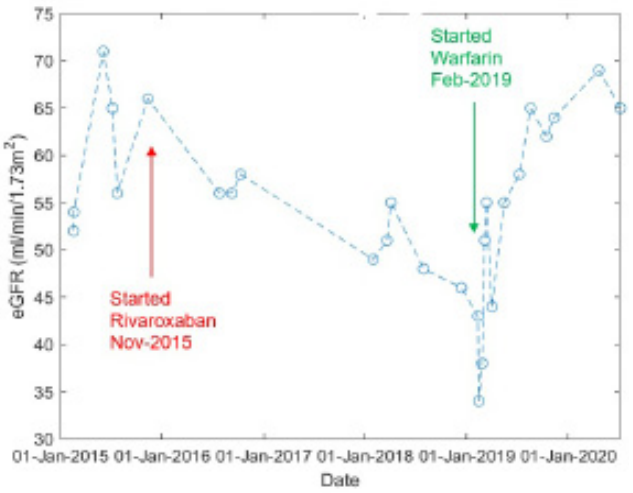

Figure 1: Variation of eGFR over Yime

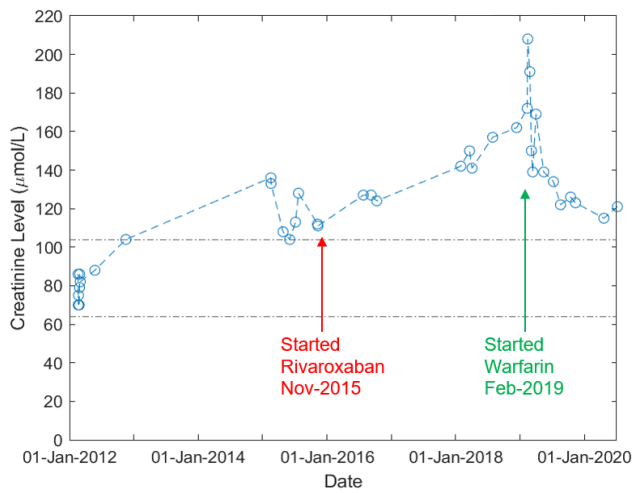

Figure 2: Variation of Creatinine Level over Yime.

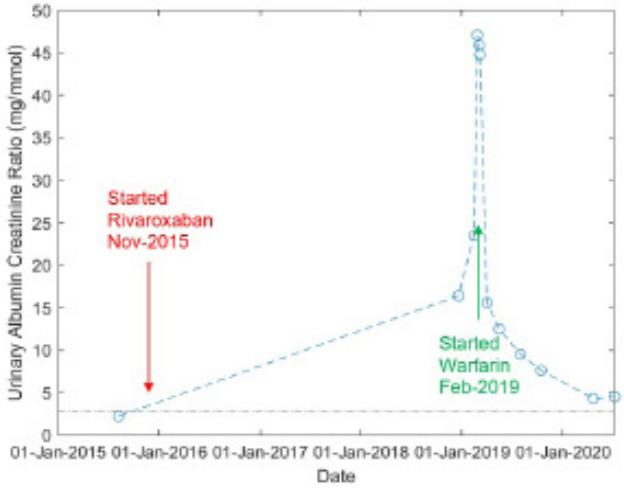

Figure 3: Variation of Urinary Albumin Creatinine Ratio over Time.

Discussion

The management of aPL positive patients should be individualized based on the patient's clinical manifestations and additional comorbidities, if present. Anticoagulant therapy is the mainstay of treatment for thrombotic APS and due to the high risk for thrombosis progression and recurrence, indefinite anticoagulation is often considered. The standard choice has been low molecular weight heparin followed by a VKA such as warfarin. However, this often presents as a challenge when it comes to ongoing monitoring and dose adjustment. VKAs have numerous interactions with other drugs both prescribed and over the counter as well as interactions with foodstuffs/alcohol and requires frequent laboratory monitoring to achieve a therapeutic INR to prevent further VTE. Apart from this, the LA can also interfere with the INR values that can result in inadequate anticoagulation. Hence to overcome these issues, DOACs have emerged as an alternative and attractive treatment modality which are considered equally efficacious and do not require frequent monitoring. However, concerns have been raised regarding the efficacy of DOACs in the treatment of APS.

There have been two previous randomized trials that have compared the treatment of warfarin with rivaroxaban for the prevention of thrombosis in patients diagnosed with APS [4,5]. Firstly RAPS trial was a prospective randomized, controlled phase II/III clinical trial of rivaroxaban versus warfarin that was carried out in two hospitals of the UK in patients with thrombotic APS, both primary and secondary. It included 116 patients who had experienced a previous episode of VTE and were already taking warfarin to maintain a target INR of 2.5 (range 2-3). Of these, six patients did not contribute any data for the primary outcome. Therefore, the primary analysis population included 110 patients (54 in the rivaroxaban group and 56 in the warfarin group). The patients were randomly selected 1:1 to continue with warfarin or receive 20 mg oral rivaroxaban daily. The primary outcome was measured as percentage change in ETP from randomization to day 42 together with other surrogate markers of thrombotic risk. The findings suggested that the overall thrombotic risk had not increased with rivaroxaban compared to that of warfarin. This study was however of short duration and used surrogate markers to assess the thrombotic risk. TRAPS trial was another investigator-sponsored, randomized, open-label, phase III, multicentre study conducted in 14

centers across Italy. Here the outcomes of rivaroxaban were compared with warfarin in patients with APS, a history of thrombosis and who persistently tested positive for all the three aPL antibodies (LA, anticardiolipin and anti-beta-2 glycoprotein-1 antibodies). The trial was stopped prematurely due to an excess of thrombotic events in the rivaroxaban arm, including 4 ischemic strokes and 3 myocardial infarctions occurring in patients treated with rivaroxaban whereas none occurred in patients taking warfarin.

As a consequence of TRAPS, a recent Drug Safety Update, the MHRA stated that there is not enough evidence to show that any DOACs offer sufficient protection against thrombosis in patients with established APS, particularly those at the highest risk of thromboembolic events. A meta-analysis review of cases from 2000 to 2018 showed that high-risk APS patients had a fourfold increased risk of thrombosis when treated with DOACs compared to warfarin [6]. This suggests that the routine use of DOACs in all patients of APS is not recommended.

According to the 2019 EULAR guidelines, although DOACs are contraindicated in APS patients with triple aPL positivity or an arterial event, its use may be considered in patents with venous APS without triple aPL positivity [7]. The 2019 ESC guidelines also recommend against the use of DOACs in APS patients both venous and arterial based on the results of the TRAPS trial.

The U.S. is also currently conducting the ASTRO-APS which will be the largest prospective study till date comparing a DOAC with warfarin among patients with APS for the secondary prevention of thrombosis and the outcomes obtained will be clinically applicable to the routine management of patients receiving indefinite anticoagulation. This study has been ongoing since December 10, 2014. It is a prospective, open-label, blinded, pilot study that will randomize patients with a history of venous thrombosis and APS already receiving anticoagulation to either warfarin or apixaban and will then assess the safety and efficacy of apixaban compared with adjusted dose warfarin for the prevention of recurrent thrombosis. Patients who consent to study participation will be randomized to anticoagulation with adjusted dose warfarin sodium or apixaban 5mg orally twice daily.

In our patient's case, we believe that there was evidence of ongoing TMA characterized by the development of proteinuria and deteriorating renal function while taking rivaroxaban which was improved on conversion to warfarin based anticoagulation. We believe this adds further support to the hypothesis of the superior efficacy of warfarin over DOACs based anticoagulation in the treatment of APS.

Learning points:

1. Long term anticoagulation with warfarin remains the gold standard in the prevention of thrombosis in APS patients.

2. Further clinical studies are required to establish the role of DOACs based anticoagulation in APS.

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