Arch Intern Med Res 2020; 3(3): 186-190 *DOI: 10.26502/aimr.0041*

Case Report

Failure of Direct Oral Anticoagulants in Three Patients with Antiphospholipid Antibody Syndrome

Firdevs Ulutaş*, Uğur Karasu, Veli Çobankara, Serdar Kaymaz, Canan Yaşar

Department of Rheumatology, Internal Medicine, Pamukkale University, Denizli, Turkey

***Corresponding author:** Firdevs Ulutaş, Department of Rheumatology, Internal Medicine, Pamukkale University, Denizli, Turkey, E-mail: firdevsulutas1014@gmail.com

Received: 13 August 2020; **Accepted:** 21 August 2020; **Published:** 24 August 2020

Citation: Firdevs Ulutaş, Uğur Karasu, Veli Çobankara, Serdar Kaymaz, Canan Yaşar. Failure of Direct Oral Anticoagulants in Three Patients with Antiphospholipid Antibody Syndrome. Archives of Internal Medicine Research 3 (2020): 186-190.

Abstract

Antiphospholipid antibody syndrome is a clinical condition that is characterized by recurrent venous and/or arterial thrombosis, and/or pregnancy morbidity in patients who have positive antiphospholipid antibodies. Clinicians firstly aim to prevent recurrent thrombosis by long-term anticoagulation in these patients. Warfarin is the mainstay drug that is most commonly used in thrombotic antiphospholipid antibody syndrome. It's narrow therapeutic window requires close regular monitoring of the International Normalized Ratio (INR), which is inconvenient and costly. In the past decade direct oral anticoagulants have been characterized. Today we do not know whether direct oral anticoagulants are safe and effective in comparison with warfarin in patients with antiphospholipid antibody syndrome. We report herein three patients with failure of thrombotic prevention during treatment with rivaroxaban and dabigatran.

Keywords: Direct Oral Anticoagulants; Antiphospholipid Antibody Syndrome; Thrombosis; Warfarin

1. Introduction

Antiphospholipid antibody syndrome (APAS) is characterized by venous and/or arterial thrombosis, and/or pregnancy morbidity in patients who have positive antiphospholipid antibodies (aPLs) such as lupus anticoagulant (LA), IgG and/or IgM anticardiolipin and/or anti-beta 2 glycoprotein I

antibodies at persistently moderate/high titers [1]. Persistent aPL positivity is defined as aPL present on at least two consecutive occasions at least twelve weeks apart. Clinicians firstly aim to prevent recurrent thrombosis by long-term anticoagulation in patients with thrombotic antiphospholipid syndrome. Warfarin is the mainstay drug that is most commonly used in thrombotic APS. It's narrow therapeutic window leads to close regular monitoring of the INR, which is inconvenient and costly. In the past decade direct oral anticoagulants (DOACs) have been characterized. They are fixed-dose orally administered agents that do not interact with dietary constituents and alcohol, unlike warfarin. They do not require bridging therapy with low-molecular-weight heparins. It is well known that they have predictable anticoagulant effects, so monitoring of their anticoagulant activity is not regularly required. These drugs are known as dabigatran etexilate (a direct thrombin inhibitor), and rivaroxaban, apixaban and edoxaban, which are direct anti-Xa inhibitors [2]. Today we do not know whether DOACs are safe and effective in comparison with warfarin in APAS patients. Marvin Kajy et al screened in total 51 manuscripts, describing 79 patients who exhibited DOAC failure. Antiphospholipid antibody syndrome (44.3%) was the disease most related to treatment failure. The treatment failure rate for rivaroxaban was (65.8%) followed by dabigatran (27.8%), apixaban (7.6%) and then edoxaban (1.3%) [3]. We report herein a series of three APAS patients with failure of thrombotic prevention during DOAC treatment, including use of rivaroxaban and dabigatran. An informed consent form was obtained for each patient.

2. Case Report

Thrombotic events in three patients with antiphospholipid antibody syndrome treated with DOACs and their clinical chracteristics are shown in Table 1.

2.1 Case 1

A 55-year-old woman was diagnosed with APAS with triple positivity of aPLs when she developed deep vein thrombosis in 2017 and pulmonary thromboembolism two years later, in 2019. Initially she was treated with rivaroxaban for two years. After failure of DOAC she is still on regular treatment with warfarin.

2.2 Case 2

A 44-year-old woman with APAS and systemic lupus erythematosus (SLE) manifested initially with a thrombotic cerebrovascular event in 2015. While on treatment with dabigatran, she developed digital ulcers on the right foot due to deep popliteal and anterior tibial artery thrombosis three years later. She had persistently high levels of all three aPLs. Her treatment was switched to warfarin.

2.3 Case 3

A 34-year-old woman with APAS and SLE developed deep vein thrombosis in 2017 and had a stroke in 2019. Her aPL profile was triple positive. She was managed with dabigatran for two years, until she developed a stroke in 2019. She is still on regular treatment with warfarin.

Case	Age	Gender	Initial manifestation of APS / time	aPL profile	DOAC treatment until event (months)	Manifestations while on DOAC	First DOAC	Presence of Systemic Lupus Erythematosus
1	55	F	Deep vein thrombosis /2017	Triple (+)	24	Pulmonary thromboembolism /2019	Rivaroxaban	Absent
2	44	F	Cerebrovascular event /2015	Triple (+)	37	Digital ulcer /2018	Dabigatran	Present
3	34	F	Deep vein thrombosis /2017	Triple (+)	25	Cerebrovascular event /2019	Dabigatran	Present

DOACs: direct oral anticoagulants, F: female, M: male, aPL: antiphospholipid antibodies, Triple (+): positivity of lupus anticoagulant, anti beta-2 glycoprotein I antibodies and anticardiolipin antibodies.

Table 1: Thrombotic events in three patients with antiphospholipid antibody syndrome treated with DOACs.

3. Discussion

The treatment experience with DOACs in APAS patients is limited. We aimed to contribute our experience with these three patients. Our case series was consistent with previously reported literature. Virginie Dufrost et al identified 122 APAS patients treated with DOACs; among them, 19 experienced a recurrent thrombosis while on DOACs, and triple positivity was a major risk factor for recurrent thrombosis (3.5-fold increased risk) [4]. Triple positivity was present in all three patients. Recent trials have investigated the pathogenic role of complement activation in thrombotic antiphospholipid antibody syndrome. Switching treatment from warfarin to rivaroxaban decreased complement activation in APAS patients. It was noticed that rivaroxaban may have potentially an additional benefit to its anticoagulant effect by limiting classical complement activation [5]. RAPS demonstrated that rivaroxaban is not inferior to warfarin in patients with APAS and previous venous thromboembolism (VTE), with or without SLE [6]. Savino Sciascia et al followed up 35 patients with rivaroxaban and none had experienced thrombotic recurrence at 10 months follow-up [7]. In another case series of 12 patients, two had recurrent thrombosis within the first few months of rivaroxaban treatment [8]. Our patient developed failure with rivaroxaban treatment after 24 months. In a systematic review, among 447 APAS patients, the rate of recurrent thrombosis was 15% in APAS patients receiving dabigatran and the mean duration until thrombosis was 12.5 months [9]. In our patients the follow-up times with dabigatran were also considerably longer than those in the above studies. According to a systematic research analysis, the most common manifestations of treatment failure with DOACs were stroke/transient ischemic attack (20.3%), pulmonary embolism (19.0%) and deep venous thrombosis (19.0%). Ultimately 55.7% of patients were transitioned

to a vitamin K antagonist (VKA) after DOAC failure [3]. Stroke and pulmonary thromboembolism were two presenting clinical entities in our patients on DOAC treatment. All of the three patients were switched from DOACs to warfarin. It was shown for venous thromboembolism (VTE) in the general population that there was no significant difference between recurrent thrombosis rates on warfarin versus DOACs, at 2.2% and 2.0%, respectively [10]. However, there are controversial results for APAS patients. APAS patients are extremely heterogeneous with their risk profile and clinical phenotype. Despite VKA use, thrombosis still occurs in 5 to 20% of APAS patients. This means that no drug protects completely against recurrent thrombosis [11]. Switching patients from a DOAC to warfarin does not mean that there is no further risk of thrombosis. In this paper we again show that there are a few patients at high-risk for recurrent thrombosis, such as with triple positivity. It is well known that these patients are less protected with DOACs. No thrombotic event was seen in our patients after warfarin treatment. Nevertheless, a long follow-up time is required to encounter recurrent thrombosis.

4. Conclusion

Currently VKA is the mainstay treatment for thrombotic APAS. DOACs are not as effective as warfarin and should not be used routinely in all APAS patients in clinical practice. The decision to use a DOAC should be discussed on an individual basis.

Relationship between Financial Support and Interest

There is no person/organization that supported the study financially and the authors do not have any interest-based relationship.

References

1. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome. J Thromb Haemost 4 (2006): 295-306.
2. Deepa Jayakody Arachchillage, Hannah Cohen. Use of new oral anticoagulants in antiphospholipid syndrome. Curr Rheumatol Rep 15 (2013): 331.
3. Marvin Kajy, Anil Mathew, Preeti Ramappa. Treatment Failures of Direct Oral Anticoagulants. Am J Ther (2019).
4. Virginie Dufrost, Jessie Risse, Stephane Zuily, et al. Direct Oral Anticoagulants Use in Antiphospholipid Syndrome: Are These Drugs an Effective and Safe Alternative to Warfarin? A Systematic Review of the Literature. Curr Rheumatol Rep 18 (2016): 74.
5. Arachchillage D R J, Mackie I J, Efthymiou M, et al. Rivaroxaban limits complement activation compared with warfarin in antiphospholipid syndrome patients with venous thromboembolism. J Thromb Haemost 14 (2016): 2177-2186.
6. Cohen H, Dore C J, Clawson S, et al. 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 24 (2015): 1087-1094.
7. Savino S, Breen K, Hunt BJ. Rivaroxaban use in patients with antiphospholipid syndrome and previous venous thromboembolism. Blood Coagul Fibrinolysis 26 (2015): 476-477.

8. Son M, Wypasek E, Lowenhoff-Celinska M, et al. The use of rivaroxaban in patients with antiphospholipid syndrome: a series of 12 cases. Thromb Res 135 (2015): 1035-1036.
9. Virginie Dufrost, Jessie Risse, Tatiana Reshetnyak, et al. Increased risk of thrombosis in antiphospholipid syndrome patients treated with direct oral anticoagulants. Results from an international patient level data meta-analysis. Autoimmun Rev 17 (2018): 1011-1021.
10. Van Es N, Coppens M, Schulman S, et al. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: Evidence from phase 3 trials. Blood 124 (2014): 1968-1975.
11. 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 14 (2015): 680-685.