Thrombosis Research 152 (2017) 93–97

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

The use of direct oral anticoagulants in 56 patients with antiphospholipid syndrome

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ARTICLE INFO

Article history:
Received 30 July 2016
Received in revised form 30 November 2016
Accepted 12 December 2016
Available online 14 December 2016

Keywords:
Antiphospholipid syndrome
Direct oral anticoagulants
Rivaroxaban
Apixaban
Dabigatran
Thrombosis

ABSTRACT

Introduction: Antiphospholipid syndrome (APS) is a common acquired thrombophilia associated with a high thrombotic risk, in which vitamin K antagonists (VKA) represent the mainstay of therapy. Case series involving up to 35 patients with APS suggested limited efficacy and safety of direct oral anticoagulants (DOACs).
Material and methods: In the prospective case series we followed 56 consecutive patients with APS (44 women and 12 men, aged from 22 to 64 years), including 33 (60%) associated with systemic lupus erythematosus (SLE) and 16 (28.6%) with triple APS who were treated with DOACs due to their preferences or unstable anticoagulation with VKA. DOACs were started at least 3 months since the thromboembolic event in patients with D-dimer below 500 ng/ml.
Results: Forty-nine (87.5%) patients were treated with rivaroxaban, 4 (7.3%) with dabigatran and 3 (5.4%) with apixaban. During follow-up of 2 to 43 (mean 22) months, 6 (10.7%, 5.8 per 100 patient-years) patients (4 women and 2 men, 4 with triple positive APS) experienced recurrent thrombosis, including deep vein thrombosis ($n = 4$, including 2 episodes preceded by nonadherence), superficial vein thrombosis ($n = 1$) and non-ST elevation myocardial infarction ($n = 1$). The recurrence rate of VTE on DOACs was 5.8 per 100 patient-years. Two patients (3.6%) experienced severe bleeding.
Conclusions: This case-series suggests that DOACs are safe in patients with APS. These findings need to be confirmed in larger studies.

1. Introduction

Antiphospholipid syndrome (APS) is an autoimmune hypercoagulable state associated with an increased risk of the venous or arterial thrombosis and recurrent miscarriages. The diagnosis of the APS is based on the clinical presentation and positive repeated results for the circulating antiphospholipid antibodies (aPL) – antibodies against cardiolipin (aCL), β2 glycoprotein I (aβ2GPI) and lupus anticoagulant (LA) [1,2]. The gold standard in the long-term treatment in APS is oral anticoagulant therapy with vitamin K antagonist (VKA) [3]. Long-term VKA therapy is fraught with several inconveniences as diverse food and drug interactions, necessity and troubles in INR monitoring, bleeding complications, difficulties in the optimal INR selection [4].

Direct oral anticoagulants (DOACs), including dabigatran, rivaroxaban, apixaban and edoxaban, are increasingly used in the VTE treatment [5,6]. In 6 phase III randomized controlled trials, the DOACs were at least as effective as the conventional treatment in preventing recurrent VTE [7].

It is unclear whether DOACs are safe and effective in APS patients with thromboembolic disorders. The largest dataset on thrombophilic patients receiving DOACs, mostly rivaroxaban, refers to APS. Until now there have been published 4 case reports and 7 case series on the use of DOACs, mostly rivaroxaban in the APS patients [8,9]. The largest study reported 35 APS patients with the longest follow-up of 36 months. A recent summary of observational studies regarding the use of DOACs in APS ($n = 87$) published by Sciascia et al. [9] documented relatively good clinical outcomes during a follow-up ranging from 0 to 29 months. Recently the results of a randomized, controlled, open-label trial on the use of rivaroxaban in APS have been published [10]. Among 54 patients receiving rivaroxaban and 56 on warfarin, after 210 days of treatment no thrombosis or major bleeding was reported [10]. Overall 152 patients with APS receiving DOACs have been published in the literature so far, including 138 subjects treated with rivaroxaban, 13 with dabigatran and 1 with apixaban. Recurrent thromboembolic events on DOACs were observed in 15 patients with APS [9–20]. The results of these studies are controversial, yet encouraging. Some experts have already recommended DOACs as an alternative to VKAs in the prevention of VTE in APS [21].

In 2015 we published a case series involving 12 patients with APS treated with rivaroxaban and two recurrent VTE after 2 and 5 months of such therapy were observed [11]. Currently, there are ongoing

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http://dx.doi.org/10.1016/j.thromres.2016.12.009
0049-3848/

interventional prospective trials on the usage of DOACs in aPL positive patients [22–24]. Awaiting the results of randomized trials, all specialists dealing with the APS patients have to consider the use of DOACs in an increasing number of high-risk patients with this common thrombophilia.

We present here the largest case series of the APS patients receiving DOACs from our center.

2. Material and methods

This is a prospective case series of 56 consecutive white Polish patients with APS who were switched from VKAs (warfarin or acenocoumarol) to rivaroxaban, dabigatran or apixaban or in whom DOACs were initiated during the acute VTE episode and maintained based on the patient preferences. The patients were recruited at the Center of Coagulation Disorders at the John Paul II Hospital in Cracow, Poland from 2013 to July 2016. They were referred to us for thrombophilia screening or long-term therapy if the disease was diagnosed in the past. The ethics committee of the Jagiellonian University approved the study which part was this analysis. All patients gave written informed consent. A specific consent to start a DOAC was not obtained. We enrolled adult patients diagnosed with APS (according to the international consensus criteria for APS [2]) after at least 3 months' anticoagulant therapy since the thromboembolic event and D-dimer below 500 ng/ml, who preferred a DOAC or had unstable anticoagulation with VKA. In 50 patients the change of the anticoagulant drug from VKAs to DOACs was due to difficulties in the maintenance of the therapeutic INR, while the remaining 6 subjects were treated since the acute VTE episode with a DOAC and the diagnosis of APS was established later in our institution.

All included patients had normal liver enzymes and serum creatinine.

The patients were followed up to July 2016 (clinic visits every 3–6 months and telephone contact). Clinical outcomes were thromboembolic events (defined as described previously [25]) and major bleeding (based on the ISTH criteria [26]).

2.1. Laboratory investigations

Diagnosis of APS was established according to the Sydney classification criteria [1,2]. LA was detected using clot-based assays according to the current criteria for LA evaluation [27]. The presence of IgG and IgM aCL and aβ2GPI were determined by enzyme-linked immunosorbent immunoassays (QUANTA Lite™ ELISAs, INOVA Diagnostic, Inc. San Diego, CA) [28]. All patients underwent thrombophilia screening, including FVL, prothrombin G20210A, antithrombin (AT), protein C (PC) and free protein S (PS). PC activity was measured using a chromogenic assay (Berichrom® Protein C, Siemens Healthcare Diagnostic, Marburg, Germany) on an automatic analyzer BCS XP (Siemens) in citrated plasma [29]. The free PS antigen was detected on automated coagulation analyzer BCS XP (Siemens) with an immunoturbidimetric assay (INNOVANCE® Free PS Ag, Siemens Healthcare Diagnostic). The AT was detected with a chromogenic assay (INNOVANCE® ATIII, Siemens Healthcare Diagnostic) on an automatic analyzer BCS XP (Siemens). Factor V Leiden mutation was determined by the Real-Time PCR with the use of TaqMan Genotyping Assays in 7900 Fast Real-Time PCT System, Applied Biosystems (Foster City, California, USA). Prothrombin G20210A (PT G20210A) polymorphism was determined by the restriction fragment length polymorphism analysis with the use of *Hin*dIII restrictase (Fermentas, USA). Factor (F)VIII activity was measured using a coagulometric assay with FVIII deficient plasma (Siemens) 12–36 h before the start of a DOAC.

2.2. Statistical analysis

Continuous variables were presented as median (interquartile range, IQR), mean ± SD and categorical variables as numbers and percentages. Quantitative parameters were checked for the normality of distribution with the Kolmogorov-Smirnov test and compared using unpaired U-Mann Whitney test. Significant results were subjected to an adjustment analysis using logistic regression. Association between the variables was expressed as odds ratio (OR) with corresponding 95% confidence intervals (CI). A p-value <0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

A total of 56 APS patients, including 12 subjects published in 2015 [11] and 44 new cases, were studied (Table 1). Twenty-three (41%) cases were identified as the primary APS and 33 (60%) were associated with systemic lupus erythematosus (SLE). Obstetric manifestations of APS, i.e. miscarriages were reported by 13 of the 44 (29.5%) females. The mean age at the start of the DOAC therapy was 44.2 ± 10.6 years (range 22–64 years). Sixteen (28.6%) patients were "triple positive" for aPL, 15 (26.8%) were "double positive" and 25 (44.6%) had only one type of aPL detected. FVL mutation was found in 5 (9%) patients and PT G20210A mutation in 2 (3.6%) patients. All the patients had a history of VTE and 6 subjects experienced more than one episode prior to the initiation of DOACs. Eight (14.5%) patients had TIA or ischemic stroke.

Forty-nine (87.5%) patients were treated with rivaroxaban, 4 (7.3%) with dabigatran and 3 (5.4%) with apixaban. The duration of treatment with the DOACs ranged between 2 and 43 months (mean 22.1 ± 7.8 months).

Factor VIII activity measured directly prior to the DOACs therapy ranged between 82 and 254% with 3 (5.4%) patients having FVIII >200% (two of them previously reported by Son et al. [11]).

3.2. Clinical outcomes during follow-up

As shown in Table 1, we observed thromboembolic events in 6 (10.7%) patients (5.8 per 100 patient-years, 95% CI: 2.2–13.0), including 4 women and 2 men. Median age of these patients was 52 years at the start of therapy (IQR 43–62, range 37 to 60 years). All of them have experienced a single previous episode of DVT (in one case combined with PE). DOACs were initiated in these patients 43 months (median) after the last event (IQR 36–64, range 6–144 months). During follow-up there were 4 cases of recurrent DVT (including 2 patients reported previously [11]), one case of superficial vein thrombosis (SVT) and one with myocardial infarction after the DOAC treatment that lasted on average (median) 19 months (IQR 18–22, range 17–24 months, Table 1). Four of them were "triple positive" for aPL. Four patients with VTE recurrence had APS secondary to SLE. All the 6 patients were switched from VKA.

Interestingly, median FVIII activity in the subgroup of APS patients with recurrent episodes was 163% (IQR 128–232, range 123 to 254%), while in the 50 patients with uncomplicated follow-up this variable was 134% (IQR 112–158, range 82 to 210%, $p > 0.05$). However when the 5 patients with recurrent DVT or SVT were analyzed, FVIII activity at the start of DOAC therapy was significantly higher compared with the remainder (median, 188 [IQR, 135–232] vs 134 [112–158]%, $p = 0.04$).

There were no differences in age, time period from the last thrombotic episode prior to the start of DOACs, duration of DOAC treatment and FVIII activity between the patients with recurrent thrombosis and those with the uneventful follow-up.