CONCISE REPORT

Direct oral anticoagulants in antiphospholipid syndrome: a real life case series

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Aim: The aim of this study was to describe a case series of patients with primary or secondary antiphospholipid syndrome (APS) treated with direct oral anticoagulants (DOACs). Patients and methods: Clinical charts of eight patients with thrombotic primary or secondary APS treated with direct oral anticoagulants (DOACs) between January 2012 and May 2015 were reviewed. Results: The mean age was 45.6 ± 14.36 (range 27–69 years). Four patients had secondary APS (50%). All patients were initially treated with warfarin by a mean time of 70.87 ± 57.32 months (range 17–153 months). Changes in anticoagulation were defined by recurring thrombosis in five patients (62.5%) and life-threatening bleeding in the other three cases. Seven patients (87.5%) received rivaroxaban treatment and one patient (12.5%) apixaban. The mean follow-up period with DOACs was 19 ± 10.06 months (range 2–36 months). There was no recurrence of thrombosis by the time of data collection. Conclusions: Despite not being the standard treatment in APS, we propose DOACs as a rational alternative for the management of patients with this diagnosis. Further interventional clinical studies are necessary for possible standardization of this therapy in APS patients. Lupus (2016) 0, 1–5.

Key words: Antiphospholipid syndrome; anticoagulation; direct oral anticoagulants; thrombosis

Introduction

The antiphospholipid syndrome (APS) is an autoimmune disorder characterized by venous and arterial thrombosis, and recurrent fetal losses, frequently accompanied by a moderate thrombocytopenia, and the presence of persistent circulating antiphospholipid antibodies (aPL).1 Antiphospholipid antibodies are detected by two solid-phase assays evaluating antibodies against cardiolipin (aCL) and β2 glycoprotein I (anti-β2GPI antibodies) plus a functional test (the lupus anticoagulant (LA)).2 The medical management of patients with APS aims mainly at avoiding the thrombotic and/or obstetric recurrences.3 To achieve that, the current mainstay of treatment is a bridge therapy for at least five days with heparin (unfractioned or low molecular weight heparin) followed by long-term anticoagulation with a vitamin K antagonist (VKA) such as warfarin, with a recommended target international normalized ratio (INR) of 2.5. Intensity of continuous anticoagulation is still being debated.3,4 Treatment with VKA is complicated because it has several pitfalls, including numerous food and drug interactions (e.g. immunosuppressive agents such as azathioprine), which require frequent INR monitoring.3,5 Furthermore, the effective evaluation of the anticoagulation effect may be difficult due to the variable response of thromboplastin reagents to aPL (particularly LA), which makes the estimation of anticoagulation intensity with prothrombin time (PT)/INR uncertain.4

To overcome these and other limitations, a group of a relatively new class of drugs that inhibit a single enzyme of the coagulation cascade, called direct oral anticoagulants (DOACs), has been introduced. Major phase III prospective and randomized controlled trials (RCTs) have shown the efficacy and safety profile of DOACs for venous thrombo-embolism (VTE) treatment. However,
these results cannot be generalized to patients with APS, despite the fact that these trials probably included patients with this syndrome. In this article, we describe the indications, follow-up, and outcomes of eight patients with primary and secondary APS treated with DOACs in a case series.

**Methods**

**Patients and definitions**

We performed a retrospective case study of eight patients attending our Rheumatology/Hematology Units at Fundación Valle del Lili (a tertiary care hospital in Colombia) between January 2012 and May 2015 with a diagnosis of primary thrombotic or secondary APS, as defined by clinical and immunological criteria according to the international Sapporo classification, who had a current or past history of treatment with the DOACs available in Colombia, namely apixaban (Eliquis®), rivaroxan (Xarelto®), and dabigatran (Pradaxa®). Each patient’s medical record contained details for every inpatient or outpatient visit, regardless of the health care provider, including the radiologic test and all laboratory and pathology results.

All patients underwent a complete physical examination and routine laboratory analyses, including immunological tests: antinuclear antibodies (ANA) detected by an indirect immunofluorescence technique with human epithelial type 2 (HEP-2) cell substrate; aCL, anti-β2GPI and LA tests, performed on serum and plasma, respectively, using ELISA, and a coagulation test (as recommended by the International Society of Thrombosis and Hemostasis). Antibodies against cardiolipin test results were expressed as immunoglobulin M (IgM) phospholipid units (MPL) and IgG phospholipid (GPL) units, respectively. LA was detected using dilute Russell Viper Venom Time (dRVVT), which screens for lupus-like anticoagulant, and Dilute Viper Venom (DVV) confirm (ratio), which confirms LA presence in plasma. Medical records were reviewed for demographic data, past obstetrical complications and SLE compromise if applicable, prior anticoagulant therapy, response to treatment, need for change of anticoagulant drug and the indications for change, adverse effects, and clinical outcomes (mainly need of hospitalization since the diagnosis including the cause) and number of thrombosis relapses while receiving anticoagulation therapy (therapeutic or on sub-therapeutic anticoagulant therapy due to labile INR—refers to unstable/high INRs or poor time in the therapeutic range of <60%). All patients gave written permission to use their clinical data and biological specimens for research purposes. The ethical committee and the institutional review boards of Fundación Valle del Lili approved this protocol, and the research was performed according to the ethical principles of the Helsinki declaration.

**Results**

**General characteristics**

Among the entire cohort of APS patients (n = 111), eight were treated with DOACs. The demographic, clinical, laboratory, and treatment characteristics of these patients are shown in Table 1. All patients were female. The mean age at time of analysis was 45 ± 14.36 years (range 27–69 years).

**Clinical and immunological features**

All patients fulfilled APS criteria by a previous thrombo-embolic event. Four patients had secondary APS (50%), including three patients with SLE (37.5%) and one patient with rheumatoid arthritis (RA) (12.5%). Seven patients had previous venous thrombosis (87.5%), with recurrence in two cases; pulmonary embolism in five cases (62.5%), and arterial thrombosis in six cases (75%), including stroke, recurrent transient ischemic attack (TIA), and thrombosis of the common femoral artery. Two patients (25%) met obstetrical criteria, including one patient with eight previous miscarriages and one preterm birth. ANAs were positive in four patients (50%). All patients had positive aPL antibodies twice, 12 weeks apart. LA was positive in seven cases (87.5%); IgM aCL in four patients (50%) and IgG aCL in two cases (25%). Both IgM and IgG types were found in one patient (12.5%). Anti-β2GPI IgG was positive in one patient (12.5%) and triple antibody positivity was found in one patient (12.5%).

**Treatment and follow-up**

All patients were initially treated with warfarin with a target INR between 2 and 3. The mean time of warfarin treatment was 70.87 ± 57.32 months (interquartile range (IR) 17–153 months).

Changes in anticoagulation were defined by relapsing thrombosis in five patients (62%; recurrent TIA in one patient, pulmonary embolism in four patients, and venous thrombosis in two patients) and life-threatening bleeding in the other
Table 1  Characteristic of the patients with APS and new oral anticoagulants

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/Gender</th>
<th>Site of thrombosis</th>
<th>Obstetric APS</th>
<th>Anti-bodies</th>
<th>SLE compromise</th>
<th>Previous anticoagulation method and duration (months)</th>
<th>Number and cause of hospitalizations</th>
<th>Cause of change of therapy</th>
<th>Time since initiation of novel anticoagulant</th>
<th>Drug used</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>42/F</td>
<td>Primary VT/PE</td>
<td>+</td>
<td>LA:+aCL IgM: – aCL IgG: +</td>
<td>N/A</td>
<td>Warfarin 153 months</td>
<td># 3. VT: 1, EP: 1, hematuria with requirement of prothrombin complex: 1</td>
<td>–Recurrence despite Warfarin INR: 2.7 – labile INR</td>
<td>19 months</td>
<td>Rivaroxaban 20 mg qd</td>
<td>No re-thrombosis</td>
</tr>
<tr>
<td>3</td>
<td>37/F</td>
<td>Primary rVT/rPE</td>
<td>–</td>
<td>LA: +aCL IgM: – aCL IgG: –</td>
<td>N/A</td>
<td>Warfarin 35 months Vena cava filter 23 months</td>
<td># 6: PE: 2, VT metrorrhagia: 3, transfusion requirement: 1</td>
<td>–Recurrence despite warfarin, –labile INR</td>
<td>13 months</td>
<td>Rivaroxaban 20 mg qd</td>
<td>No re-thrombosis</td>
</tr>
<tr>
<td>4</td>
<td>44/F</td>
<td>Secondary PE, stroke</td>
<td>+ 8 miscarriages</td>
<td>LA: + aCL IgM: – aCL IgG: –</td>
<td>Transverse myelitis, cutaneous, arthritis, Raynaud, arthritis, hemolytic anemia</td>
<td>Warfarin 126 months</td>
<td>#1. PE: 1</td>
<td>Recurrence despite warfarin – labile INR</td>
<td>23 months</td>
<td>Rivaroxaban 20 mg qd</td>
<td>No re-thrombosis</td>
</tr>
<tr>
<td>5</td>
<td>27/F</td>
<td>Secondary PE/VT</td>
<td>–</td>
<td>LA: + aCL IgM: + aCL IgG: –</td>
<td>Warfarin 152 months, enoxaparin 18 months</td>
<td># 2. SAH: 1, haemorrhagic ovarian cyst with oophorectomy requirement: 1</td>
<td></td>
<td>–Labile INR Bleeding</td>
<td>27 months</td>
<td>Rivaroxaban 20 mg qd</td>
<td>No re-thrombosis</td>
</tr>
<tr>
<td>6</td>
<td>55/F</td>
<td>Primary VT/common femoral artery</td>
<td>–</td>
<td>LA: + aCL IgM: + aCL IgG: –</td>
<td>N/A</td>
<td>Warfarin 17 months</td>
<td>No events</td>
<td>Labile INR</td>
<td>23 months</td>
<td>Rivaroxaban 20 mg qd</td>
<td>No re-thrombosis</td>
</tr>
<tr>
<td>7</td>
<td>69/F</td>
<td>Secondary rVT/rPE</td>
<td>–</td>
<td>LA: – aCL IgM: + aCL IgG: –</td>
<td>Rheumatoid arthritis, Sjögren, temporal arteritis</td>
<td>Warfarin 40 months</td>
<td>#1. PE</td>
<td>Recurrence despite warfarin</td>
<td>36 months</td>
<td>Rivaroxaban No</td>
<td>re-thrombosis</td>
</tr>
<tr>
<td>8</td>
<td>28/F</td>
<td>Primary VT</td>
<td>–</td>
<td>LA: + aCL IgM: + aCL IgG: +</td>
<td>N/A</td>
<td>Warfarin 22 months</td>
<td>No recurrence</td>
<td>Labile INR</td>
<td>2 months</td>
<td>Apixaban 5 mg tid</td>
<td>No re-thrombosis</td>
</tr>
</tbody>
</table>

three cases, one patient requiring treatment with prothrombin complex and another with vitamin K and red blood cell transfusion. Two patients (25%) required another anticoagulant or alternative method to prevent a thrombotic event prior to starting DOACs: one patient received anticoagulation with low-molecular weight heparin (enoxaparin for 18 months) and the other an inferior vena cava filter.

Seven patients (87.5%) received rivaroxaban and one (12.5%) apixaban. Dabigatran was not used. The mean time of DOACs use was 19 ± 10.06 months (IR 2–36 months). There was neither thrombosis recurrence at the time of data collection nor hemorrhagic complications during the follow-up.

Discussion

The main goal of clinical management of APS is to avoid thrombotic and/or obstetric recurrences. Long term anticoagulation with oral VKA constitutes the cornerstone of the pharmacological approach to thrombotic APS. However, the use of warfarin is sometimes problematic. Prospective RCTs support the current recommendation of anticoagulation at a target INR of 2.5 (range 2–3) for an indefinite period in APS patients with/without SLE, presenting with a first or recurrent VTE event, occurring while there was no treatment.

To date, clinical trials with DOACs have been undertaken in more than 150,000 patients. It is likely that a number of patients with APS were included in the phase III clinical trials of rivaroxaban and dabigatran vs VKA in patients with VTE, considering that among patients with VTE, 9.5% have aPL. In fact, a small subset of patients with known thrombophilia (5%–7%) were included in the randomized open-label non-inferiority trials of rivaroxaban vs enoxaparin followed by VKA, including a subset of patients with aPL (personal communication, Janssen Scientific Affairs, LLC). As these patients were not identified as “APS” in the analyses, the results of these DOAC trials cannot be generalized to APS patients.

However, based on these results we can assume that their use could be extrapolated to patients with APS diagnosis. A recent report issued by the task force on aPL stated that VKA remains the mainstay of anti-coagulation in APS, and that DOACs may be considered in APS patients with a first or recurrent VTE, occurring off or on sub-therapeutic anticoagulation, only when there is known VKA allergy/intolerance or poor anticoagulant control.

There is growing information from case series where DOACs have been used in APS with controversial results. Previous reports of failure by Schafer et al. and Signorelli et al., as well as Win and Rogers, mainly focused on the treatment of patients with the common denominator of recurrent thrombosis, arterial thrombosis, autoimmune disease, triple antibody positivity, and non-thrombotic manifestations of the disease, these being the patients with the highest risk profile. The majority of episodes of thrombosis recurrence in these case series occurred in the first six months after therapeutic switch.

In contrast, there is also success reported in larger case series, such as the series of Sciascia et al. with 35 patients who did meet the criteria for rivaroxaban in the Antiphospholipid Syndrome (RAPS) study. In this case series rivaroxaban was used for secondary prevention in patients with previous VTE, requiring a target INR of 2–3, but with poor anticoagulant control with VKA. Patients with previous arterial thrombosis were excluded. In Noel et al., a study of 26 patients, the main indication for DOACs was therapeutic simplification in most of the cases. In this case series thrombosis recurrence was observed in only one patient. In comparison, in our cases we had a more heterogeneous population of patients with high-risk predictors, including recurrent and arterial thrombosis in the majority of them, and we found no recurrences in the first six months of follow-up or to date. The absence of thrombosis in patients at high risk is hypothesized to be due to the low presence of triple positive patients in our series, consistent with previous reports, suggesting that these patients are less protected with DOACs. This issue will be resolved by a currently recruiting trial: Rivaroxaban in Thrombotic Antiphospholipid Syndrome (TRAPS) in 535 triple aPL-positive patients with clinical manifestations of APS, arterial events, and/or pregnancy morbidity.

Despite the fact that we included patients with history of obstetric criteria of APS, DOACs should be avoided in pregnancy and during breast-feeding, because there is no data available of their safety in pregnant women, and there could be some hemorrhagic complications, which have been found in animal experimental models, making outcome trials in other forms of APS but thrombotic unlikely.

This description is important because it is the first report of positive findings. Namely, no thrombosis recurrences while using DOACs in patients with both primary and secondary APS—because
there is a difference in thrombosis recurrence between patients with SLE and non-SLE associated thrombotic APS—with an important follow-up (mean time of 19 months) and clear indications of use, as stipulated in the task force report on APS treatment trends.4

While it is not the standard of management, and we have been using DOACs in an off-label indication, we consider that their use is a rational alternative for the management of these patients. Results of the ongoing interventional clinical study in aPL-positive patients, the RAPS trial,15 are expected to confirm these observations. If this study proves that the anticoagulant effect of Rivaroxaban is not inferior to that of warfarin in terms of adverse effects, it will provide sufficient supporting information to change the practice for APS patients, making rivaroxaban the standard management for patients with APS with or without SLE, who have VTE requiring a target of 2.5 in first instance. The RAPS trial will later clarify their use in more risky patients.14,15

In conclusion, DOACs can be used in APS patients with previous thrombo-embolic disease who cannot receive warfarin. However, in the absence of prospective RCT data, reports of therapeutic failures in clinical practice should alert clinicians of their potential limitations.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

14 Pengo V, Banzato A, Bison E, Zoppellaro G, Padayattil JS, Denas G. 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 2015; Epub, pii: 0961203315611495.