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Can we use NOACS in APS?

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A B S T R A C T

Secondary thromboprophylaxis with low molecular heparin or vitamin K antagonists (VKAs) is recommended in patients with definite antiphospholipid syndrome (APS). Direct oral anticoagulant (DOACs) have been approved in different prothrombotic conditions and have numerous advantages compared to VKAs. Whether DOACs can be used for secondary prophylaxis in APS is an open question. Data from the TRAPS randomized controlled Trial, meta-analysis and case reports indicate that we should not treat patients with triple positive APS and/or arterial thrombi with routine doses of DOACS. On the other hand, data from the literature including, case series, meta- analysis and the RAPS trial indicate that there are low risk patients, such as patients who suffered from a venous but not an arterial thromboembolism and are LAC negative who may benefit from the treatment with DOACs. Prospective trials addressing these low risk patients are needed in order to consider DOAC treatment in such patients.

1. Introduction

Anti-phospholipid syndrome (APS) is a systemic autoimmune disease described in the 80s and characterized by vascular thrombosis and obstetric morbidity mediated by anti-phospholipid antibodies (aPL). APS can occur as an isolated disease (primary APS, PAPS) or associated with other systemic autoimmune diseases (secondary APS, SAPS), such as systemic lupus erythematosus (SLE).

According to the international classification criteria for anti-phospholipid syndrome, APS is defined by the presence of both clinical and laboratory criteria: clinical criteria include arterial or venous thrombosis and pregnancy morbidity, such as recurrent early miscarriages and late pregnancy losses; laboratory criteria include anticardiolipin antibodies (aCL), anti beta2 glycoprotein I antibodies (anti-β2GPI) and lupus anticoagulant (LA). Laboratory Criteria must be confirmed 12 weeks apart [1].

Antiphospholipid autoantibodies have not only a diagnostic role, but they exert also a direct pathogenic role [2]. Moreover, it has been demonstrated that the aPL profile, based on type, titer and number of positive aPL tests (single, double or triple), defines the thrombotic risk of a patient [3,4].

According to the most recent international recommendations for the management of antiphospholipid syndrome, long-term anticoagulation as secondary thromboprophylaxis should be prescribed in all patients with definite APS and an unprovoked venous thrombosis and can be considered in patients with provoked venous thrombosis with a persistent high-risk aPL profile or other risk factors for recurrence. Moreover, long-term anticoagulation is recommended also in APS patients with arterial thrombosis [5].

In clinical practice, anticoagulation after a venous or arterial thrombosis in an APS patient is obtained with low molecular weight heparin (LMWH) in therapeutic doses and subsequent vitamin K antagonists (VKA). However, VKA treatment is characterized by several limitations, such as INR monitoring, frequent failures to achieve target INR and interferences with LA test results. Moreover, recurrences of thrombosis are reported in treated patients, despite anticoagulation with VKA [6].

In the last few years, a new generation of direct-acting oral anticoagulants (DOACs) has been studied in the treatment of venous thromboembolism (VTE). These drugs act by blocking a single enzyme of the coagulation cascade, such as factor Xa (targeted by rivaroxaban, apixaban, edoxaban) or thrombin (targeted by dabigatran etexilate). DOACs have been approved in different prothrombotic conditions, such as non-valvular atrial fibrillation, VTE and surgical VTE prophylaxis. Their use in the treatment of venous thrombosis rapidly increased over the years, thanks to their numerous advantages compared to VKAs: for example, they are used in fixed doses, don't require INR monitoring and they have less interactions with drugs or food.

Based on the positive experience with DOACs use in these prothrombotic conditions, they have been proposed also for secondary

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Table 1
aPL profile and their reliability.

	Lupus Anticoagulant	Anti-cardiolipin	Anti β2-Glycoprotein	Level of reliability
Triple positive*	Positive	Positive	Positive	+ + +
Double positive*	Negative	Positive	Positive	+ +
Single positive	Positive	Negative	Negative	+/-
Single positive	Negative	Positive	Negative	+/-
Single positive	Negative	Negative	Positive	+/-

thromboprophylaxis in APS patients, that were asking for a more convenient anticoagulant treatment. However, since there are limited and contrasting data about DOACs effectiveness and safety in APS, their use in APS patients is still a matter of debate. This review reports the debate held at the CORA meeting (Controversies in Rheumatology and Autoimmunity) held in Florence, March 14–16, 2019 on this still unresolved issue.

2. Should we use DOACs in APS: NO

In order to discuss the issue of DOACs treatment in APS it is important to understand that not all APS laboratory profiles are equivalent. The level of reliability of anti-phospholipid antibody profiles and their clinical relevance are quite different (Table 1). For instance, triple positivity is always confirmed after 12 weeks while single test positivity is confirmed after 12 weeks in < 50% of cases [7]. The lack of confirmation of single positivity might be due to the presence of transient antibodies or laboratory errors. During the past ten years or so, we have demonstrated that triple positive patients are at high risk to incur a first thrombotic episode or recurrences and to develop Chronic Thromboembolic Pulmonary Hypertension [8–11]. Moreover, all the 14 catastrophic APS (CAPS) seen in a single center were triple positive patients [12].

On the other hand, isolated Lupus Anticoagulant (LAC) shows a much lower incidence of thrombotic events (1.3% pt./yrs) [13] compared with that of triple positive patients (5.3%pt./yrs) [10]. All the single positive patients have an incidence of thrombotic events not much different than that of age matched Caucasian normal population (1.36%pt./years vs 0.4%pt./yrs) [14,15].

Currently, other tests checking the presence of aPL are emerging in the literature, namely IgG anti Domain 1 (aDm1) and IgG anti Domain 4/5 (aDm4/5) of β2-glycoprotein I (β2GPI) plus IgG and IgM anti-phosphatidyl/ prothrombin antibodies (aPS/PT). These new tools could help us in refining the risk of thromboembolic events in aPL positive patients.

After these considerations on aPL profiles, it is clear that triple positive patients (in most cases tetra positive patients) should be regarded as a group of patients at high risk of a new thrombotic event despite treatment [9]. This is why we chose these patients to test the efficacy and safety of rivaroxaban as compared against warfarin. This trial was organized under the pressure of many APS patients that did not want any more to be subject to blood drawn to control the intensity of anticoagulant treatment.

The Trial on Rivaroxaban in high risk thrombotic antiphospholipid syndrome (TRAPS) is a prospective, randomized, phase 3, open-label, non-inferiority trial [16]. The trial included patients aged 18–75 with triple positive aPL profile (IgG or IgM > 40 GPL/MPL units or > 99th percentile and positive LAC test) with a proven history of thrombosis (venous, arterial or biopsy proven microvascular thrombosis). The randomization was performed using random block and patients were stratified for sex and autoimmune disease.

The Intervention arm used Rivaroxaban 20 mg QD (15 mg if CrCl 30–50 ml/min) and the control arm warfarin to maintain an INR between 2 and 3. The Primary outcome (on treatment and ITT) was cumulative and included the incidence of thromboembolism, major bleeding and vascular death. The follow up visits were at 1–3-6 months and every 6 months thereafter. The patients were well balanced in the two arms. The trial was stopped early after 120 patients randomized due to excess arterial thromboembolic events in the rivaroxaban arm (7 (4 ischemic stroke and 3 MI) in the rivaroxaban arm vs none in the warfarin group). There were also more major bleeding events in the rivaroxaban treated patients (4 vs 2). Reasons for rivaroxaban failure remain elusive. Possible explanations may be related to poor adherence (which was not seen in this study), insufficient drug concentration, or the different mechanism of action of rivaroxaban with respect to warfarin. Only a small proportion of patients were taking aspirin and hydroxychloroquine and they were well balanced in the 2 groups, so this did not affect the results of the trial [17].

In conclusion, we should not use rivaroxaban in triple positive APS patients. Whether this statement might be extrapolated to other DOACs or to patients with single or double aPL positivity is currently unknown.

3. Should we use DOACs in APS: YES (in specific cases)

3.1. Case series

Resseguir described 23 patients with APS treated prospectively with rivaroxaban. APS involved the veins only (n = 19), arteries only (n = 2) or both (n = 1) and 1 patient exhibited catastrophic antiphospholipid syndrome (CAPS). 2 patients were triple positive. Initial treatment of VTE with rivaroxaban was given in six patients, and VKAs were replaced by rivaroxaban in 17 cases due to unstable INR or quality of life. The mean duration of follow up was 35.6 (range, 29–40) months. 1 patient developed bilateral distal pulmonary embolism (PE) after 20 month. This patient was triple positive, with previous venous thrombosis and obstetric manifestations but no recurrent thrombosis on VKA, no inherited thrombophilia and considered compliant. To note that another 5 patients did not complete treatment due to side effects or refusal to take treatment. The conclusion of the authors was that rivaroxaban might be useful for patients with APS with venous thromboembolism who presumably need standard intensity anticoagulation, in particular those with poor INR control and who are not at the highest risk of recurrent thrombosis, such as those with triple positivity [18].

Haladyj et al. published their departments experience with 23 APS patients receiving rivaroxaban. 6 patients also had SLE. All received hydroxychloroquine. Reasons for rivaroxaban introduction were: INR lability/therapeutic simplification (n = 7), patient's choice (n = 8), recurrent thrombosis (n = 6) and pulmonary embolism (n = 2). Twenty patients had been previously treated with VKA, while for the others it was the first anticoagulant. In the previous history, arterial thrombotic events occurred in 8 patients, only venous in 9 and both in 5 patients. aPL status was variable – 4 patients were a triple positive, 8 were double positive, and 11 were single positive aPL profile. After a median follow-up of 20 months, one relapse of thrombosis was reported (pulmonary embolism). This patient's characteristics were not reported [19].

Kunk et al. described retrospectively 11 patients with APS who were treated with Apixaban or Rivaroxaban. All patients suffered from a previous VTE, 4\11 were triple positive, 2\4 had recurrent thrombi while on warfarin. None of those patients developed recurrent thrombi during a mean follow-up of 11 months (5–39 months) [20].

Malec et al. followed prospectively 56 consecutive patients with APS who were treated with DOACs, mostly rivaroxaban due to their preferences or unstable anticoagulation with VKA. The patients were started on a DOACs at least 3 months after receiving treatment with another anticoagulant and D—dimer was below 500 ng\ml. 60% had also SLE, 28.6% were triple positive and 26.8% double positive. All patients had a previous VTE. 6 patients had more than one episode and 8 patients had a TIA or ischemic stroke. During a mean follow-up of 22 months (2–43 months), 6 patients experienced recurrent thrombosis (10.7%, 5.8 per 100 patient years, 4 VTE, one superficial vein

thrombosis and 1 non STEMI) 0.4\6 were triple positive and 4\6 has concomitant SLE. Mean factor VIII activity at the start of NOACs therapy was significantly higher in those patients [21].

These case series overall show a rate of recurrent thrombosis, in non-triple positive patients treated with DOACs, of 2–3\113 (1.7–2.6%) during a variable follow up time (mean 11 m–35.6 m and median 20 m) in the trials described.

The place of case series in the hierarchy of evidence-based medicine is low due to selection bias, lack of a comparator arm, and, in some studies a retrospective design and there are contradicting results from the various published case series. Several meta-analysis and randomized controlled trials on this subject were published.

4. Meta-analysis

Dufrost et al. published a meta-analysis summarizing 47 studies (4 RCT, 14 case series,21 case reports and 9 abstracts) corresponding to 447 APS patients treated with DOACs from 2000 to 3\2018. Three DOACs were analyzed: rivaroxaban (n = 290, 65%), dabigatran etexilate (n = 144,32%) and apixaban (n = 13. 3%) and the primary outcome was a recurrent thrombosis documented by appropriate imaging or histology occurring while on DOACs treatment. The rate of recurrent thrombosis was 16% (16.9% and 15% in anti-Xa inhibitors or dabigatran respectively), with a mean duration until thrombosis of 12.5 months. Thrombotic events included 28 VTE, 31 arterial thrombosis, 13 small vessel thrombosis and 8 unknown location. 3 had catastrophic APLA.

In low-risk APS patients (defined as patients with history of a single VTE, with no reference to their antibody status), arterial, small vessel thrombotic events as well as catastrophic APS occurred in 5%, 3% and 1% respectively during DOACs treatment. Risk factors for recurrent thrombosis were triple positivity (a four-fold increased risk 56% vs. 16% with a mean time until thrombosis of 16 months), a higher number of clinical criteria for definite APS, recurrent thrombosis while on warfarin treatment and a history of arterial thrombosis (only the first 3 with statistical significant). An underlying autoimmune disease was not found to affect thrombosis risk [22].

On the other hand, Elsebae et al. [23] evaluated the efficacy and safety of direct oral anticoagulants in the treatment of acute venous thromboembolism in patients with thrombophilia by performing a systematic review and met analysis of eight phase 2 and phase 3 randomized controlled trials comparing DOACs to VKA's in patients with VTE including patients with thrombophilia.

These studies included a heterogeneous group of 1994 patients with known hereditary thrombophilia as well as those with known APS. DOACs used were rivaroxaban (4 trials) dabigatran (3 trials) and edoxaban (1 trial). No relevant data was available concerning patients with thrombophilia from the apixaban trials.

In this group of patients no statistically significant difference in VTE recurrence rate was observed between patients treated with DOACs compared to VKA's and meta regression analysis showed that the treatment efficacy of DOACs vs. VKAs was not significantly affected by the presence or absence of thrombophilia. Bleeding events were both low and comparable in patients with various thrombophilia's receiving either treatment.

The subgroup analysis of patients with APS included eight studies and 476 patients. No statistically significant differences were observed between DOAC and VKA recipients in risk of recurrent VTE (RR, 0.88; 95% CI, 0.26–2.98) or clinically relevant bleeding (RR, 0.80; 95% CI, 0.37–1.73). Arterial thromboembolisms, including myocardial infarction, ischemic stroke, and systemic embolism, were a secondary outcome in the phase 3 studies included in this analysis. Upon further data acquisition, none of the APS patients receiving DOACs in EINSTEIN, Hokusai or RAPS studies experienced arterial thrombotic events. The number of triple positive APS patients in EINSTEIN, or Hokusai trials was not available.

This subgroup analysis restricted to APS patients indicates that DOACs can be as efficacious and safe as VKAs in preventing VTE recurrence among APS patients. However, in the absence of specific data on the proportion of high-risk triple-positive APS patients or those with a history of previous arterial thrombosis enrolled in the included studies, no solid conclusions can be made regarding DOACs use in these particular groups. It is also unknown whether APS testing was performed according to clinical guidelines that require two positive test results at least 12 weeks apart and there might be a selection bias for low risk patients in those trials. The low number of events also led to imprecise estimates (wide 95% CIs) precluding strong conclusions about the efficacy and safety of DOACs. Strengths of this analysis include the use of specific data on thrombophilia patients obtained from well-designed large robust randomized controlled clinical trials [23,24].

5. Randomized controlled trials

There are three RCT's comparing VKAs and DOACS in APS patients that were published or have interim results.

The ASTRO-APS study is an ongoing phase four prospective randomized open label blinded event pilot study initiated in 2016 testing the secondary prevention of thrombosis in patients with APS (patients with a continuum of laboratory data supportive of the diagnosis of APS including a history of thrombosis, but not all meeting the strict Sapporo criteria).

ASTRO-APS was originally designed to compare dose-adjusted warfarin with apixaban 2.5 mg twice a day (which is half of the recommended dose in AF) in patients with a history of arterial or venous thrombosis receiving indefinite anticoagulation. The primary clinical outcomes are rates at one year of arterial or venous thrombosis, death caused by thrombosis, major bleeding, and clinically relevant non-major bleeding [25]. After accrual of the first 25 patients, a pre-specified Data Safety Monitoring Board (DSMB) review recommended the protocol be modified to increase apixaban to 5 mg twice a day. After 30 patients were enrolled, a possibly higher than expected rate of stroke among patients with a history of stroke randomized to apixaban was observed. This potential safety signal led to an ad hoc DSMB review. The DSMB recommendations at that time were to continue the trial with s three amendments: increasing the apixaban dose to 5 mg twice a day instead of 2.5 mg twice a day, enrolling only patients with clinical APS and a history of venous thrombosis (excluding patients with prior arterial thrombosis from enrollment) and obtaining a brain MRI for all otherwise eligible candidates, and enrolling only those patients without radiographic evidence of prior stroke or white mater changes disproportionate for the patients age. The protocol was modified in 2018 and the ASTRO-APS is actively screening and endeavors to enroll 200 patients [26]. To note that according to previous works by Crowther and Finazzi rates of recurrent VTE or vascular death among patients with APS anti coagulated with a target INR of 2.5 (range 2–3) approximate 1.5% per year [27,28]. Thus the sample size of 200 patients will not large enough to identify statistically significant differences in thrombosis or mortality rates under a non-inferiority, superiority or equivalence test design. But results might inform a future randomized clinical trial.

Another RCT is the TRAPS trial which was presented above. The conclusion of the TRAPS trial is that Rivaroxaban is not effective in preventing recurrent thrombosis in triple positive APS patients [17]. This conclusion is of course justified; never the less the dose of rivaroxaban used in this trial (20 mg per day) might not be the ideal dose for APS. The half-life of Rivaroxaban is similar to that of Apixaban and Dabigatran which are given twice a day. The requirement for higher anti-Xa activity and plasma rivaroxaban levels for the prevention of arterial vs. venous events has been demonstrated in animal models. In addition, high inter individual variability may expose some patients to inadequate plasma levels of the drug. Therefore some ongoing trials are

using higher doses of NOACs in a twice daily dose: The RISAPS study which compares the use of high intensity warfarin (target INR 2.5–3.5) with a twice daily dose of Rivaroxaban (15 mg BID) in patients with a previous confirmed CVA/TIA due to arterial disease and the ASTRO-APS trial which increased the dose of Apixaban used in their study to 5 mg twice a day as mentioned above [26].

The third RCT is the RAPS trial. The RAPS trial was a randomized, controlled, open label, phase 2/3, non-inferiority trial. Eligible patients had taken standard-intensity warfarin for at least three months after the last VTE. Exclusion criteria were arterial thrombosis, recurrent VTE while taking warfarin at a therapeutic INR, and age younger than 18 years. 53% of the patients included in the study were positive for only one of LAC\anticardiolipin \beta 2 glycoprotein (mostly LAC). The RAPS trial randomly allocated 116 APS patients to rivaroxaban or warfarin. 20% and 12% of the patients in the rivaroxaban and warfarin groups respectively were triple positive. The primary outcome of this study was a laboratory outcome ETP (endogenous thrombin generation, which is the area under the curve of thrombin generation). Although the ETP for rivaroxaban did not reach the non-inferiority threshold, peak thrombin generation was lower with rivaroxaban and therefore the overall thrombogram indicated no difference in thrombotic risk. It is suggested that the higher ETP associated with rivaroxaban can be explained by altered reaction kinetics that do not affect the thrombotic risk. Importantly none of the patients developed a new thrombotic event nor a major bleeding episode during six months of treatment [29].

Taking all this data into account, we recommend to consider NOACs treatment in APS in a personalized approach. APS is not a single medical entity but includes a spectrum of patients with different risks of recurrent thrombosis depending on various variables including the antibody profile, previous type of thrombotic event (gestational, venous or arterial), smoking status, and other medical problems such as diabetes. In a prospective observational cohort with 150 LAC positive patients (74.2% with APS), the risk of non-smoking, non-diabetic, LAC negative patients to develop recurrent thrombosis was relatively low: 9.7% in 10 years compared with 57% in 10 years in smoking, diabetic and LAC positive patients. (3/4 of the events occurred while on anticoagulant therapy) [30].

6. Conclusion

Secondary thromboprophylaxis with low molecular heparin or VKA is recommended in patients with definite antiphospholipid syndrome (APS). Whether DOACs can be used for secondary prophylaxis in APS is an open question. Data from the TRAPS randomized controlled Trial, meta-analysis and case reports currently indicate that we should not treat patients with triple positive APS and/or arterial thrombi with routine doses of DOACS. On the other hand data from the literature including, case series, meta- analysis and the RAPS trial indicate that there are low risk patients such as patients who suffered from a venous but not an arterial thromboembolism and are LAC negative who may benefit from treatment with DOACs. DOACs treatment in such patients may be considered especially in patients who refuse, fail or are intolerant to warfarin due to NOACS improved compliance, lack of required monitoring and improved rates of major bleeding.

Recommendations from the 15th APLA task force congress state that rivaroxaban might be useful in selected APS patients with a single venous thromboembolism requiring standard intensity anticoagulation, however this needs to be confirmed with additional studies using clinical outcome measures [31]. Similarly, the 2019 Eular recommendations for the management of APS in adults recommend to avoid rivaroxaban in patients with triple aPL positivity or arterial events but states that DOACs may be considered in patients with difficulty achieving a target INR of 2–3 despite compliance with VKA or who have contraindications to VKA. Switching from treatment with VKA to DOACs due to low adherence to VKA or INR monitoring should be avoided [5]. Prospective trials addressing low risk patients are needed in order to consider whether DOACs treatment can be given to such patients and whether an increased dose or a twice daily dose is needed.

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