



New Oral Anticoagulants in Antiphospholipid Syndrome Treatment

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Abstract

Antiphospholipid Syndrome (APS) is an autoimmune acquired thrombophilia characterized by recurrent thrombosis and pregnancy morbidity in the presence of persistent antiphospholipid antibodies. Current therapeutic recommendations for thrombosis prevention in patients with APS are limited to anticoagulation with Vitamin K Antagonists (VKA) or heparins and to anti-platelet aggregating agents. Maintaining optimized anticoagulation to prevent recurrent thrombosis or bleeding remains a therapeutic challenge. Direct Oral Anticoagulants (DOACs) DOACs have been approved to prevent recurrent thrombotic events in different prothrombotic conditions, such as non-valvular atrial fibrillation, deep vein thrombosis still aim the same target and thromboprophylaxis after elective orthopedic surgery. The mechanism of action of these new anticoagulants involves the direct inhibition of either factor Xa (rivaroxaban, apixaban, edoxaban or betrixaban) or thrombin (dabigatran etexilate), in a reversible, competitive, highly selective and dose-dependent manner. In the pivotal trials, DOACs showed safety and efficacy profiles similar to those of VKAs, in conditions not related to APS. Due to their pharmacokinetic and pharmacodynamic characteristics, there are some very appealing advantages of DOACs over VKAs, namely the lack of need for laboratory monitoring, the usage of a fixed dosage for all patients, absence of significant interaction with dietary components and drugs, and rapid anticoagulant onset after drug initiation. On the other hand, assays to measure drugs levels and antidotes are not routinely available in clinical practice, raising concerns about hemorrhagic complications. Recent experiences of rivaroxaban in secondary thromboprophylaxis of APS have not been good to avoid arterial thrombosis. Therefore the use of NAOs in the APS thromboprophylaxis is debatable.

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The Antiphospholipid Syndrome (APS) is characterized by thrombosis, venous and/or arterial, and/or morbidity and mortality in pregnancy in association with persistently positive Antiphospholipid Antibodies (aPL), which consist of a family of heterogeneous immunoglobulins directed against plasma binding proteins to the phospholipid. The Sydney classification criteria for APS includes the IgG and IgM isotypes of Anticardiolipin Antibodies (aCL), anti- β_2 -Glycoprotein-I ($\alpha\beta_2$ GPI) antibodies and a positive test for Lupus Anticoagulant (LA) [1]. The triple positivity of the aPL implies a greater risk of developing APS. However, triple positivity is not essential in clinical practice, but it is good to confirm the presence of aPL and to homogenize clinical trials and scientific publications in patients with APS. Thrombotic APS is a life-threatening condition in which thrombosis has been described in almost all vessels in the body, arteries, veins and microcirculation. Catastrophic Syndrome by aPL (CAPS) is a more serious form with small and large vessel thrombosis, multiple-organ dysfunction of rapid onset and in a short period of time. Finally, some APS cases present only thrombotic microangiopathy, with the kidney and brain target organ. Patients with positive aPL exist without aPL-related thrombosis with or without morbidity during pregnancy, or only with manifestations of aPL "without criteria" APS, for example, thrombocytopenia, hemolytic anemia, livedo reticularis, chorea or heart valve disease. aPL positive invite an evaluation of autoimmune disease such as SLE (systemic lupus erythematosus), or in the establishment of a time of high partial Activation Of Thromboplastin (APTT) or a laboratory test of research of false positive venereal diseases. The clinical practice is to quantify the risk of thrombosis, prevention of the first thrombosis and secondary prophylaxis of thrombosis after the first event [2].

Thrombosis Treatment of APS

The treatment of hypercoagulation of APS is to prevent the first thrombosis event, prevention of thrombosis in risk situations and acute thrombosis is treated with low molecular weight heparin and

secondary prophylaxis of thrombosis with long-term anticoagulation with oral Vitamin K Antagonists (VKA), such as warfarin or acenocoumarol (the most used in Spain). However, the results are not totally satisfactory since some patients still have new thrombosis episodes and VKA have the disadvantages of being dependent on oral vitamin K intake, need periodic checks, the margin between bleeding risk and thrombosis is narrow and many others drugs interfere with his liver metabolism. The treatment with VKAs to secondary thromboprophylaxis of APS patients is not completely successful and new strategies are justified.

The New Oral Anticoagulants (NOA) have been approved for several indications post phase III trials, prospective randomized controlled clinical trials that use VKA with a target INR of 2.5 (range 2.0 to 3.0) as a comparator [3]. However, these trials results can't be directly applicable to patients with APS when possible. The NOA are being used for thromboprophylaxis of APS but have not yet been approved by the drug agencies for lack of trials demonstrating its effectiveness. However, many cases of patients with primary health care have been treated or are being treated with NOA [4].

The New Oral Anticoagulants

The New Oral Anticoagulants (NOA) include dabigatran etexilate (Pradaxa[®]), a direct inhibitor of thrombin, and rivaroxaban (Xarelto[®]), Apixaban (Eliquis[®]), Edoxaban (Lixiana[®]) and Betrixaban (Bevyxxa[®]) which are direct anti-Xa inhibitors with appreciably pharmacokinetic characteristics different among all of them (Table 1) [5]. In 2008, the first NOA, dabigatran and rivaroxaban were approved by the European Medicines Agency (EMA), followed by apixaban in 2011 and edoxaban in 2015. To date, NOA are approved for the following therapeutic indications: prevention of Thromboembolism Venous (VTE) in patients who underwent hip or knee surgery replacement; prevention of stroke and systemic embolism in patients with Non-Valvular Atrial Fibrillation (NVAF); the treatment of Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE), and the prevention of recurrence of these conditions with long-term therapy; It is also indicated for the prevention of athero-thrombotic events in adult patients after an Acute Coronary Syndrome (ACS) without Atrial Fibrillation (AF), in addition to Acetylsalicylic Acid (ASA) alone or in combination with clopidogrel or ticlopidine. On June 23rd, 2017, the Food and Drug Administration (FDA) approved betrixaban for the prevention of VTE in adult patients hospitalized for acute medical illness who are at risk of thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE. However, on March 22nd, 2018, the Committee for Medicinal Products for Human Use (CHMP) of the EMA adopted a negative opinion of the APEX trial on betrixaban in its effectiveness when used to prevent blood clots in patients admitted to the hospital. For recent medical attention to illness and because the benefits did not outweigh the risks (for example, risk of bleeding). A second examination requested by the betrixaban pharmaceutical company, the CHMP confirmed the refusal of commercialization for this utility.

The NOA in APS Thrombosis

For now, VKA and low molecular weight heparin remain the first line anticoagulants in patients with APS, but NOA may be considered due to VKA failure, severely labile INR, patient preference or other reason. The NOA are administered at fixed doses, their anticoagulant effect is a few hours instead of days of the VKA, do not require laboratory monitoring of the degree of coagulation and absence of

significant interaction with dietary components and drugs. On the other hand, assays to measure drug levels and antidotes are not routinely available in all of NOA, in clinical practice, raising concerns about hemorrhagic complications, Apixaban and rivaroxaban both have the same pharmacological interactions and predictable pharmacokinetics Both agents have been approved for the prevention of stroke in non-valvular atrial fibrillation, VTE prophylaxis and for the treatment of acute Venous Thromboembolism (VTE). The highest doses are used during the first 1 week to 3 weeks of VTE therapy. The maintenance dose for rivaroxaban is 20 mg once a day and for apixaban it is 5 mg twice a day. A 2.5 mg option twice a day is used as extended therapy after the first 6 months. The apixaban, it is less dependent on kidney function for its routine metabolism and may be preferable to rivaroxaban in patients with renal failure. Rivaroxaban is very attractive for its dosage once a day. In any case, the half-life of apixaban and rivaroxaban is similar, have similar pharmacokinetics and their pharmacodynamic effects correlate closely with their plasma concentration [5].

The NAO in SAP Secondary Thromboprophylaxis Observational Studies

NAO have been used in the secondary prophylaxis of venous or arterial thrombosis in the SAP with usually favorable results [6-10]. The series published by Malec et al., [6] should be highlighted, with 56 patients (49 of them with rivaroxaban) with a mean follow-up of 22 months and VTE recurrence of 5.8%. The investigations developed by Haladyj and Olesinsk in 23 patients and Son et al., [8], in 12 rivaroxaban treatments, recurrence occurred in 1 and 2 cases, respectively and Signorelly et al., [9] present the results of a series of 8 cases with APS treated with rivaroxaban: all had presented venous thrombosis, two cases arterial thrombosis and two cases triple positivity for antiphospholipid antibodies [7]. During these treatment five patients developed arterial thrombotic events and the authors conclude that until new results it is not indicated to treat rivaroxaban in patients with APS since it seems that the APS are more protected with the VKA than with the NAO type rivaroxaban. Several authors have reported case series and cohort studies describing thromboembolism recurrence in APS patients switched from warfarin to a NOA and even development of a catastrophic syndrome by antiphospholipid antibodies [7-13].

These results have been confirmed by a recent systematic review of MEDLINE, EMBASE and Cochrane databases (2000-2018) of patients with APS treated with los differences NOA utilizados an increase in the risk of re-thrombi was detected; a total of 73 patients out of 447 (16%) experienced a recurrent thrombosis while they were with the NAO (290 cases with rivaroxaban 290, dabigatran etexilate 144 and apixaban 13) with an average treatment duration of 12.5 months [14]. Recurrence rates were 16.9% with anti-XA and 15% with those treated with dabigatran. The risk factors ODIs might be an alternative therapeutic option in APS were the triple positivity of the aPI (56% versus 23%), more clinical manifestations of APS and the history of arterial thrombosis in those treated with anti-Xa (32% versus 14%). However, Noel et al., [15] report a 26 APS patients treated with NOA concluding that it could be an alternative therapeutic option in APS; six patients received the NOA as a first-line and second-line treatment in 20, 19 who had previously been treated with VKA and one with fondaparinux; the NAOs were indicated due to the flexibility of INR\ therapeutic simplification (n=17), recurrent thrombosis (n=1), bleeding event associated with VKA (n=1) and

Table 1: Summary of pharmacokinetic characteristics of NOA.

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Action	Anti-Thrombin	Anti-Xa	Anti-Xa	Anti-Xa	Anti-Xa
Activity	Irreversible	Irreversible	Irreversible	Irreversible	Irreversible
Half-life (h)	12 to 14	5 to 9 in young adults 11 to 13 in older adults	8 to 15	10 to 14	19 to 27
Volume n distribution (L)	60 to 70	50	21	107	32
Pro-drug	Yes	No	No	No	
Absorption with food	Delay	No effect	No effect	No effect	No effect
C_{max} (h)	0.5 to 2	2 to 4	3 to 4	1 to 2	3 to 4
Plasma Protein Binding	34% to 35%	92% to 95%	87%	40% to 59%	60%
Bioavailability	~ 6.5%	80% to 100% (10 mg) 66% (20 mg)	50%	62%	34%
Metabolism	Glucuronic acid Conjugation	CYP3A4 CYP2J2	CYP2J2, CYP3A4/5 CYP2C9, CYP2C19	CYP3A4/5 CYP1A2	CYP450 CYP2C8

atrial fibrillation (n=1). After a median follow-up of 19 months, a relapse of arterial thrombosis, two bleeding events (hyper menorrhea and rectal bleeding under rivaroxaban) and a recurrent migraine were reported, leading to discontinuation of treatment in these patients.

The NAO in APS Secondary Thromboprophylaxis: Controlled Studies

The efficacy results of NOA in the secondary prophylaxis of thrombosis in patients with APS have been disparate or inconclusive, therefore controlled studies of NOA use in APS were necessary. Several trials have been developed in the last five with results already published in some of them [15-18]. The first published (RAPS study) by Cohen et al., [15] after randomizing 59 patients to the rivaroxaban arm and 61 patients to the warfarin arm, the study was terminated due to occurrence of more events in the rivaroxaban group; thromboembolic events and major bleeding occurred in 12% and 7% in the rivaroxaban arm compared with 0% and 3% in the warfarin arm, respectively. Noteworthy, seven arterial events were documented in the rivaroxaban group versus none in the warfarin group. The group of patients with APS and rivaroxaban showed that thrombin generation markers are not increased with rivaroxaban compared with warfarin in patients with APS who had previous venous thromboembolism. Taking also into account the absence of clinically significant bleeding, the study concluded that rivaroxaban could be efficacious and safe in this subgroup of patients with APS. Of note, 28% of patients in RAPS had triple positivity for lupus anticoagulant and antibodies against cardiolipin and β_2 GPI at baseline and, therefore, had a particularly high-risk antibody profile. The TRAPS study by Pengo et al., [16] published the results of a randomized non-inferiority, open-label, multicentre study with blind allocation of endpoints. Rivaroxaban, 20 mg once daily (15 mg once a day according to renal function) was compared with warfarin (objective INR 2.5) for the prevention of thromboembolic events, major bleeding and vascular death in patients with antiphospholipid syndrome. Only patients with high triple-positive risk for lupus anticoagulant, anti-cardiolipin and anti- β_2 -glycoprotein-I of the same isotype (triple positivity) were included in the study. The trial ended prematurely after enrollment of 120 patients (59 randomized to rivaroxaban and 61 to warfarin) due to an excess of events among patients in the rivaroxaban arm. The mean follow-up was 569 days. There were 11 events (19%) in the rivaroxaban group and 2 events (3%) in the warfarin group.

Thromboembolic events occurred in 7 (12%) patients randomized to rivaroxaban (4 ischemic strokes and patients with APS was associated with an increased rate of events compared to warfarin, so it did not show benefits or excessive risk.

Finally, our study, a randomized, controlled, open-label, phase 3, non-inferiority trial included patients with APS receiving Vitamin K Antagonists (VKA) [17]. The transition from VKA to rivaroxaban an intermediate step to therapeutic Low Molecular Weight Heparin (LMWH). After randomizing 180 patients (90 rivaroxaban and 90 acenocoumarol) and 3 years of follow-up, recurrent thrombosis occurred in 11 patients in the rivaroxaban group (11.58%, 4.39/100 patient-years) and 6 in the VKA group (6.32%, 2.26/100 patient-years) (hazard ratio in the rivaroxaban group, 1.88;95% confidence interval 0.67-5.27). Stroke occurred frequently in rivaroxaban-treated patients (9 events (3.59/100 patient-years)) compared with those receiving VKA (0 events). Major bleeding occurred in 6 patients (6.32%, 2.84/100 patient-years) in the rivaroxaban, and in 7 patients (7.37%, 3.14/100 patient-years) (hazard ratio 0.88; 95% CI 0.30-2.63). Post-hoc analysis suggested in rivaroxaban-treated patients an increased risk of recurrent thrombosis in the presence of previous arterial thrombosis, livedo reticularis and APS-cardiac valve disease (paper in press). The other two studies the results have not yet been reported [18,19].

The NOA in APS Patients in Clinical Practice. Primary and Secondary Thrombosis Prophylaxis

For now, low-molecular-weight warfarin and heparin remain the first-line anticoagulants in patients with APS, but NOA can be considered due to VTK failure, severely labile INR, patient preference or other reason. The optimal intensity of anticoagulation is still controversial. Historical retrospective studies propose a greater intensity of VKA therapy to prevent recurrence, but two prospective studies have suggested that an INR between 2 and 3 could have similar effects with fewer bleeding complications [20-22]. The efficacy of VKA varies according to genetic or environmental factors (diet or disease states) and drug interactions. Thromboplastins respond differently to antiphospholipid antibodies; some patients with abnormal baseline prothrombin time disturb the INR monitoring and the dosage of dependent vitamin K factors through chromomeric substrates is necessary in 20% of patients [23]. VKA and NOA interfere in the

determination of LA in plasmas of patients with APS in treatment with VKA or NOA [2].

Recurrences of thrombosis despite VKA occur in up to 5% to 20% of patients with APS and long time follow up. In such situations the treatment trends of these cases of APS suggest the use of Low Molecular Weight Heparin (LMWH), hydroxychloroquine and statins as additional therapies despite the deficiency of evidence levels. The use of NOA has been suggested in this condition, but both the results of some observational studies or the few available controls contradict the possibility of using the NAOs indiscriminately in patients with APS. Ribaroxaban has been the NOA most used in APS, probably because it is a daily dose. However, the few clinical experiences with antithrombin like dabigatran or others anti-Xa have not shown better results either [14].

The phenotype of patients with APS, arterial and small vessel thrombosis manifestations, cutaneous livedo reticularis, a higher number of criteria for definite APS and anti-phospholipids antibody triple positivity would be contraindicated to give NOA. Thus, a high-risk aPL profile, i.e. triple positivity, is associated with lower effectiveness of NOA in APS patients. These would only be indicated in well selected APS patients in whom the VKA could not be used [12,14].

The primary prophylaxis of thrombosis in patients with APS is very poorly established although aspirin low dose is used, which does not seem effective and there are no studies conducted with VKA at non-therapeutic doses. The main advantage of NOA over VKA lies on their pharmacodynamics and pharmacokinetics which produce a predictable and stable anticoagulant response. As a consequence, they do not require routine laboratory monitoring of coagulation. NOA may be suitable since intraterrapeutic doses may be more stable without bleeding risk because of less interference from food or other drugs in the metabolism of NAO. However, the triple positivity of aPL antibodies is good for homogenizing patients for a clinical trial or for reporting clinical results but clinical practice shows patients with only lupus anticoagulant or high levels of aCl exhibit thrombotic phenomena. We propose studies in this regard with both antithrombin and anti-Xa.

APS Thrombosis: Unsolved Problems

The mechanism of thrombosis due to aPL is unknown and probably complex, because patients have venous and/ or arterial thrombosis, thrombotic microangiopathy or even both in the same patient. In addition, in some patients a second prothrombotic stimulus is detected at the time of thrombosis. On the other hand, some patients with aPL antibodies do not have thrombosis after prolonged follow-up. But even if we knew the thrombosis mechanism by aPL, the treatment would be similar since we have anticoagulants and antiaggregants and, the other hand, the immunosuppressive treatment to diminish or make disappear the aPL does not exist actually [24]. However, a majority of patients with PSA evolve well with VKA for secondary thromboprophylaxis. The minorities who still present thrombosis are those with the phenotype of arterial thrombosis, livedo reticularis and cardiac valve disease and the antithrombotic regimen to follow is not well established. The intensity of anticoagulation with anti-vitamin K is still a matter of debate especially in high-risk APS patients or those with a history of arterial manifestations; most authors recommend a target INR of 2-3 + aspirine or a target INR of 3-4 without aspirine [25]. It follows that the optimal intensity of NOA in patients who experience recurrent VTE while on standard intensity VKA is not

established. NOA targets only one coagulation factor either Xa or IIa. It is unclear whether inhibition of only one coagulation factor rather than several with VKA could explain treatment failures by NOA. The central question is not only how much thrombin is generated but kinetics of thrombin generation and inhibition is also important. In the dosing of NOA should body weight be taken into account and dosed according to body weight always better than standard dose? In our study, we found that in APS patients treated with anti-Xa inhibitors a positive history of arterial thrombosis, livedo reticularis or migraine was associated with recurrent thrombosis. This finding suggests that in patients with a history of arterial thrombosis are not good candidates for treatment with anti-Xa [26].

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