CASE REPORT

# Variability in the international normalised ratio (INR) in patients with antiphospholipid syndrome and positive lupus anticoagulant: should the INR targets be higher?

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## SUMMARY

We present the case of a 34-year-old woman with a history of antiphospholipid syndrome with triple positivity for antiphospholipid antibodies, who had multiple thrombotic events, predominantly pulmonary embolic events, despite treatment with enoxaparin. She is currently on warfarin, with which she has been adequately controlled most of the time, presenting with only one haemorrhagic event consisting of haematuria and prolonged international normalised ratio (INR) without bleeding. This kind of patient represents a challenge for clinicians, particularly due to INR therapeutic targets, which should be higher than recommended in other patients due to the lupus anticoagulant positivity.

## BACKGROUND

Antiphospholipid syndrome (APS) is an autoimmune disorder characterised by hypercoagulability requiring anticoagulant therapy as the basis, with warfarin as the treatment of choice in cases requiring long-term management. However, patients with positive lupus anticoagulant (LA) present a challenge because they have an increased risk of thrombotic events, in addition to the fact that the monitoring of the international normalised ratio (INR) is unreliable because these antibodies generate interference with the laboratory tests based on phospholipids, as is the case for prothrombin time (PT) with prolonged baseline INR, even before the start of anticoagulant therapy.

For this reason, we present the case of a patient with primary APS and positive LA who had multiple thrombotic events despite receiving anticoagulant therapy.

## CASE PRESENTATION

We present a case of a 34-year-old woman with gynecobstetric profile G2P1A1V1 and surgical sterilisation after delivery. She weighed 50 kg. Her first episode of deep venous thrombosis occurred in 2005, after which warfarin therapy was started for 3 years, presenting only a single serious adverse event of chronic haematuria that led to anaemia, for which she was hospitalised and transfused with red blood cells (RBCs). At that time, in 2008, therapy with enoxaparin 60 mg subcutaneous every 12 h was started, under which she presented 15 pulmonary thromboembolism events, despite being adherent to the therapy. Levels of antifactor Xa were never measured. For this reason, in May 2012, 20 mg/day oral rivaroxaban was started, lasting only 3 months, as the patient presented upper gastrointestinal bleeding requiring hospitalisation for 45 days, transfusion of RBCs and administration of prothrombin complex concentrate. For this reason, she was reverted to enoxaparin 60 mg SC every 12 h but she presented a new pulmonary embolism in May 2013. Finally, therapy with warfarin 2.5–5 mg/day was started, without new thrombotic or haemorrhagic events to date. The usual INR prolongations (up to 10) with no associated bleeding were the only documented adverse events. The patient mentioned that she had to change the brand of the drug several times and follow dietary recommendations to avoid interactions with food, and that she has not undergone genetic testing for CYP2C9 and VKORC1.

## INVESTIGATIONS

Creatinine (26/07/2013) 0.67 mg/dL.

In 2013, the following immunological profile (09 August 2013) was obtained: antinuclear antibodies: negative, antiDNA: negative, extractable nuclear antigens: negative, C3: 16 mg/dL, C3: 70 mg/dL. Anticardiolipin IgG and IgM: positive. Lupus anticoagulant IgG and IgM: positive. Anti β2 glycoprotein 1 antibodies IgG and IgM: positive.

Baseline INR prior to the start of anticoagulant therapy is not available.

## TREATMENT

In May 2014, the patient underwent thromboendarterectomy.

She currently receives oxygen 12 h at night with nasal cannula at 2 L/min from an oxygen tank

- Warfarin 5 mg daily
- Sildenafil 50 mg every 8 h
- Furosemide 40 mg daily
- Atorvastatin 40 mg daily
- Calcium carbonate 600 mg daily
- Carvedilol 6.25 mg every 12 h
- Chloroquine 150 mg daily
- Spironolactone 25 mg daily
- Omeprazole 20 mg daily

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## OUTCOME AND FOLLOW-UP

Currently, the patient is stable, with good adherence to treatment and an INR target of 3.0–4.0, without new thrombotic events since May 2013, in joint management by rheumatology, internal medicine, pulmonology, anticoagulation clinic, physical therapy and rehabilitation. After thromboendarterectomy, pulmonary hypertension has improved, although there is still the need for supplemental oxygen at night. It should be noted that pulmonary hypertension occurred because of chronic thromboembolism due to insistent anticoagulation with enoxaparin, despite the obvious therapeutic failure.

## DISCUSSION

APS is an autoimmune disorder characterised by thrombosis (venous and/or arterial), recurrent abortions and persistently positive antiphospholipid antibodies (aPL) such as LA, anticardiolipin IgG and/or IgM, and/or anti-β2 glycoprotein one antibodies.[1] Persistently positive aPL is defined as their presence on at least two occasions. The second confirmatory APA lab test should be carried out at least 12 weeks after the initial test.[2]

APS affects 0.5% of the population and occurs mainly in young women (only 12% of cases are diagnosed over the age of 50 years) in association with other autoimmune diseases, such as systemic lupus erythaematosus or lupus-like syndrome (secondary APS), or in idiopathic form (primary APS).[3]

Patients with APS have an increased risk of thrombotic events, and the main therapeutic goal is precisely to prevent such events; thus, patients with this condition require anticoagulation for long periods of time,[2 4] either as primary or secondary prevention, and warfarin is currently the drug of choice in non-pregnant patients.[3 4]

The anticoagulant effect of warfarin is monitored with the international normalised ratio (INR), which is based on the patient's PT.[1] The current therapeutic INR target in patients with APS, according to the anticoagulation guidelines of the American College of Chest Physicians (CHEST), is between 2.0 and 3.0.[5] However, the recommendations are not clear for patients with APS who are positive for LA, in whom the risk of thrombosis is higher, as these antibodies mediate the activation of platelets, monocytes and endothelial cells, causing an inflammatory process that alters the natural anticoagulant and fibrinolytic system.[3] Some authors have questioned the targets set by CHEST due to the limitations and lack of statistical significance of the clinical trial supporting this recommendation, which is categorised as Grade 2B.[3]

Additionally, anticoagulation monitoring in LA-positive patients with APS is problematic because this antibody can prolong the patient's baseline INR, even without the patient having started anticoagulation therapy, and in patients on warfarin therapy, the INR may be considered supratherapeutic, not reflecting the true state of anticoagulation.[1 6 7] Such was the case in our patient, who had an INR of 7.3 without associated bleeding. However, the frequency with which LA interferes with PT is not well established.[8]

It is proposed that the alteration in the INR is due to the sensitivity of the reagents used in the test to the presence of LA.[3] However, some studies show variability in INR with most commercially available reagents.[9] Other studies, in contrast, show that INR results do not vary in the presence of LA, regardless of the reagent used.[10] Therefore, the reliability of INR in this subtype of patients is uncertain, and the best course of action must be determined based on the available evidence.

Therefore, there is a need to establish the best anticoagulant therapy and the best monitoring method in LA-positive patients with APS.

Low-molecular-weight and unfractionated heparins are effective in anticoagulant therapy; however, their parenteral administration, the risk of heparin-induced thrombocytopenia, and their association with osteoporosis in prolonged therapy recommend them only at the start of therapy while therapeutic INR ranges are achieved with warfarin administration.[11] According to The Task Force Report on APS Treatment Trends published in 2014, current treatment for thrombotic APS consists of heparin followed by a vitamin K antagonist in the long term.[12] In our patient, the use of enoxaparin for 4 years at therapeutic doses was associated with multiple thromboembolic events, and for that reason a therapeutic failure of the drug was confirmed, possibly related to the underlying pathology of the patient.

One group of authors suggests that patients with APS who present a first venous thrombotic event require indefinite anticoagulation with warfarin with an INR target of 2.0–3.0. However, patients with APS presenting one arterial thrombotic event and/or recurrent thrombotic events, despite treatment with warfarin reaching an INR between 2.0 and 3.0, should also receive indefinite anticoagulation with warfarin, but with an INR target of 3.0–4.0.[2] Although these authors do not differentiate LA-positive patients with APS, it can be assumed that these patients can be cast in the second group mentioned.

For primary prevention, these authors suggest the administration of hydroxychloroquine with low-dose aspirin in LA-positive patients with APS and/or positive anticardiolipin antibodies.[2] Chloroquine was one of the drugs started in our patient.

Chromogenic Factor X (CFX) is another phospholipid test proposed as an alternative for monitoring LA-positive patients with APS who are being anticoagulated with warfarin.[1 3 6 8] In this test, factor X is activated by Russell's viper venom in the presence of calcium; subsequently, factor Xa hydrolyses a highly specific chromogenic substrate, producing a yellow pigment analysed by spectrophotometry at a wavelength of 405 nm.[8] CFX results are reported as a percentage of normal activity of factor X and are inversely related to INR values. It is considered that the therapeutic range of CFX is 20–40%; therefore, 40% CFX would be equivalent to an INR of 2.0 and 20% CFX to an INR of 3.0.[3 7] Although CFX is an attractive alternative to monitoring LA-positive patients with APS on warfarin therapy, this test is more expensive than INR, is not readily available, and its result can only be known 24–72 h after taking the sample.[3]

Another alternative for the monitoring of warfarin anticoagulation is factor II. This test is performed based on the patient's PT, which may also present variability in the presence of LA, either by direct interference or due to the presence of anti-factor II antibodies, which have been documented in LA-positive patients. When comparing factor II against CFX, CFX has shown greater precision and stability.[6]

Rosborough and Shepherd[7] compared the activity of CFX and INR in LA-positive patients versus LA-negative patients, showing that the therapeutic INR range for LA-positive patients is higher than currently recommended with reference to the therapeutic activity of CFX; thus, according to these results, in these patients, the optimum INR should be between 3.0 and 4.0.[2]

In many LA-positive patients on warfarin therapy, INR could be a valid measure of anticoagulation, but it is prudent to validate this measurement with the concomitant activity of CFX,

which may be repeated after every cycle of 4–6 INR tests performed.[1 7]

One optional treatment for LA-positive patients with APS, in whom INR monitoring is doubtful, is the use of new oral anticoagulants, such as dabigatran, rivaroxaban, apixaban and edoxaban; however, there are no studies supporting the efficacy and safety of these anticoagulants in these patients. Arachchillage and Cohen[1] advise conducting studies with rivaroxaban because it is the oral anticoagulant that has been approved in the most indications (prevention of thrombotic events in patients with non-valvular atrial fibrillation, treatment and prevention of deep vein thrombosis and pulmonary embolism, and thromboprophylaxis in hip and knee replacement).

Indeed, Bachmeyer and Elalamy[13] reported one successful case of treatment with rivaroxaban at doses of 20 mg daily in a 26-year-old patient with recurrent superficial thrombophlebitis and primary APS.

Two clinical trials are currently being conducted, TRAPS (phase III) and RAPS (phase IV). The TRAPS (rivaroxaban in thrombotic APS) study aims to demonstrate the non-inferiority of rivaroxaban versus warfarin with respect to the occurrence of thrombotic events, major bleeding and death in patients with APS and triple positivity aPL. The RAPS study (rivaroxaban for APS) aims to monitor a group of patients receiving rivaroxaban for 1 year and determine the incidence of bleeding and thrombosis. The results of these studies are expected in 2018 and 2016, respectively.[14 15]

We did not find a predisposing factor to explain bleeding as an adverse effect of rivaroxaban in our patient. Among the drugs that the patient was using at that time (prednisolone, calcium carbonate, sildenafil, folic acid, omeprazole, alprazolam), drug interactions are not reported.

In conclusion, warfarin remains the drug of choice for long-term anticoagulant therapy in patients with APS as a secondary prevention strategy. However, LA-positive patients with APS pose a challenge, as they have a higher risk of thrombotic events, in addition to the fact that they can have a prolonged baseline INR, which therefore does not reflect the true state of anticoagulation. All patients with a diagnosis of APS should have a full aPL profile, and if any antibody is positive, it should be confirmed at least 12 weeks after the initial test.

Once the need for anticoagulant therapy is determined, it must be started with unfractionated or low-molecular-weight heparin in conjunction with warfarin until therapeutic INR ranges are obtained. It is important to highlight that the following recommendations are perhaps not strongly grounded in evidence, but they are supported by a comprehensive literature review and perhaps represent the best current consensus guidelines:

Patients with positive anticardiolipin IgG and/or IgM and/or anti-β2 glycoprotein 1 antibody, but LA negative and first venous thrombotic event: INR targets should be between 2.0 and 3.0. If the thrombotic event was arterial or recurs despite treatment with warfarin, INR should be between 3.0 and 4.0.[1 2 7]

LA-positive patients with prolonged baseline INR, regardless of the nature of the thrombotic event (primary vs recurrent and venous vs arterial): INR targets should be between 3.0 and 4.0. In addition, the activity of CFX should be determined after every six INR tests performed.[1 2 7]

LA-positive patients with normal baseline INR and no prolongation and first venous thrombotic event: INR targets should be between 2.0 and 3.0.[1 2 7]

LA-positive patients with normal baseline INR and no prolongation but with arterial or recurrent thrombotic event despite warfarin therapy: INR targets should be between 3.0 and 4.0.

Finally, in triple aPL-positive patients, regardless of the nature of the thrombotic event suffered and of the prolongation or not of baseline INR, INR targets should be between 3.0 and 4.0. Additionally, the activity of CFX should be determined after every six INR tests performed. We categorise our patient in this group.

Of the therapeutic options currently available for anticoagulant therapy, warfarin is the most effective and safest drug for use in patients with APS,[3 4] provided there is good adherence to treatment by frequent INR monitoring in an anticoagulation clinic, together with compliance with dietary recommendations, using the same brand of drug and avoiding the use of concomitant medications that may interfere with the anticoagulant effect of warfarin. Similarly, performing genetic testing for CYP2C9 and VKORC1 before the start of therapy is recommended.[16]

In the case of our patient, it was demonstrated that among all anticoagulant therapies she received (low-molecular-weight heparin, inhibitor of activated Factor X and coumarin), warfarin was the most effective therapy, probably as the result of close monitoring by the anticoagulation clinic, therefore ensuring her adherence to therapy. It is unclear why this patient experienced such a poor response to LMWH and why enoxaparin was used so many times. We hypothesised that possibly due to the history of haematuria with warfarin, and since the patient was seen by different doctors in different institutions between 2008 and 2012, enoxaparin was started many times in spite of repeated therapeutic failure, becoming an evident medication error.

Results from clinical trials currently underway are expected and may establish the efficacy and safety of rivaroxaban in patients with APS.[14 15]

## Learning points

- The diagnosis of antiphospholipid syndrome (APS) is performed in the presence of at least one of the antiphospholipid antibodies, which should be positive twice with an interval of at least 12 weeks.
- Warfarin remains the therapy of choice for thrombotic APS in secondary prevention.
- Patients with APS and persistently positive lupus anticoagulant (LA) should have international normalised ratio (INR) performed before the start of anticoagulant therapy to detect the prolongation of baseline INR.
- The therapeutic targets of LA-positive patients with APS and prolonged baseline INR, should be between 3.0 and 4.0, with joint monitoring of the activity of Chromogenic Factor X after every six INR tests performed.
- The efficacy and safety of rivaroxaban in patients with APS has to be established (pending trial results).

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