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Management of Antiphospholipid Syndrome in Patients with Systemic Lupus Erythematosus

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Abstract

Purpose of review To provide an approach to primary and secondary prevention of thrombotic events and obstetric complications in patients with antiphospholipid antibodies (aPL) with or without antiphospholipid syndrome (APS), particularly in association with systemic lupus erythematosus (SLE).
Recent findings The available evidence would suggest that direct oral anticoagulants are inferior to warfarin at prevention of recurrent thrombosis, particularly in patients with a history of arterial thrombosis or triple aPL positivity. Novel therapies currently being considered for APS include eculizumab, and B cell inhibitors, which may have a role in refractory or resistant APS.
Summary Patients should be risk-stratified for risk of thromboembolism, and traditional cardiovascular risk factors addressed. Primary prophylaxis with aspirin should be considered in patients with SLE and aPL. Secondary prevention for APS is with warfarin with an INR of 2.0–3.0. Pregnant SLE patients with aPL/APS are managed with aspirin and heparin.

Introduction

What is antiphospholipid syndrome?

Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by thrombotic events and pregnancy morbidity in a patient with persistent antiphospholipid antibodies (aPL) [1, 2]. Definite APS by the 2006 classification criteria involves (1) history of thrombotic event or pregnancy morbidity; and (2) persistent aPL [persistently positive lupus anticoagulant (LA), anticardiolipin antibody (aCL), and/or anti-β2 glycoprotein-1 antibody (β2-GP-1) at moderate- or high-titre measured at least 12 weeks apart and within 5 years of the clinical manifestation] [1]. Several non-criteria features of APS have also been recognized, including heart valve disease, livedo reticularis, thrombocytopenia, nephropathy, neurologic manifestations, and other associated antibodies [1].

How is APS associated with systemic lupus erythematosus?

While the pathogenesis of APS is incompletely understood, aPL are thought to mediate thrombosis and other manifestations through immune activation. The role of immune activation in APS is supported by the association between APS and systemic lupus erythematosus (SLE) [3]; 30–40% of patients with SLE have aPL, and 9–25% meet criteria for APS [3–5]. Also, patients initially diagnosed with primary APS (PAPS) may subsequently develop SLE [6].

How is APS different when associated with SLE?

While the approach to diagnosis and management of APS associated with SLE is similar to that of PAPS, there are a few aspects of diagnosis and treatment where particular evidence and/or recommendations are available specifically for patients who have APS associated with SLE, and will be highlighted throughout the article.

Screening

When should a clinician screen for aPL?

To date, there is no clear consensus as to when to screen for aPL; however, several groups have provided guidance. The UK guidelines on the investigation and management of APS [7] recommend testing for aPL in patients with unprovoked venous thromboembolism (VTE) and in adults < 50 years of age with ischemic stroke. This is in contrast to the guidance provided by subcommittee on lupus anticoagulant/phospholipid-dependent antibodies which recommends limiting testing to patients with a significant probability of having APS by grading patients into low, moderate, or high-risk categories. Low-risk patients, such as elderly patients with unprovoked VTE, would not typically undergo testing, while those at moderate risk (accidentally found prolonged aPTT in asymptomatic subjects, recurrent spontaneous early pregnancy loss, provoked VTE in young patients) or high-risk (unprovoked VTE/arterial thrombosis in patients < 50 years of age, thrombosis at unusual sites, late pregnancy loss, any thrombosis or pregnancy morbidity in patients with autoimmune diseases) would typically be considered for testing [8].

For patients diagnosed with SLE without a history of thromboembolic events, the 2018 Canadian Rheumatology Association recommendations for baseline and follow-up investigations of patients with SLE advise that laboratory monitoring "possibly include" aPL [9•]. However, in the peripartum period, they recommend that laboratory evaluation should include aPL as further testing may depend on results [9•].

Bottom line:

- SLE patients who experience thrombosis or pregnancy morbidity should be tested for aPL.

- APL screening could be considered for patients with SLE without a history of thromboembolism.
- APL screening should be performed for pregnant SLE patients.

Risk of thromboembolic events in patients with aPL and APS

How should a patient's risk of thrombosis be determined?

Management involves stratifying the individual patient risk through consideration of the specific aPL profile, traditional cardiovascular risk factors, and considering the presence or absence of concomitant SLE. The aPL profile is associated with the degree of thrombotic risk. A meta-analysis conducted in 2014 that assessed the risk of thrombosis in patients with aPL without SLE determined that the odds ratio (OR) for VTE was 6.14 in patients with LA and 1.46 in patients with aCL; the OR for arterial thrombosis was 3.58 for LA, 2.65 for aCL, and 3.12 for β2-GP-1 [10]. A systematic review by Galli et al. independently concluded a similar result [11]. Furthermore, having more than one positive aPL is associated with increased thrombosis risk [12], particularly triple positivity (OR 33) [13].

Cardiovascular risk factors also contribute to increasing risk of thrombosis in patients with APS, including hypertriglyceridemia, hypertension, smoking, diabetes, and obesity [14–18]. In the Hopkins lupus cohort, APS associated with SLE was associated with approximately three times the risk of thromboembolism and fetal death as compared to a PAPS cohort [14]. Combining the above risk factor categories of aPL profile and cardiovascular risk factors, the global antiphospholipid syndrome score (GAPSS), developed by Sciascia et al., has been validated in both PAPS and SLE cohorts as a tool for predicting risk of thrombosis [19–21]. This score can help with decision-making regarding primary prophylaxis in patients with aPL.

Bottom line:

- The risk of thrombosis is increased in patients with LA compared to aCL or β2- GP-1, and patients with double or triple aPL positivity have successively higher risk of thrombosis than single aPL positivity.
- Presence of traditional cardiovascular risk factors and concomitant SLE increases risk of thrombosis.
- The GAPSS can be used to combine known risk factors to predict risk of thrombosis in patients with APS and with SLE.

Primary prevention in patients with antiphospholipid antibodies

Should cardiovascular risk factors be addressed in patients with positive aPL?

Primary prevention of thrombosis involves addressing modifiable risk factors. This includes regular screening and optimization of blood pressure, cholesterol, triglycerides, and diabetes, as per current guidelines, as well as addressing smoking cessation [22].

Should patients with positive aPL with no history of thrombosis take aspirin?

Beyond addressing modifiable risk factors, treatment with acetylsalicylic acid (ASA) can be considered, but the evidence for this is limited. In one meta-

analysis, subgroup analysis showed a protective effect of ASA against a first arterial event [OR 0.48 (0.28–0.82)] but not a first venous event [OR 0.58 (0.32–1.06)], and only in retrospective but not prospective studies [23]. Overall, there is insufficient data to recommend ASA routinely for unselected patients with positive aPL, though it could be considered in individual patients. However, in the subgroup of patients with SLE, significant reduction in the risk of thrombosis was demonstrated; ASA should be thus considered as primary prophylaxis for this subgroup [23].

Should patients with positive aPL with no history of thrombosis be anticoagulated?

The available evidence suggests that the risk of bleeding likely outweighs the benefits of anticoagulation for patients with aPL. A 5-year, prospective, open-label randomized controlled trial (RCT) involving 166 aPL-positive patients with SLE and/or obstetric morbidity comparing low-dose ASA to low-dose ASA plus warfarin. There was no difference in the number of thromboses, but more episodes of bleeding occurred in the low-dose aspirin plus warfarin group [24].

Should patients with positive aPL with no history of thrombosis take hydroxychloroquine?

In addition to hydroxychloroquine's (HCQ) role in treating SLE and preventing flares, the use of HCQ is associated with significantly lower odds of having a persistently positive aPL in patients with SLE [25]. In addition, a retrospective, cross-sectional study found that asymptomatic aPL-positive SLE patients on HCQ and/or ASA had a lower risk of first episode of thrombosis [26]. Based on these two studies, HCQ is generally recommended in patients with SLE who have positive aPL. The evidence supporting use of HCQ is less robust in patients without SLE who have positive aPL—one RCT was terminated due to low recruitment rate [27•]. Thus, patients with positive aPL without history of SLE do not routinely receive primary prophylaxis with HCQ. Bottom line:

- Modifiable cardiovascular risk factors should be addressed in all patients with positive aPL.
- Patients with SLE with persistently positive aPL should be offered ASA for primary prophylaxis against thromboembolic events, in contrast to unselected patients for whom ASA may be considered but is not thought to be generally indicated.
- Patients with aPL with no history of thrombosis should not receive anticoagulation.
- Patients with SLE and persistently positive aPL should receive HCQ.

Secondary prevention after thromboembolic event in patients with APS

What is the typical anticoagulation regimen used to prevent recurrent thromboembolic events in patients with APS?

The mainstay of long-term treatment for APS to prevent recurrent thromboembolic events are Vitamin K antagonists (VKAs), with warfarin being the agent most commonly prescribed [22, 28]. Two studies have demonstrated that a targeted international normalized ratio (INR) between 2.0–3.0 leads to a

similar risk of recurrent thrombosis compared to higher treatment target of INR > 3.0, and is associated with significantly less bleeding [29, 30]. There are no studies comparing different durations of anticoagulation, however the persistence of thrombotic risk in APS leads most experts to support indefinite warfarin therapy for these patients [31].

Can direct oral anticoagulants be used to prevent recurrent thromboembolic events in APS patients?

Direct oral anticoagulants (DOACs) have been approved to prevent recurrent thrombotic events in a variety of prothrombotic conditions, and they have many appealing advantages over VKAs [32]. There has been a small number of studies to date evaluating the use of DOACs in patients with APS. A 2016 systematic review of available case reports identified recurrent thrombosis in 19/122 accumulated patients, with a 3.5-fold increased risk in patients with "triple positivity" [33]. An RCT comparing rivaroxaban to warfarin in APS patients evaluating change in markers of thrombin generation and coagulation activation concluded that effective anticoagulation was achieved with both rivaroxaban and warfarin; however, was not powered for clinical outcomes [34]. An RCT of triple-positive APS patients was terminated early due to an excess of arterial thromboembolic events in the rivaroxaban group compared to the warfarin group [35••]. A prospective RCT comparing apixaban with warfarin in APS recently underwent protocol modifications for concern for increased rate of stroke [36]. The available evidence would suggest that DOACs are inferior to warfarin at prevention of recurrent thrombosis, particularly in the populations of APS patients with a history of arterial thrombosis or triple aPL positivity.

How are patients managed when they have a recurrent thromboembolic event despite management with VKA?

If a patient with APS on a VKA with target INR 2.0–3.0 has a recurrent VTE, there is little evidence to guide the next steps; however, an increase of VKA dose to target INR > 3.0 may be considered [28, 37]. Alternatives could be to switch to an alternative anticoagulant such as low molecular weight heparin (LMWH), or addition of ASA or HCQ [22].

Are there special considerations for prevention of recurrent thromboembolic events in patients with a history of arterial thrombosis?

The prevention of recurrent thrombosis following an episode of arterial thrombosis in a patient with APS represents a more challenging decision due to limited available data about optimal treatment [22]. The standard recommendation for secondary prophylaxis of thromboembolic events in the subpopulation of patients with a history of arterial events does not differ from those with venous events [38]; however, it is important to note that the landmark RCTs of warfarin use in APS included only relatively small numbers of patients with prior arterial thrombosis [29, 30].

Other potential strategies employed in patients with a history of arterial thrombosis include the addition of ASA to VKA, particularly in cases where the patient has additional atherosclerotic risk factors that would be an indication

for antiplatelet therapy in the absence of aPL [22]. Other alternatives are similar to those considered in standard- dose VKA "failures", as above [22, 31].

Are there ancillary therapeutic considerations in APS?

Vitamin D

Vitamin D insufficiency in APS patients has been found to correlate with venous and arterial thrombosis and non-criteria manifestations [39]. The 14th International Congress on aPL Task Force on Treatment Trends recommended that "vitamin D deficiency and insufficiency should be corrected in all aPL-positive patients", with further studies needed to clarify the prognostic role of vitamin D deficiency and the benefit of supplementation [37].

Statin

Several in vitro and in vivo studies using surrogate markers have suggested that statins improve the pro-inflammatory profile and downregulate the pro-thrombotic and pro-inflammatory biomarkers found in APS [40, 41]. While there is currently no clinical trial data to support the use of statins in APS, statins can be considered in APS with high risk for cardiovascular events and in APS patients with recurrent thrombosis despite anticoagulation [42].

Are there novel therapies under consideration for APS?

Complement inhibition

Complement activation contributes to thrombosis and fetal injury in APS animal models [43, 44]. There have been several case reports publishes demonstrating efficacy of complement inhibition with eculizumab [45]. Phase II studies are underway for treatment of non-criteria manifestations of APS [46], and while results are pending, the current recommendation is that "patients with life-threatening disease resistant to other interventions may be candidates for complement inhibitors as salvage therapy" [42].

Cell inhibition

Animal models have shown that B cells play an important role in the pathogenesis of APS [47]. As there is currently limited supporting evidence for rituximab and belimumab in treatment of APS, in the form of case reports/series, CAPS registry data, and one open-label pilot study, the expert consensus is that "B-call inhibition may have a role in difficult-to-treat APS patients, possibly in those with hematologic and microthrombotic/microangiopathic manifestations" [37].
Bottom line:

- For prevention of recurrent thromboembolic events in patients with and without SLE, first-line therapy is anticoagulation with VKA, usually warfarin dosed to a target INR of 2.0–3.0.

- The available evidence would suggest that DOACs are inferior to warfarin at prevention of recurrent thrombosis, particularly in the populations of APS patients with a history of arterial thrombosis or triple aPL positivity.
- Management of patients with recurrent thrombosis despite warfarin dosed to a target INR of 2.0–3.0 could include strategies such as increase of VKA dose to target INR > 3.0, switch to an alternative anticoagulant, or addition of ASA or HCQ.
- Supplementation to correct Vitamin D deficiency/insufficiency is recommended.
- The addition of statin therapy may be considered in APS patients with high risk for cardiovascular events and in those with recurrent thrombosis despite anticoagulation.
- Eculizumab may be considered as salvage therapy for life-threatening APS resistant to other interventions, and B cell inhibition may be considered in difficult-to-treat APS patients.

Catastrophic antiphospholipid syndrome (CAPS)

What is CAPS?

CAPS is a rare, life-threatening variant of APS characterized by multiple small vessel thrombosis that can lead to multi-organ failure [48]. The preliminary criteria for classification of the catastrophic antiphospholipid syndrome published in 2003 by Asherson et al. [49] can be used for diagnosis [50]. Concomitant SLE has been found to be a poor prognostic factor for mortality in CAPS [51].

What are the recommendations for management of CAPS?

The McMaster-RARE Best Practices clinical practice guidelines for diagnosis and management of CAPS provided a strong recommendation for therapeutic dose anticoagulation, and conditionally recommended glucocorticoid, IV heparin and plasmapheresis and/or IVIg for first-line treatment [52•]. There were no recommendations specific to the SLE population made; however, tailoring the therapeutic regimen to manage any concurrent active SLE manifestations would be reasonable. In addition, other therapies used for specific SLE manifestations may merit consideration; for example, cyclophosphamide may be associated with improved survival in CAPS patients with SLE [51].
Bottom line:

- Concomitant SLE is a poor prognostic factor in CAPS.
- First-line treatment of CAPS includes glucocorticoid, IV heparin, and plasmapheresis and/or IVIg.
- Cyclophosphamide may be indicated for CAPS associated with SLE.

How should pregnant patients with positive aPL be managed?

Warfarin is contraindicated in pregnancy due to teratogenicity; thus, treatment of APS in pregnancy is typically heparin and ASA [53]. Recent clinical practice guidelines have recommended treatment strategies based on previous thrombotic event and risk profile. For patients with

previous thromboembolism, therapy with ASA and therapeutic dose heparin is recommended. For those with previous obstetric APS, treatment with ASA and prophylactic dose heparin is recommended, with consideration for HCQ in those with a high-risk profile ± additional risk factors (including SLE). For patients with aPL with low-risk profile, ASA alone is recommended, with ASA and prophylactic heparin to be considered in those with a high-risk profile [54•].

Can SLE patients with aPL take oral contraceptives?

Although a study of SLE patients SLE randomized to combined oral contraceptive pill (OCP) or placebo suggested that there was no increased risk of SLE flare or VTE with OCP use, patients with positive aPL or thrombotic history were excluded [55]. The combined OCP is not recommended in patients with SLE and aPL/APS. EULAR guidelines suggest that progestin-only compounds are suitable for anticoagulated patients with a low-risk aPL profile, although the risk of thrombosis should be weighed against their benefit. The intrauterine device is the method of contraception recommended, particularly copper IUD; levonorgestrel-containing IUD should be used only in cases where its benefits outweigh the risk of thrombosis [56].
Bottom line:

- Pregnant SLE patients with aPL/APS are managed with ASA and heparin (prophylactic dose in aPL alone or previous obstetric event alone, and therapeutic dose for prior thrombotic event).
- Copper IUD is the lowest-risk method of contraception in patients with SLE and APS.

Conclusion

While the approach to diagnosis and management of APS associated with SLE is similar to that of PAPS, patients with SLE should be considered at higher thromboembolic risk. Differences in management include consideration of HCQ in all SLE patients with aPL/APS, primary prophylaxis with ASA in patients with aPL and SLE, and consideration for alternative agents such as cyclophosphamide in patients with CAPS.

Compliance with Ethical Standards

Conflict of Interest
Mary-Clair declares that she has no conflict of interest. Kimberly was an investigator on a study that received in-kind research support from Bayer.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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