Arch Rheumatol 2023;38(2):163-173
doi: 10.46497/ArchRheumatol.2023.41875

INVITED REVIEW

The ABCs of antiphospholipid syndrome

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ABSTRACT

Antiphospholipid syndrome (APS) is a thromboinflammatory syndrome characterized by thrombotic, microvascular, obstetric, or non-thrombotic events in the setting of persistent antiphospholipid antibodies (aPL), namely anticardiolipin antibody (aCL), anti-β2 glycoprotein-I antibody (aβ2GPI), and lupus anticoagulant (LA). The diagnosis of APS requires careful assessment of the aPL profile, the clinical phenotype, and additional risk factors. The standard management of aPL-related thrombosis is anticoagulation, which is not effective for microvascular and non-thrombotic events. In parallel to our improved understanding of aPL-related mechanisms, the role of immunosuppression has been increasingly investigated. In this review, we summarize the basic concepts and future perspectives in APS.

Keywords: Antiphospholipid antibody, antiphospholipid syndrome, thrombosis.

Antiphospholipid syndrome (APS) is a thromboinflammatory disease characterized by thrombosis (venous, arterial, or microvascular) or pregnancy morbidity in individuals with antiphospholipid antibodies (aPL).[1] Three main tests used to detect aPL are anticardiolipin antibody (aCL), anti-β_2 glycoprotein-I antibodies ($a\beta_2$GPI), and lupus anticoagulant test (LA). Antiphospholipid antibody positivity alone, without aPL-related clinical symptoms, does not qualify for an APS diagnosis. Antiphospholipid syndrome may be seen in patients with other autoimmune diseases, such as systemic lupus erythematosus (SLE), or in otherwise healthy individuals (primary APS).

The prevalence and incidence of APS are difficult to accurately calculate due to the wide range of aPL-related clinical presentations, inconsistent definitions of aPL-positivity, and limited population-based studies. However, the overall prevalence of APS is about 50 per 100,000 individuals, and the estimated incidence ranges between 7.1 and 13.7 per 100,000 person-years.[2,3]

The clinical manifestations of aPL have a wide spectrum. The most common vascular events are thromboses of the lower extremity deep veins, and the arterial circulation of the brain. However, vascular events may vary from superficial venous thrombosis to small-moderate-

Received: May 28, 2023 ***Accepted:*** May 28, 2023 ***Published online:*** June 05, 2023

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Citation:
Keleşoğlu Dinçer AB, Erkan D. The ABCs of antiphospholipid syndrome. Arch Rheumatol 2023;38(2):163-173. doi: 10.46497/ArchRheumatol.2023.41875.

large vessel thrombosis to multiple simultaneous organ thromboses (catastrophic APS [CAPS]). An important obstetric manifestation of aPL is late pregnancy loss, commonly associated with placental vascular insufficiency. Microvascular manifestations such as diffuse alveolar hemorrhage (DAH), and non-thrombotic manifestations such as thrombocytopenia can also develop in aPL-positive patients.

The cornerstone of thrombosis treatment and recurrence prevention in APS is anticoagulation, usually with vitamin K antagonists. Direct oral anticoagulants (DOACs) are not recommended in APS, particularly in those with history of arterial thrombosis and triple aPL-positivity. Anticoagulation is not effective for microvascular and/or non-thrombotic manifestations for which immunosuppressive treatments are preferred. In parallel to our improved understanding of the pathophysiology of APS, novel treatment approaches targeting the immune components of the disease have been increasingly investigated.

In this review, we briefly discuss the basic concepts in APS, i.e., etiopathogenesis, clinical symptoms, diagnosis, and management, as well as the future perspectives. Detailed information can be found elsewhere.[1,4-6]

ETIOPATHOGENESIS

The interaction of aPL with plasma proteins, mainly β_2GPI, but also with others such as prothrombin, plasminogen, antithrombin III, protein C, protein S, annexin II and annexin V, triggers a proinflammatory state by activating endothelial cells, monocytes, platelets, neutrophils, complement system, and tissue factor.[7] Antiphospholipid antibodies also activate the hemostatic pathways by a variety of other mechanisms leading to a prothrombotic state. Despite this proinflammatory and prothrombotic state, thrombosis does not develop in all aPL-positive patients; thus, based on the "two-hit" hypothesis, additional risk factors are required for thrombosis in aPL-positive patients.[8]

Placenta is a major target particularly for β_2GPI-dependent antibodies that bind to human trophoblast. During trophoblast differentiation, phosphatidylserine is externalized, allowing β_2GPI to be expressed on the cell surface and becoming a target for aPL. Complement activation also plays a role in obstetric APS; when aPL binds with β_2GPI on trophoblastic cells, the complement system is activated through the classical pathway, causing placental injury, and eventually fetal loss and/or intrauterine growth restriction.[9]

Some of the recent findings contributing to our understanding of APS pathogenesis include: *(i)* aPL-induced release of neutrophil-extracellular traps (NETs) resulting in the upregulation of the coagulation cascade via activated complement system and thus, thrombosis formation (anti-NET immunoglobulin (Ig) G and/or IgM levels are higher in patients with primary APS compared to healthy controls, these antibodies are associated with recurrent venous thrombosis and, based on a recent multi-center study, almost half of the aPL-positive patients have high anti-NET IgG and/or IgM levels);[10-12] *(ii)* potential role of type-1 interferon activation (higher type-1 interferon levels correlate with aβ_2GPI, triple aPL positivity, and obstetric APS;[13,14] and *(iii)* aPL-induced upregulation of the mechanistic target of rapamycin (mTOR) complex on endothelial cells (mTOR is a kinase that plays a role in many signaling pathways regulating cell growth, proliferation, and survival), which may have a role in the pathogenesis of microvascular manifestations of APS.[15] Although multi-center and well-defined large-scale studies are lacking, a genetic association of HLA Class II alleles and non-HLA (STAT4 and C1D) genetic loci in APS has been suggested.[16] Detailed information on the etiopathogenesis of APS can be found elsewhere.[4]

CLINICAL PRESENTATION

Deep venous thrombosis (DVT), which is usually seen together with pulmonary embolism is the most common manifestation of APS. Unusual venous distributions may be affected, such as renal or splenic vein thrombosis. The most frequent arterial event is stroke, which accounts for approximately one-fourth of the APS presentations. However, arterial thrombosis may also develop at unusual locations such as peripheral and mesenteric thrombosis. Unexplained late fetal losses (beyond the 10th week of gestation), associated with placental vascular problems such

as preeclampsia or intrauterine growth restriction, is the most specific event for obstetric APS. Other manifestations such as pre-fetal losses are less specific.

Livedo reticularis, symmetrical mottling of the skin, has poor specificity and is common in healthy individuals, usually induced by the cold exposure. In contrast, livedo racemosa, broken asymmetrical mottling of the skin, is more specific for APS. Cutaneous necrosis or ulcerations may develop due to underlying livedoid vasculopathy.

Antiphospholipid antibodies can affect the entire renal vasculature (i.e., arteries, arterioles, and glomerular capillaries) resulting in large vessel thrombosis, as well as microvascular disease in intrarenal arteriolar and glomerular capillaries, leading to aPL-nephropathy.[17] Kidney biopsies in aPL-nephropathy patients can demonstrate: *(i)* acute thrombotic microangiopathy (TMA) lesions such as fibrin thrombi in arterioles or glomeruli without inflammatory cells or immune complexes; and *(ii)* chronic lesions, including organized microthrombi with/without recanalization, focal cortical atrophy, arterial fibrous intimal hyperplasia, fibrous/fibrocellular occlusions of arteries and arterioles, and chronic or organized glomerular thrombi.[18]

Valvular heart disease (vegetations and/or valve thickening) can occur in aPL-positive patients. Moreover, cardiac microthrombosis may cause symptoms similar to a coronary artery with normal coronary angiogram. Diffuse alveolar hemorrhage is a rare microvascular manifestation of aPL characterized by the red blood cell leak from alveolar capillaries into the intraalveolar space.[5]

Neurological involvement, particularly in the form of cognitive dysfunction independent of stroke, can develop in aPL-positive patients. Chorea, transverse myelitis, multiple sclerosis-like syndrome, and seizures are reported in aPL-positive patients; however, these features are rare and controversial.

Thrombocytopenia (usually $>100\times10^9$/L) is usually mild and presents in 20 to 40% of APS patients.[19] Despite low platelet counts, APS patients remain at risk for thrombosis. Coombs-positive autoimmune hemolytic anemia (without schistocytes) can also develop in less than 5% of patients with primary APS.[20]

Catastrophic APS is a rare, life-threatening subgroup of APS that multiple thromboses of small, medium, and large-size vessels occur over a period of days (further discussed below and elsewhere).[5]

DIAGNOSIS

Disease assessment in aPL-positive patients should start with the review of the aPL profile (Table 1), the clinical phenotype (Table 2), and additional venous thromboembolism (VTE)

Table 1. Diagnostic assessment of antiphospholipid antibody tests and profile

Lupus anticoagulant (LA) test
- Three-step functional coagulation assay
- False positivity can occur due to anticoagulation, infections, and severe inflammation

Anti-cardiolipin antibody (aCL) and anti-β_2 glycoprotein-I antibody (aβ_2GPI)
- Enzyme-linked immunosorbent assay (ELISA)
- Low level (20 to 39 U)*
- Moderate-to-high level (≥40 U)*
- False positivity can occur due to infections

Assessment of antiphospholipid antibody profile for diagnostic purposes[1]
- Lupus anticoagulant positivity has a strong association with APS-related events
- IgG positivity has a stronger association with APS-related events compared to IgM positivity; isolated IgM positivity reduces the confidence in APS diagnosis
- Lupus anticoagulant positivity with additional moderate-to-high levels of aCL and/or aβ_2GPI IgG increases the confidence in APS diagnosis in the context of aPL-related clinical symptoms
- There are no strong data supporting the clinical relevance of low level aCL/aβ_2GPI
- Demonstration of persistent aPL positivity (at least at two occasions 12 weeks apart) is important to rule out transient aPL positivity.

* For research and diagnostic purposes, our definition of low level aCL/aβ_2GPI is 20-39 ELISA units, and moderate-to-high level is >40 ELISA units.

and cardiovascular disease (CVD) risk factors (approximately half of thrombotic APS patients have additional thrombosis risk factors at the time thrombosis).[5] Age, male sex, CVD risk factors, combined VTE risk factors, and additional systemic autoimmune diseases independently increase the risk of thrombosis in aPL-positive patients.[5] Since the laboratory and clinical findings vary widely, APS diagnosis may be challenging; overinterpretation of aPL results is relatively common. There are no diagnostic criteria for APS; thus, physician judgement is critical (see below).

Catastrophic APS diagnosis can be also challenging given that: *(i)* half of CAPS patients do not have a prior APS or aPL positivity history;[5,21] *(ii)* false positivity of LA test may occur due to sepsis, ongoing anticoagulation treatment, and infection;[21] and *(iii)* CAPS may mimic or co-exist together with other systemic TMA syndromes (thrombocytopenia, microangiopathic hemolytic anemia, and organ failure - usually kidney), such as thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome (HUS), complement-mediated TMA (CM-TMA), HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets), sepsis, or heparin-induced thrombocytopenia. Detailed information on CAPS diagnosis can be found elsewhere.[5,22]

CLASSIFICATION

Classification criteria aim to specify homogeneous cohorts of patients for clinical and translational research, while the goal of diagnostic criteria is to identify all patients with a specific condition, including those with rare and atypical clinical manifestations of the disease.[1] Thus, classification criteria should not be used for diagnosis; however, they can serve as a guide while evaluating aPL-positive patients. Based on the revised Sapporo APS Classification Criteria,

Table 2. Diagnostic assessment of antiphospholipid syndrome (APS)- and catastrophic antiphospholipid syndrome (CAPS)-related clinical symptoms

Updated sappora APS classification criteria clinical items*[23]	Diagnostic assessment
Arterial, venous, or small vessel thrombosis	Arterial/venous thrombosis: Absence of cardiovascular disease or venous thromboembolism risk factors increases the confidence in APS diagnosis
	Microvascular disease, e.g., lung (diffuse alveolar hemorrhage), kidney ("antiphospholipid antibody [aPL]-nephropathy"), or skin (livedoid vasculopathy) increase the confidence in APS diagnosis (in patients with arterial/venous thrombosis).
Pregnancy morbidity: a) recurrent (≥3) (pre) embryonic loss before 10 weeks gestation; b) ≥1 morphologically normal fetal loss at or beyond 10 weeks gestation; or c) >1 preterm delivery of a morphologically normal fetus due to severe pre-eclempsia, eclempsia or placental insufficiency ≤34 weeks gestation	Other causes of pregnancy morbidity, e.g., chromosomal abnormalities, endocrine disorders, or uterus anatomical defects should be excluded.
	Late pregnancy loss, particularly occurring together with placental vascular problems increases the confidence in APS diagnosis
-	Some of the additional aPL-related clinical symptoms not included in the Updated Sapporo Classification Criteria include thrombocytopenia, autoimmune hemolytic anemia, cardiac valve disease, livedo reticularis/racemosa, and cognitive dysfunction.
Catastrophic APS classification criteria clinical items*[22]	
Three or more organ, system and/or tissue thromboses developing simultaneously or in less than a week, generally accompanied by microvascular disease	History of persistent and clinically relevant aPL profile with/without APS increases the confidence in CAPS diagnosis in patients with rapidly developing multiple organ thromboses
	Catastrophic APS patients may develop systemic thrombotic microangiopathy (TMA) (microangiopathic hemolytic anemia with schistocytes, thrombocytopenia, and organ failure); other conditions resulting in systemic TMA, e.g., sepsis, heparin-induced thrombocytopenia, or complement-mediated TMA, may co-exist and create diagnostic challenges.

* Classification criteria should not be used for diagnosis; however, they can provide partial guidance for clinical judgment while evaluating aPL-positive patients.

at least one clinical (thrombotic or obstetric) and one laboratory (aPL) criterion are required APS (Table 2).[23] The new APS classification criteria, supported by the American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR) are expected to be published this year.[24,25]

Catastrophic APS classification criteria define definite CAPS as thromboses in ≥3 organs developing in less than a week, microvascular thrombosis in ≥1 organ, and persistent aPL positivity. When only three of four requirements are met, a patient can be classified as probable CAPS (Table 2).[22] Similarly, CAPS classification criteria should not be used for diagnosis; however, they can serve as a guide while evaluating aPL-positive patients with multi-organ thrombosis.

PREVENTION AND TREATMENT

Primary thrombosis prevention

The first step in prevention is the modification of reversible VTE (such as estrogen therapy) and CVD risk factors (such as hypertension), prophylaxis during high thrombosis risk periods (such as surgical interventions), and optimal management of other systemic autoimmune diseases.

Low-dose aspirin (LDA) is not beneficial for primary thrombosis prevention based on a placebo-controlled randomized-controlled trial (RCT), as well as prospective cohort studies.[26] Nevertheless, LDA is prescribed by some physicians based on retrospective data implying that it may be protective against first thrombosis.[27] Risk stratification based on the aPL profile and concomitant risk factors is important before LDA is initiated.[28,29] Our approach is to use LDA in aPL-positive patients with additional CVD risk factors.

Hydroxychloroquine (HCQ) has antithrombotic effects in mouse models and in SLE patients through multiple mechanisms including protecting annexin A5 shield from aPL-related disruption.[30-32] However, there are no prospective, controlled studies showing the efficacy of HCQ for primary thrombosis prevention in aPL-positive patients. Our approach is to use HCQ in patients aPL-positive patients, if they have with lupus or lupus-like disease.

Secondary thrombosis prevention

Warfarin remains the cornerstone for long-term recurrent thrombosis prevention in APS patients with a target international normalized ratio (INR) of 2 to 3. Despite retrospective cohort studies demonstrating that high-intensity (INR 3-4) anticoagulation is more effective than moderate intensity (INR 2-3), two prospective RCTs of moderate- versus high-intensity warfarin did not show any difference between the treatment groups in the prevention of recurrent thrombosis.[33,34] Since the number of APS patients with arterial events were relatively low in these two RCTs, high-intensity anticoagulation is still preferred by some centers. Our approach for secondary thrombosis prevention in APS is warfarin with a target INR of 2.5 to 3, adding LDA if patients have additional CVD risk factors.

In patients who experience recurrent thrombosis despite therapeutic range INR, options include higher-intensity warfarin (INR 3-4) or switching to low-molecular-weight heparin (LMWH). Additional LDA, HCQ, a statin drug, or a combination of these drugs is also commonly used.

Direct oral anticoagulants are currently not recommended for secondary thrombosis in APS. An open-label, non-inferiority RCT of aPL-positive VTE patients demonstrated that rivaroxaban was inferior to warfarin with respect to the percentage change in endogenous thrombin potential (a quantitative measurement of thrombin generation) on Day 42, which was the primary outcome measure of the study.[35] However, no patients in either group developed thrombosis or major bleeding during the six-month safety period. A subsequent open-label, multi-center, non-inferiority RCT (warfarin *vs.* rivaroxaban), investigating triple aPL-positive patients with history of arterial or venous thrombosis, was terminated early due to the increased risk of thrombosis and bleeding in the rivaroxaban group.[36] A three-year open-label randomized non-inferiority study of rivaroxaban *vs.* warfarin demonstrated approximately two times increased risk of recurrent thrombosis, particularly arterial thrombosis and stroke, in the rivaroxaban group, although it was not

statistically significant.[37] An RCT of apixaban *vs.* warfarin was terminated early due to the higher occurrence of stroke in patients randomized to apixaban (6/23 patients) compared to warfarin group (0/25).[38] Thus, as emphasized by the 16th International Congress on aPL Task Force on Treatment Trends, DOACs should be avoided in APS patients with arterial thrombosis, and in patients with recurrent thrombosis while on standard intensity warfarin.[39] In triple aPL-positive thrombotic APS patients, if the patient is already on DOAC following the first VTE, then switching to vitamin K antagonists is recommended. If a patient declines the switch, close clinical surveillance while on DOAC is important, which also includes the magnetic resonance imaging of the brain for ischemic lesions.[39]

Microvascular and non-thrombotic manifestations

There is no uniform approach to the management of microvascular APS due to heterogeneous organ involvement, and the lack of controlled studies and strong literature supporting any treatment strategy.[5] Microvascular manifestations of APS do not respond to anticoagulation, and may develop while patients are on therapeutic anticoagulation. Given the increasing awareness of the mechanisms involved in APS pathogenesis as discussed above, both glucocorticoids and immunosuppressive agents (traditional agents such as azathioprine or mycophenolate mofetil [MMF], or biologic agents such as rituximab [RTX] or eculizumab) are increasingly used in the management of patients with microvascular disease or non-thrombotic manifestations, mostly based on case reports or series.[40-42] Details are discussed elsewhere.[6]

Rituximab is a monoclonal antibody against CD-20 on B-cells, which causes depletion of CD-20 expressing B-cells.[43] A small (n=19) open-label study of RTX for aPL-positive patients with thrombocytopenia or microvascular disease demonstrated no change in the aPL profile during 12 months of follow-up; however, some patients with thrombocytopenia, aPL-nephropathy, skin-ulcers, and cognitive dysfunction had complete or partial response without major adverse events.[44] Belimumab, which is a B-lymphocyte stimulator neutralizing monoclonal antibody, was used in two primary APS patients with DAH and recurrent skin ulcers with a partial clinical response.[45]

Eculizumab is a C5 monoclonal antibody and is approved for the treatment of atypical hemolytic uremic syndrome and paroxysmal nocturnal hematuria.[46] When eculizumab binds to complement protein C5, it inhibits its cleavage to C5a and C5b and prevents the assembly of terminal complement complex C5b-9. In several case reports or studies, eculizumab was shown to be effective for the improvement of thrombocytopenia, hemolytic anemia, and renal function in APS patients with systemic TMA.[46,47]

In a study of APS patients requiring renal transplantation, the inhibition of mTOR pathway by sirolimus prevented the recurrence of vascular lesions by inhibiting the vascular proliferation, and improved the survival of the renal allografts.[15] A recent case report also showed that sirolimus successfully inhibited the mTOR pathway, and was associated with significant improvement in kidney function and kidney findings in a patient with active aPL-nephropathy.[48]

Our approach for the management of selected microvascular and non-thrombotic manifestations can be summarized as follows:[5] *(i)* for DAH and aPL-nephropathy, glucocorticoids, MMF with/without RTX, and adding intravenous IG (IVIG) for DAH and switching to sirolimus for aPL-nephropathy if the disease activity persists; *(ii)* for livedoid vasculopathy-related skin ulcers, RTX; *(iii)* for platelet counts less than 50×10^9/L, glucocorticoids, IVIG, and/or RTX; and *(iv)* for hemolytic anemia, glucocorticoids with RTX, azathioprine, or MMF.

In all aPL-positive patients with microvascular disease, despite the lack of strong clinical support, adding HCQ as discussed above and a statin drug to the main treatment regimen should be considered. In mouse models, fluvastatin reduced the leucocyte adhesion to endothelial cells, and also the thrombus size.[49] Although there are no controlled data to show the efficacy of statins on primary or secondary prevention in APS patients with normal lipid levels, they may be beneficial as a concomitant therapy for patients with anticoagulant-refractory disease.[39] Of note, a recent meta-analysis did not show an association

between congenital malformation and statins; however, statins are still accepted to be teratogenic and contraindicated during pregnancy.[39,50]

CATASTROPHIC APS

Catastrophic APS management requires a multidisciplinary team approach. Early treatment is critical; the highest survival rate is achieved with the combination of anticoagulation (unfractionated intravenous heparin), glucocorticoids, and plasma exchange and/or IVIG.[5]

Based on the McMaster RARE-Best Practices Clinical Practice Guideline on the diagnosis and management of CAPS, for first-line treatment, combination therapy with heparin, glucocorticoids, and either IVIG or plasma exchange is recommended over single agents or other combinations of therapies.[51] Given the small number of CAPS patients treated with rituximab and based on limited data on long-term outcomes, the guideline does not recommend rituximab for the first-line treatment. However, rituximab use was supported by the panel members in refractory cases and in those with thrombocytopenia.[51]

Our approach for CAPS management is also anticoagulation, glucocorticoids, and IVIG and/or plasma exchange. If clinical improvement is not achieved, second-line treatment depends on if a patient has prominent systemic TMA symptoms, microvascular disease, and/or thrombocytopenia. Complement inhibition is chosen for those with well-defined systemic TMA, whereas RTX is preferred for those without systemic TMA but with microvascular disease or thrombocytopenia.[5]

OBSTETRIC MANIFESTATIONS

In patients with obstetric APS who have not experienced thrombosis, LDA and prophylactic doses of LMWH during pregnancy, and in the 8- to 12-week postpartum period are recommended. In women with a history of thrombosis and APS, LDA and therapeutic dose LMWH should be used during pregnancy, even in the absence of any history of pregnancy complications. In aPL-positive patients who have never experienced pregnancy complications or thromboses, a prophylactic dose of LMWH is recommended during the 8- to 12-week postpartum period, but not during pregnancy. Low-dose aspirin has been generally used in this setting without strong supportive prospective data.

FUTURE DIRECTIONS

There have been ongoing efforts to develop new APS classification criteria,[24] disease activity index, as well as updating the current APS damage index.[52] All these efforts are expected to increase the quality of APS research, with the ultimate goal of improving patient care, and the number of APS clinical trials. Based on mouse models and/or case reports, anti-tumor necrosis factor (TNF) agents,[53] daratumumab (anti-CD38 human monoclonal antibody targeting CD38 molecule on plasmablasts and plasma cells; approved for multiple myeloma),[54] chimeric antigen receptor T-cell (CART) therapy,[55] adenosine receptor agonists such as defibrotide and dipyridamole,[56] and coenzyme Q10[57] were suggested as potential future treatments.

Two ongoing APS clinical trials that deserve attention:

- The IMProve Pregnancy in APS with Certolizumab Therapy (IMPACT: ClinicalTrials.gov Identifier: NCT031 52058) in patients with obstetric APS investigating the efficacy of an anti-TNF agent in obstetric APS (increased levels of TNF-α is associated with pregnancy loss in mouse models;[58] a case series of 18 anti-TNF-treated [16 adalimumab and 2 certolizumab] obstetric APS patients [despite LMWH, LDA, and HCQ] showed favorable obstetric outcomes in 70% of patients without any congenital malformations.[53]
- A Phase 1b open-label study of daratumumab in APS (DARE-APS: ClinicalTrials.gov Identifier: NCT05671757) (daratumumab resulted in clinical improvement and significant reduction in anti-double stranded levels in two SLE patients;[59] another SLE patient with cerebral vasculitis was successfully treated with daratumumab

without any significant adverse effects;[60] and a triple aPL-positive patient with refractory VTE despite anticoagulation received daratumumab and plasma exchange in addition to heparin [there was partial improvement of aPL]).[54]

Conclusion

In conclusion, APS is a thromboinflammatory syndrome with systemic clinical manifestations. Primary thrombosis prevention needs a risk-stratified approach and LDA is considered in selected patients with additional CV risk factors. Anticoagulation remains as the cornerstone of thrombosis treatment and recurrence prevention; however, DOACs are not recommended. With our increasing knowledge on APS pathogenesis and molecular mechanisms, novel immunosuppressive approaches are emerging, particularly for patients with microvascular disease.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: All authors contributed equally to the article.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

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