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REVIEW

Antiphospholipid syndrome: an update

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ABSTRACT

Background Antiphospholipid syndrome (APS) or 'Hughes syndrome' is a prothrombotic disease characterized by thrombosis and pregnancy morbidity in the presence of antiphospholipid antibodies (aPL). More than three decades have passed, and experts are still uncovering new pieces of this disease complex pathogenesis and management.

Materials and methods We searched in literature using MEDLINE and PubMed databases focusing on the latest development on disease pathogenesis, risk assessment of thrombosis and treatment of APS.

Results The phosphatidylinositol 3-kinase (PI3K)–AKT-mTORC pathway was most recently identified to have a crucial role in activating inflammation among endothelial vessel wall causing vascular lesions in APS. Additionally, new variables are being implemented to assess the risk of thrombosis in patients with APS. Global APS Score (GAPSS) utilizes cardiovascular risk factors and new autoimmune antibodies as part of the score assessment and is the most valid so far. It can be a promising tool in the future for prediction of thrombosis. Anticoagulation remains the cornerstone in APS; however, many new potential therapeutic agents are developing and are currently under investigation.

Conclusions The most recent advances in pathogenesis, risk stratification and treatment provide a platform for high yield studies with the ultimate goal of providing the optimal management to patients with APS.

Keywords Antiphospholipid antibodies, antiphospholipid syndrome, management, pathogenesis, risk stratification.

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Introduction

Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by recurrent arterial or venous thrombosis and/or recurrent pregnancy morbidities in the presence of persistent positive antiphospholipid antibodies (aPL) which includes anticardiolipin antibodies (aCL), anti-β2 glycoprotein I (anti-β2GPI) and lupus anticoagulant (LA) [1]. The most recent classification for APS in 2006 requires the presence of one positive clinical criterion whether manifested by thrombosis or pregnancy loss plus one positive laboratory criterion (positive PL, this can be any antibody of the three antibodies mentioned before) on two different occasions separated by 12 weeks [2]. There is a strong need to standardize and validate the laboratory tests for the detection of aPL to have accurate results and to avoid false-positive results that can lead to drastic consequences as bleeding due to unnecessary anticoagulant intake. APS can be primary or secondary to an underlying autoimmune disease. Systemic lupus erythromatosus (SLE) is the most common cause of secondary APS [3]. All organs can be affected in APS with deep vein thrombosis (DVT) being the most common followed by thrombocytopenia and livedo reticularis [4].

Neurologic involvement in APS is common and can be manifested by headaches, memory impairment, dizziness and blurred vision, but the most common presentations are transient ischaemic attacks and ischaemic strokes. The presence of aPL in patients of all ages with stroke was estimated to be 13·5% according to a systemic review conducted by Antiphospholipid Syndrome Alliance For Clinical Trials and International Networking (APS ACTION) [5]. Another systematic review conducted recently on patients with cerebrovascular events who are less than 50 years old has shown 17·4% prevalence of positive aPL with five times increase in the risk of ischaemic stroke [6].

Antiphospholipid syndrome affects the renal vessels as well and at all levels of renal vasculature, leading to nephropathy, renal artery stenosis, renal vein thrombosis, thrombotic microangiopathy, hypertension and infarction [7]. It was estimated

that up to 50% of patients with SLE and positive aPL will develop APS [8]. The prevalence of aPL is high in patients with end-stage renal disease [9]. It can be challenging to differentiate between APS and thrombotic thrombocytopenic purpura or haemolytic uraemic syndrome. However, there are certain clinical criteria that can help us as the presence of schistocytes on blood smear, severe thrombocytopenia and haemolytic anaemia does not occur frequently in APS [10]. It also noteworthy to mention that special attention should be given to patients with lupus nephritis with positive aPL as there is a probability of renal vein occlusion post-renal transplantation [11]. Renal biopsy is essential especially in cases of nephritis where SLE coexist with positive aPL as the therapeutic measures can be totally different. In addition, some data in literature have shown an increased risk of serious bleeding post-renal biopsy especially among lupus nephritis patients with positive LA, so caution should be taken in these patients [12]. Lungs are also affected where aPL-positive patients may develop pulmonary veno-occlusive disease leading to fatal pulmonary hypertension, where microvascular changes in these patients can be very similar to those with idiopathic pulmonary hypertension [13]. On additional note, APS has also been associated with a wide range of hepatic manifestations such as Budd–Chiari syndrome, hepatic veno-occlusive disease and occlusion of small hepatic veins, nodular regenerative hyperplasia, hepatic infarction, cirrhosis, portal hypertension, autoimmune hepatitis and biliary cirrhosis [14].

Obstetric APS is usually manifested by recurrent micarriages that can happen early or late during pregnancy. Obstetric morbidity has different clinical presentations as intrauterine growth restriction, foetal death, pre-eclampsia, placental abruption and placental insufficiency. Recent *in vitro* studies and animal models have shown that obstetric morbidity in APS is mainly inflammatory mediated by cytokine release, complement release and activation of immune cells [15].

Catastrophic antiphospholipid syndrome (CAPS) is a rare form of rapidly progressive APS that can be devastating over a one-week period ending up with disseminated intravascular thrombosis, multiorgan failure and death, where mortality rate exceeds 50% [16,17]. Seronegative APS is a new entity proposed in 2003 defined as having the same clinical manifestations of seropositive APS but having negative standard aPL. We have found other antigens such as zwitterionic phospholipid (phosphatidylethanolamine) that can trigger antibodies other than LA, aCL or anti-β2GPI, but their clinical significance is still controversial [18].

These data and the wide range of organ system involvement described above warrant that APS diagnosis should not be limited by the known clinical and laboratory criteria. With every new discovery about the different aspects of APS, clear guidelines and advanced sub-classifications are required to study the disease thoroughly and adapt management accordingly. This review will highlight recent advances in pathogenesis, risk stratification of thrombosis, and current and potential future management options for APS.

Recent advances in the pathogenesis

Although the full pathogenesis of APS is not clear yet, key discoveries were described recently. As mentioned earlier, thrombosis is the major disease mechanism, enhanced mainly by activating endothelial cells, monocytes, platelets, coagulation and complements pathways in addition to inhibiting fibrinolytic and anticoagulation pathways [19]. However, vasculopathy enhanced mainly by severe intimal hyperplasia is the major contributor to arterial stenotic lesions and can also play a role in vascular occlusions and pregnancy morbidity [20].

A recent study performed on patients with primary and secondary APS nephropathy, which is mainly mediated by vasculopathy rather than thrombosis, revealed that the activation of mammalian target of rapamycin complex (mTORC) enzyme stimulates intimal hyperplasia, leading to the formation of the chronic vascular lesions as seen in APS.

In vitro, aCL and anti-β2GPI activated the phosphatidylinositol 3-kinase (PI3K)–AKT pathway and subsequently mTORC, leading to proliferation of vascular endothelial cells. Sirolimus has improved renal allograft survival and has prevented chronic vascular lesions in this study [21]. Moreover, the intensity of mTORC activation in endothelial cells has shown significant correlation with aPL titres and a statistically significant correlation is also detected between the phosphorylations of AKT on residue Ser^{473} with the amount of both anticardiolipin and anti-B2GPI antibodies. Discovering all the steps that lead to the mTORC pathway recruitment and the molecular consequences of its activation is needed [22]. However, there is a growing evidence that these enzymes are prothrombogenic and can cause thrombosis [23]. This will be an obstacle in proceeding further to test these drugs in patients with APS [24].

Risk stratification of thrombosis in antiphospholipid syndrome

Studies have shown increased risk of thrombosis among patients who are positive for more than one aPL [25–27].

It is very crucial to predict the risk of thrombosis in patients with APS as this can help in the prevention of its occurrence. Recent risk assessment scores have been developed to help in the prediction of risk of thrombosis and pregnancy loss. The strongest score was Global APS Score (GAPSS) as it encompasses the assessment of aPL profile plus cardiovascular risk factors including hypertension, dyslipidemia, smoking, diabetes and autoimmune antibodies (ANA, ENA and anti-dsDNA) which were not included in the other scores [28]. This score has

proven to be valid in two different large prospective studies carried on patients with primary and secondary APS. This score appears to be a promising tool in quantifying the risk of thrombosis and obstetric morbidity in patients with APS. Randomized controlled trials (RCTs) are needed to prove its validity and therefore be able to utilize it as a routine measurement for the risk assessment of thrombosis among patients with APS [29,30]. Cardiovascular risk factors were chosen over the other risk factors because data from literature have revealed premature atherosclerosis in patients with APS [31,32]. Antiprothrombin antibodies (aPT) and antiphosphatidylserine/prothrombin antibodies (aPS/PT) are associated with APS, but their clinical relevance has not been clear [33]. A recent systematic review was carried out to clarify this debate. The results showed significantly higher risk of thrombosis (3–18 times) in aPS/PT-positive APS patients compared to controls. However, (aPT) antiprothrombin antibodies failed to show any significant increase in the risk of thrombosis among patients with APS [34].

Mean platelet volume (MPV) reflects platelet activation and thus can be employed in the risk assessment of thrombosis in patients with APS. MPV was found to be higher especially among those with triple positive aPL and was identified as a predictive factor for the recurrence of thrombosis [35]. In addition, plasminogen, plasminogen activator inhibitor (PAI-1) type 1 gene and 4G/5G polymorphism of PAI-1 gene may be good indicators for the occurrence of thrombosis in APS [36].

Despite the fact that the role of anti-β2 glycoprotein I IgA (aβ2GPI IgA) antibodies is debatable in the clinical significance of APS, a recent retrospective study disclosed that identifying the target domains 1 and 4/5 of these antibodies can be useful for the identification of lupus patients with positive aPL that are at high risk of thrombosis. They can be helpful in the diagnosis and prediction of thrombosis risk, but further large prospective studies are required to establish this correlation [37,38].

Treatment

Treatment regimens of APS are many, and they include oral anticoagulants, hydroxychloroquine (HCQ), statins, B-cell inhibitors, complement inhibitors, blocking of aPL/B2 GPI receptors on target cells and tissue factor inhibitors.

Anticoagulation in primary thromboprophylaxis

General measures to control cardiovascular risk factors and other factors that do contribute to thrombosis in aPL-positive patients should be taken [39]. The 13th Task Force recommendations for primary thromboprophylaxis in APS are shown in Table 1 which supports the use of aspirin. A recent meta-analysis conducted on a total of 1208 asymptomatic patients with persistently positive aPL has shown that low-dose aspirin (LDA) is associated with significant risk reduction in arterial but not in venous thrombosis when compared to placebo. However, no significant reduction was noted after excluding retrospective and low-quality studies [40], thus creating controversy regarding LDA use in the prevention of venous thrombosis. Then, after obtaining raw database and, not only, the extracted data from five cohort studies included in this meta-analysis, LDA was again associated with significant decrease in the risk of the first thrombotic event as well as the first arterial thrombotic event among SLE and asymptomatic aPL individuals [41].

The use of LDA vs. LDA plus warfarin in persistently positive aPL patients were compared in a RCT. There was no difference in the thrombosis risk between the two groups. However, the risk of bleeding was higher among patients receiving the combination therapy [42].

Table 1 Primary and secondary thromboprophylaxis in APS

Primary thromboprophylaxis (+ve aPL)	Secondary thromboprophylaxis
• Long-term primary thromboprophylaxis with LDA (75–100 mg/day) is recommended in non-lupus patients with a high-risk aPL profile, especially in the presence of other thrombotic risk factors • Primary thromboprophylaxis with hydroxychloroquine (200–400 mg/day) ± LDA (75–100 mg/day) is recommended for lupus patients with positive lupus anticoagulant or isolated persistent anticardiolipin antibodies at medium–high titres	• aPL-positive patients with arterial or venous thrombosis not meeting criteria for APS should be managed in the same manner as aPL-negative patients with similar thrombotic events • Patients with definite APS and first venous event should receive oral anticoagulant therapy to a target INR 2·0–3·0 • Patients with definite APS and arterial thrombosis should receive warfarin at an INR > 3·0 or combined anti-aggregant–anticoagulant therapy (INR 2·0–3·0) • Patient's bleeding risk should be estimated before prescribing high-intensity anticoagulant or combined anti-aggregant–anticoagulant therapy • For patients without systemic lupus erythromatosus with a first non-cardioembolic cerebral arterial event who have a low-risk aPL profile and reversible trigger factors, consider antiplatelet agents on an individual basis

APS, antiphospholipid syndrome; aPL, antiphospholipid antibodies; LDA, low-dose aspirin.

Anticoagulation in secondary thromboprophylaxis

Patients with definite APS and first venous event need anticoagulation with warfarin to a target international normalized ratio (INR) of 2·0–3·0 indefinitely. Duration of treatment can be limited to 3–6 months in patients with low-risk aPL profile and other precipitating factors at the time of thrombosis [43,44]. However, patients with definite APS and arterial events on warfarin need to target their INR above > 3·0 [45] (Table 2).

A retrospective small cohort of 11 patients with primary APS manifested mainly by recurrent miscarriages, pulmonary embolisms (PEs) and DVT and persistently negative aPL has suggested the possibility of stopping anticoagulation as no thrombotic events were detected [46]. Large prospective cohorts are needed to clarify whether anticoagulation can be stopped in APS patients with persistently negative antibodies.

Anticoagulation in refractory and difficult cases

These are meant to be patients with recurrent thrombosis, fluctuating INR levels or high risk of major bleeding; further therapeutic options rather than vitamin K antagonist VKA including warfarin might be considered. Long-term low molecular weight heparin (LMWH) (e.g. subcutaneous enoxaparin 1 mg/kg every 12 h or 1·5 mg/kg/day or subcutaneous dalteparin 100 IU/kg every 12 h or 200 IU/kg/day), hydroxychloroquine (200–400 mg/day) or statins have been suggested in these very selected cases [47–49].

Table 2 Summary of the recommendations for clinicians in the 14th International Congress on APS treatment task force

NOAC	Can be used in a first or recurrent venous thromboembolism only in the presence of VKA allergy/intolerance or poor anticoagulant control
Older non-hepain/ warfarin anticoagulants	Danparoid, fondaparinux and argatroban can be used in heparin induced-thrombocytopenia
Hydroxychloroquine	Recommended in lupus patients with positive APLs May be considered in refractory cases as an adjuvant therapy No strong evidence to be used in persistently aPL-positive patients without an underlying autoimmune disease
Statins	Might be of benefit in patients with recurrent history of thromboembolism despite adequate anticoagulation
B-cell inhibition	Recommended for refractory cases of APS possibly in patients with haematologic and microthrombotic/ micro-angiopathic manifestations
Complement inhibition	Not recommended yet but might have a role as an adjuvant or main therapy for patients refractory to anticoagulation

APS, antiphospholipid syndrome; aPL, antiphospholipid antibodies.

Anticoagulation in obstetric antiphospholipid syndrome

The switch from warfarin to LMWH should be performed before 6 weeks of gestation to avoid teratogenicity. Combination therapy with aspirin (75–100 mg/day) and heparin, either LMWH (e.g. subcutaneous enoxaparin 40 mg/day, subcutaneous dalteparin 5000 U/day or subcutaneous tinzaparin 4500 U/day) or unfractionated heparin, is generally recommended in recurrent early miscarriages [50–52]. However, two RCTs have shown no difference in the pregnancy outcome between the use of aspirin alone vs. combination therapy with LMWH [53,54]. Based on that, in addition to some observational studies, aspirin alone can be used in selected cases. The combination of aspirin and LMWH is always given in late pregnancy as well. However, this is based on expert opinion rather than on a strong scientific evidence as there are no RCTs conducted in late pregnancy. Also women with APS and previous thrombotic event should be treated with LDA plus intermediate to full therapeutic dose of heparin or LMWH [55] (Table 3). Mak *et al.* [56] reported in his meta-analysis in 2010 live birth rate of 74% in pregnant patients on aspirin and LMWH compared with a rate of 56% resulting from aspirin intake alone. Long-term use of LMWH is more favourable than unfractionated heparin due to the increased risk of osteoporosis during pregnancy [57]. Antithrombotic coverage with prophylactic dose of heparin or LMWH of the post-partum period is recommended in women with positive aPL with no previous thrombosis for a period of 6 weeks depending on the presence of other risk factors [58].

Novel direct oral anticoagulants

Anticoagulation with warfarin is limited by its drug–drug and food interactions, teratogenicity, high variability in patients' responses and the necessary frequent monitoring of INR which can be inconvenient to many patients [59].

Novel direct oral anticoagulant (NDOAC) directly inhibits a single enzyme of the coagulation cascade and seems to be promising in the prevention of thrombosis in APS. Minimal drug and food interactions and fixed dosing without the need for laboratory monitoring contribute to the advantage of these agents compared to warfarin. However, the lack of antidotes is still a limitation.

Table 3 Summary of treatment of obstetric antiphospholipid syndrome

Recurrent early miscarriage (< 10 weeks gestation)	Late complications (> 10 weeks gestation)	Pregnant patients with previous thrombosis
LDA plus unfractionated/LMW heparin combination at thromboprophylactic doses	LDA plus unfractionated/LMW heparin combination at thromboprophylactic doses	LDA plus unfractionated/LMW heparin combination at therapeutic doses
LDA alone in selected cases		

LDA, low-dose aspirin.

Some studies reported increased risk of major bleeding ranging between 0·57 to 10% per year [60]. This class of drugs includes direct thrombin inhibitor as dabigatran (Pradaxa) and direct anti-Xa inhibitors as rivaroxaban (Xarelto), apixaban (Eliquis) and edoxaban (Lixiana). Many of these agents are licensed by the European Medicines Agency (EMA) and approved by the United States Food and Drug Administration for the prevention of venous thromboembolism, stroke, pulmonary and systemic embolism in addition to the treatment of DVT and PE [61–64]. Currently, two RCTs are ongoing. Another RCT 'rivaroxaban in APS' (RAPS) recently completed aiming at the comparison between the efficacy and safety of rivaroxaban vs. warfarin in 156 APS patients with or without SLE, who have had a DVT and/or PE on warfarin for at least 6 months with a target INR of 2·5. Patients were randomized to either to continue with warfarin or to switch to a daily 20 mg dose of rivaroxaban for 6 months (http://www.controlled-trials.com/ISRCTN68222801).

Expectantly, the results of this trial will show a clear picture of the superiority of one drug over the other in APS management. Win K *et al*. [65] has reported recurrence of thrombosis in three cases of severe APS treated with rivaroxaban and dabigatran.

Hydroxychloroquine

The task force in the 14th International Congress recommended the use of hydroxychloroquine in SLE patients with positive aPL [66]. A recent European multicentre study has assessed the pregnancy outcome in 30 patients with APS or asymptomatic aPL carriers in 35 pregnancies by adding HCQ to previous conventional therapy. The results have revealed dramatic decline in pregnancy losses from 81% to 19% with significant *P* value among all pregnancies when compared to controls and live born babies in 78% of patients (11/14) with refractory obstetric APS. A larger prospective study is needed to confirm the benefits of the use of HCQ as an added therapy in cases of refractory obstetric APS [67]. HCQ has antiplatelet, anti-inflammatory and anticoagulant properties [68–70]. It has also shown efficacy in preventing pregnancy loss by interfering with the binding of Annexin A5, anticoagulant protein that bind to phospholipids present in the placental villi [71]. Albert *et al*. [72] revealed that HCQ reversed the aPL-inhibition of trophoblast interleukin (IL)-6 secretion and partially limited aPL-inhibition of cell migration, suggesting that combined therapy that includes HCQ could be of benefit in pregnant patients with APS.

Decrease in aPL titres following HCQ was first reported in 2013 [73]. A recent small prospective study conducted over 3 years on primary patients with APS receiving a combination of fluindione with HCQ indicated no thromboembolic events, while 30% of patients receiving fluindione alone have developed venous thromboembolism [74]. The risk of thrombosis was reduced in patients with APS on HCQ that had never had DVT before [75]. A multicentre RCT (APS ACTION) is currently ongoing to assess the efficacy of HCQ on patients with positive aPL without the history of thrombosis (http://clinicaltrials.gov/show/NCT01784523).

Statins

HMG CoA reductase inhibitors lower cholesterol levels and possess anti-inflammatory, immunoregulatory and antithrombotic effects [76].

A prospective study has shown that daily 20 mg of fluvastatin over a month might contribute to the prevention of thrombosis in patients with APS by inhibiting the tissue factor and other markers of monocytes that help in activating the coagulation pathway [77]. Another prospective study using 40 mg of fluvastatin over 3 months has shown significant decline in many biomarkers responsible for thrombus formation, such as interleukin one beta, vascular endothelial growth factor, tumour necrosis factor alpha, inducible protein-10, soluble CD40 ligand and soluble tissue factor [78].

Corticosteroids, immunosuppressive drugs, intravenous immunoglobulin or plasmapheresis

Limited data support the use of steroids, immunosuppressive drugs, intravenous immunoglobulin or plasmapheresis in the treatment of APS patients with thrombosis. Some of these therapies can have severe side effects when given for prolonged

periods, and aPL are not always suppressed by these agents. The use of these drugs is probably justified as rescue therapy only in patients with repeated episodes of thrombosis despite adequate anticoagulant therapy or in catastrophic APS [79,80]. A small cohort carried out on seven patients with APS, given intravenous immunoglobulin (IVIG) once monthly for 2 years in addition to the conventional therapy with anticoagulants or antiplatelets, has shown significant reduction in aCL (IgG and IgM) and of IgM anti-β2-glycoprotein I antibodies.

Thromboembolic events were not reported in patients who received IVIG after two years of follow-up. However, three patients had recurrent thrombosis in the group that was not administered IVIG [81]. In cases of refractory obstetric APS that have failed the regular combined anticoagulation, addition of HCQ, low-dose prednisolone (10–15 mg/day) and/or pentoxifylline, antiTNF (antitumour necrosis factor alpha) and IVIG can be considered in stepwise approach, respectively, as there is limited data in literature supporting their use [82].

B-cell inhibition

Rituximab is an anti-CD20 monoclonal antibody that depletes CD20+ B-cell populations. It has been used in APS-related thrombocytopenia, haemolytic anaemia, venous and arterial thrombosis, ischaemic cardiac and bowel events, cutaneous lesions, diffuse alveolar haemorrhage, nephropathy and CAPS [83–86]. It is usually used in refractory cases of APS after failure to anticoagulation [87,88]. Studies revealed conflicting results regarding the effect of rituximab on aPL titres; some studies showed reduction, while others showed no effect following rituximab treatment [89,90]. Paradoxical thrombosis was reported in three cases post-rituximab infusion. The mechanism of how the rituximab might have contributed to the thrombosis is unknown [91]. It is not even known whether rituximab or other patient-/disease-related factor is the illiciting agent. An open-label phase II trial of rituximab in patients with APS called RITAPS was carried out to assess its safety and efficacy for non-criteria manifestations of APS. Results have supported its safety but did not control all the non-criteria manifestations of APS [89].

A combined therapy of anticoagulation, glucocorticoids, plasma exchange and IVIG (especially in the presence of infection) can be used in complicated cases of multiorgan failure due to thrombosis as in CAPS. Cyclophosphamide can also be used in CAPS in the presence of secondary autoimmune disease such as SLE. Rituximab can also be used in refractory cases after failure or inability to take the above-mentioned combined therapies or in the presence of micro-angiopathic haemolytic anaemia [92] (Table 4).

Belimumab is an inhibitor of B-cell activating factor monoclonal antibody used mainly in the treatment of SLE. There are no data regarding its use in APS. However, there is only one RCT conducted on patients with lupus that has shown decrease in aCL IgA at the dosage of 10 mg/kg [93].

Table 4 Summary of the recommendations for clinicians in the 14th International Congress on CAPS treatment task force

Medications	Grade of recommendation
AC + GC should be the backbone of therapy	B
AC + GC + plasma exchange and/or IVIG	B
IVIG should be used in the presence of infection	D
AC + GC + plasma exchange and/or IVIG + cyclophosphamide in systemic lupus erythromatosus or other autoimmune disease	D
Rituximab can be used as: • Initial adjuvant therapy in MHA • Second-line therapy in patients refractory to standard triple therapy • Alternative adjuvant therapy when AC is contraindicated	–

AC, anticoagulation; GC, Glucocoticoid; IVIG, intravenous immunoglobulin; MHA, micro-angiopathic haemolytic anaemia.

Complement inhibition

Complement system is part of the innate immunity related to APS pathogenesis, which contributes to the activation of the endothelial cells and induction of thrombosis [94,95]. Complement C5a interaction with aPL induces neutrophils to express tissue factor that leads to foetal injury [96]. In the last 4 years, successful treatment with eculizumab has been reported on few patients. All these case reports have shown that it was successful whether in treating refractory cases of CAPS or in preventing the recurrence of APS among renal transplant recipients [97–104].

Blocking of antiphospholipid antibody/B2 GPI receptors on target cells

Annexin A2 protein is a receptor found on the surface of placental syncytiotrophoblasts, monocytes and endothelial cells. aPL bind to these receptors leading to thrombosis [105]. A mimicker of the Vth domain of B2GPI succeeded in reducing thrombosis in mice by competing with B2GPI in binding to the target cells [106]. Ioannou *et al.* [107] found that the recombinant domain I (DI) of B2GPI inhibits the pathogenic effect of

aPL in mice, hence supporting the development of recombinant DI to be tried on patients. A1-A1, a new molecule that targets the binding of β2GPI to negatively charged cellular surfaces and ApoE receptor 2- that are two prothrombotic mechanisms in APS, was tried in mice and succeeded in blocking the thrombotic effects of β2GPI [27]. Further studies are required to elucidate the significance of aPL/β2GPI receptor blockade in the course of APS management.

Tissue factor inhibitors

Tissue factor is a transmembrane glycoprotein that binds to factor VII/factor VIIa complex, initiating *in vivo* coagulation by thrombin and fibrin formation. aPLs are thought to increase the tissue factor expression promoting thrombosis [108] Sunol-cH36, a chimeric monoclonal antibody against TF, showed good safety profile in patients with stable coronary artery disease [109].

Trials studying the efficacy of this drug in patients with APS are worthwhile.

Conclusion

Thanks to the ongoing research and enthusiasm of clinicians from different medical fields; knowledge of the various aspects of APS has significantly improved over the last 30 years. Today, we are more aware that APS is not as simple as aPL-positive sera within a limited group of patients whose risk of thrombosis is higher than the general population, but a serious disease that can affect almost every organ system with an extensive range of clinical features and a complex underlying pathophysiology.

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Conflict of interest

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