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Treatment of antiphospholipid syndrome beyond anticoagulation

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ABSTRACT

Antiphospholipid syndrome (APS) is a systemic autoimmune disorder marked by thrombosis and/or pregnancy morbidity in the presence of antiphospholipid antibodies (aPL). At the present time, treatment is primarily focused on anticoagulation. However, there is increasing awareness of the mechanisms involved in APS pathogenesis, which has led to the trial of novel therapies targeting those mechanisms. Following a brief review of the etiopathogenesis of and current management strategies in APS, this paper focuses on the evidence for these potential, targeted APS treatments, e.g., hydroxychloroquine, statins, rituximab, belimumab, eculizumab, defibrotide, sirolimus, and peptide therapy.

1. Introduction

Antiphospholipid syndrome (APS) is defined by the development of venous thromboses, arterial thromboses, and/or pregnancy morbidity in the setting of positive antiphospholipid antibodies (aPL). Pregnancy morbidity is defined as three or more spontaneous abortions prior to 10 weeks' gestation, any number of fetal losses after 10 weeks, or premature birth prior to 34 weeks as a result of eclampsia, severe pre-eclampsia, or placental insufficiency. Antiphospholipid antibodies should be present on two or more occasions, with testing completed 12 or more weeks apart [1]. These criteria are together known as the revised Sapporo (or Sydney) APS Classification Criteria, which have been developed for research purposes and do not uniformly capture all APS cases [2].

Other clinical problems that can occur in APS patients include thrombocytopenia, hemolytic anemia, livedo, cardiac valve disease, nephropathy, and cognitive impairment [1,3]. These are known as "non-criteria manifestations". Valvular disease is defined as sterile vegetations and/or thickening of valves [4]. Livedo consists of red or blue discoloration of the skin in a reticular pattern [5]. Nephropathy is characterized by aPL-associated thrombotic microangiopathy, arteriosclerosis, fibrous intimal hyperplasia, focal cortical atrophy, and/or fibrous obliteration of arteries [6].

Catastrophic APS (CAPS) is defined by presence of aPL in a patient with rapidly developing thromboses of three or more organ systems in less than one week, as well as small vessel thrombosis on biopsy. In contrast to the large vessel occlusions seen in thrombotic APS, CAPS tends to present with diffuse small vessel occlusions [7]. A small minority of APS patients, approximately 1%, develop CAPS, which carries a mortality risk of 40–50% [8,9].

Laboratory tests used to detect aPL include the anticardiolipin antibody (aCL) enzyme-linked immunosorbent assay (ELISA), anti-β_2-glycoprotein-I (aβ_2GPI) ELISA, and the lupus anticoagulant (LA) coagulation assay. Positive serology for all three aPL, especially with high titer aPL ELISA, carries a worse prognosis [3,10] as does positive testing for LA [11,12]. Most pathologic aPL, including aCL, cause clinical sequelae by attacking phospholipid-binding plasma proteins (β_2-glycoprotein-I [β_2GPI] in particular). This is in contrast to non-autoimmune aCL targeting, cardiolipin, which is a phospholipid and a mitochondrial membrane component [13,14]. There have been additional aPL identified, but the clinical relevance is undetermined and they are not included in the classification criteria [15].

2. Etiopathogenesis of antiphospholipid antibody-related clinical events

Although the pathogenesis of APS is imperfectly understood, it is clear that the generation of aPL plays a vital role [3,10,16]. Despite a higher risk of thrombosis and obstetric morbidity in patients with aPL, many patients, especially those with single aPL positivity, never develop clinical sequelae [17]. This points toward a "two hit hypothesis", i.e., the generation of aPL is necessary but not sufficient to develop clinical symptoms. The second "hit" is not clearly delineated but it is hypothesized that inflammation, infection, or other pro-thrombotic triggers contribute to the development of clinical events [18]. As well, aPL-positive patients with traditional thrombotic risk factors including

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smoking and obesity, are known to have a higher risk of developing thrombotic events [12].

β_2-glycoprotein-I is a circulating apolipoprotein which has a crucial role in the pathophysiology of APS [3,10,19,20]. Under normal circumstances, β_2GPI functions as a complement control protein and also has a role as a natural anticoagulant [21]. In its unbound form, β_2GPI assumes a circular conformation. It can bind to phospholipid membranes when anionic phospholipids are present. Anionic phospholipids are present on normal trophoblasts and on activated platelets and endothelial cells. Specific binding proteins of β_2GPI have recently been described, with β_2GPI showing particular affinity for AnnexinA2 and Toll-like receptor-4 (TLR-4) [3,22,23]. Once bound to phospholipid membranes, β_2GPI opens up to assume a more linear shape. This conformational change allows aβ_2GPI to bind to β_2GPI [10]. In fact, aPL that bind to a specific area of β_2GPI known as domain I are now considered to be particularly pathogenic [24–30]. Once bound, the aPL-aβ_2GPI complex can activate a number of intracellular pathways and ultimately lead to thrombosis and pregnancy loss. Of note, transient aPL, usually in the form of aCL IgM, are well known to be produced during infections; in this setting, the aPL interestingly do not bind to β_2GPI, but rather directly to phospholipids and are rarely associated with clinical events [31].

One of the key pathways activated by aPL-aβ_2GPI binding is the classical complement pathway, which generates C5a. This in turn upregulates tissue factor (TF) and intracellular adhesion molecule-1 and also activates platelets, neutrophils, and monocytes. Together, these changes lead to an increase in inflammatory markers and a prothrombotic state, and are a necessary step in the development of APS [32–34]. The mammalian target of rapamycin (mTOR) pathway is also upregulated by aPL-aβ_2GPI binding. Activation of this pathway increases TF and interleukin (IL)-8 concentrations, and also promotes endothelial proliferation, contributing to APS vasculopathy and vascular occlusion [35–37]. Nuclear factor kappa B (NF-kB) is a further intracellular pathway activated by aPL-aβ_2GPI binding [3]. This signaling pathway is considered a prototypical inflammatory pathway; NF-kB is involved in the regulation of numerous chemokines, cytokines, and adhesion molecules, playing an active role in many inflammatory conditions [38].

The pathogenesis of pregnancy morbidity in APS is also closely tied to the binding of aPL to β_2GPI and to complement activation. Antiphospholipid antibody-β_2GPI binding inhibits trophoblast migration and growth, as well as the release of gonadotropins, prolactin, and insulin growth factor binding protein-1 (IGFBP-1) [19,39]. As in thrombotic APS, obstetric APS also requires activation of the complement cascade to induce clinical symptoms, in part because of dysregulation of angiogenic factors [32,40,41]. Pregnancy morbidity is not entirely caused by fetal thrombosis, as was originally hypothesized [42]; heparins improve pregnancy outcomes [43] likely due to the ability of heparin to inhibit complement [44] and also inhibit binding of β_2GPI by aPL [45].

In addition to the APS mechanisms described above, there are many other factors which play a role in the development of APS-mediated thrombosis and pregnancy morbidity. These include but not limited to inhibition of annexin5, protein C, protein S and nitric oxide. More information regarding these various mechanisms can be found in recent review articles [3,10,46,47].

3. Current management strategies in antiphospholipid syndrome

3.1. Thrombosis

At the present time, anticoagulation remains the central focus of thrombosis treatment and prevention in APS [48–50]. Heparin is used for treatment of acute thrombosis, whereas warfarin with an international normalized ratio (INR) target of 2.0–3.0 is the standard treatment for secondary prevention of both arterial and venous thromboses, with additional low-dose aspirin or higher intensity (INR target 3.0–4.0) anticoagulation used by certain centers for arterial thrombosis [51–53]. Our strategy is to keep the INR target at 2.5–3 for both venous and arterial thrombosis, and adding low dose aspirin in patients with other cardiovascular disease risk factors. For patients with recurrent thromboses despite optimal warfarin therapy, a higher INR target of 3.0–4.0 is utilized with or without low-dose aspirin, hydroxychloroquine, and/or a statin drug (further discussed below) [18].

Four randomized clinical trials have been initiated to assess the effectiveness of the direct oral anticoagulants (DOACs) rivaroxaban and apixaban for treatment of APS. These include the *Rivaroxaban versus warfarin to treat patients with antiphospholipid syndrome* (RAPS) trial, the *Trial on Rivaroxaban in AntiPhospholipid Syndrome* (TRAPS), *Rivaroxaban for AntiPhospholipid Syndrome* (RAPS) study (ClinicalTrial.gov Identifier: NCT02116036; separate study from initial RAPS trial), and *Apixaban for the Secondary Prevention of Thrombosis Among Patients with Antiphospholipid Syndrome* (ASTRO-APS) trial [53–57]. The RAPS trial evaluated endogenous thrombin potential (ETP) as the primary outcome in APS patients randomized to receive either rivaroxaban or warfarin. With respect to this primary endpoint, they failed to show non-inferiority of rivaroxaban. Pending the results of other studies with clinical outcome measures, currently DOACs are not recommended in APS.

3.2. Pregnancy morbidity

Patients with obstetric APS only should receive prophylactic dose low-molecular-weight heparin (LMWH) and low dose aspirin throughout pregnancy, and continue heparin until six to 12 weeks' postpartum [58,59]. Thrombotic APS patients, independent of pregnancy morbidity history, should continue anticoagulation during pregnancy, but be switched to therapeutic dose LMWH, given the teratogenic effects of warfarin. There is no evidence of benefit for the use of heparin in pregnant patients with asymptomatic aPL, or for patients who have a history of pregnancy morbidity but do not meet APS criteria [60].

3.3. Catastrophic antiphospholipid syndrome

Immunosuppression is currently indicated in addition to anticoagulation, when a patient develops CAPS. Pulse-dose glucocorticoid therapy, i.e., methylprednisolone 500 to 1000 mg intravenous daily for three days followed by maintenance dose, is used in conjunction with heparin, intravenous immunoglobulin (IVIG), and/or plasmapheresis [61]. Evidence for this Level II recommendation is based on case series and expert opinion [62]. Importantly, the patient should be treated for any precipitating factors that may have led to the development of CAPS. The trigger is frequently infection, but may also include surgery, lupus flare, malignancy, withdrawal of anticoagulation, or obstetrical complications, among others [62,63].

4. Treatment of antiphospholipid syndrome beyond anticoagulation

As outlined above, there is increasing awareness of the mechanisms involved in APS pathogenesis, which has led to the trial of novel therapies targeting these mechanisms. In this section, we will focus on the evidence for these potential, targeted APS treatments, including statins, hydroxychloroquine, rituximab, belimumab, eculizumab, sirolimus, defibrotide and peptide therapy. A summary of key points is provided in Table 1.

4.1. Statins

Statins are a class of lipid-lowering medications, which inhibit hydroxymethylglutaryl coenzyme A reductase (HMG-CoA). Statins can also exert anti-inflammatory and anti-thrombotic effects in the general

Table 1
Summary of the potential targeted treatment strategies in antiphospholipid syndrome (APS)

Medication	Mechanism	Potential use in APS
Statins	Pleiotropic anti-inflammatory, and anti-thrombotic effects.	Use in patients with statin indication, i.e., hypercholesterolemia; consider in refractory APS; do not use in pregnancy.
Hydroxychloroquine	Pleiotropic anti-inflammatory, and anti-thrombotic effects.	Use in patients with hydroxychloroquine indication, i.e., lupus; consider in refractory APS.
Rituximab	Anti-CD-20 monoclonal antibody; B-cell depleting agent; inhibition of ICOS/CD4 + .	Consider for hematologic and/or microthrombotic manifestations of aPL; consider for CAPS.
Belimumab	BAFF/Blys inhibiton.	More data needed to formulate recommendations (only two reported patients treated with belimumab).
Eculizumab	Complement 5 inhibitor.	Consider in refractory CAPS patients; consider in aPL-positive patients with renal allograft rejection.
Sirolimus	mTOR inhibition.	Only a small retrospective APS cohort undergoing renal transplantation were reported
Defibrotide	Adenosine receptor agonist; inhibits platelets and thromboxane.	More data needed to formulate recommendations (only a small retrospective APS cohort undergoing renal transplantation was reported).
Peptide therapy	Non-complement fixing peptide binding to β_2GPI, domain I, or domain V.	Not currently available for use.

BAFF/Blys: B-cell activating factor/B-lymphocyte stimulator; CAPS: catastrophic antiphospholipid syndrome; ICOS: inducible co-stimulator; mTOR; mammalian target of rapamycin.

population [64]. These findings have prompted the investigation of statins as a potential treatment for APS; two studies examined the effects of statin therapy on clinical outcomes in APS patients.

The first study, a small, non-randomized, prospective pregnancy outcome study, was published in 2016 [65]. Twenty-one consecutive obstetric APS patients were enrolled; each developed preeclampsia and/or intrauterine growth restriction (IUGR) despite treatment with low dose aspirin (80 mg oral daily) and prophylactic LMWH, i.e., enoxaparin or tinzaparin 40 mg subcutaneous daily. The first 10 patients were continued on low dose aspirin and prophylactic dose of LMWH only. The following 11 APS patients were prescribed pravastatin 20 mg daily in addition to continuing aspirin and LMWH, at the time of diagnosis of preeclampsia and/or IUGR. Authors observed the following: among the first 10 patients who received low dose aspirin and LMWH, there were three stillbirths and two neonatal deaths; the mean gestational age of delivery of this group was 26.3 weeks and all delivery methods were by emergent cesarean section. Among the 11 patients who received pravastatin 20 mg daily in addition to low dose aspirin and LMWH, there were no neonatal deaths or stillbirths; each birth occurred at 34 weeks' gestation or later. Despite these findings, we would like to emphasize the non-randomized observational nature of this study, which significantly limits the clinical application of results due to selection, surveillance, and calendar time biases. As well, statins are still considered to be teratogenic (Category X) according to the Food and Drug Administration (FDA); despite increasing evidence that statins do not produce teratogenic effects [48,66,67], we do not recommend statin use during pregnancy.

A second clinical outcome study examining the effects of statins on thrombosis in SLE patients was recently published [68]. This single center retrospective study described the incidence of thrombosis in aPL-positive and aPL-negative lupus patients, with and without statin therapy. Of 152 lupus patients (80 aPL-positive and 72 negative), none had a prior history of thrombosis, and 22 (14%) developed thrombosis during the mean follow-up of 65 months (15 in the aPL-positive group and seven in the aPL-negative group). Authors do not provide details regarding the dose of statin treatment, compliance, or the use of other medications including hydroxychloroquine. Among aPL-positive patients with and without thrombosis, one of 15 (7%) and 22 of 65 (34%) received statins, respectively. The primary analysis in this study included patients who tested positive for non-criteria aPL, i.e, phosphatidylserine-dependent anti-prothrombin antibodies (aPS/PT), which yielded positive results for the protective effect of statins against thrombosis (multivariate analysis with Cox's proportional hazards model revealed a HR of 0.12, 95% CI 0.01–0.98). However, among the 76 participants who were positive for criteria aPL, multivariate analysis showed no benefit of statin therapy; HR 0.16, 95% CI 0.02–1.30. It is not delineated in the paper how many patients with criteria aPL were using statins and developed thrombosis. Among aPL-negative patients with and without thrombosis, two of seven (29%) and 21 of 65 (32%) received statins, respectively; there was no protective effect of statins in this group.

In addition to the two studies above which examine clinical outcomes, multiple mechanistic and animal studies assessed the use of statins in APS [69–72], each demonstrating a down-regulation of multiple pro-inflammatory and pro-thrombotic factors. In 2001, Meroni et al. [69] demonstrated that fluvastatin could decrease monocyte adhesion, and endothelial cell expression of E-selectin and intercellular adhesion molecule 1 (ICAM-1) in a dose-dependent manner. This study also demonstrated similar outcomes with simvastatin, although with lesser effect, prompting the use of fluvastatin in multiple studies that follow. Ferrara et al. demonstrated in 2004 that fluvastatin inhibits the upregulation of TF by aPL on endothelial cells [70]. In 2011, Lopez-Pedrera et al. showed that fluvastatin can produce a significant inhibition of TF, protein activator receptors 1 and 2, vascular endothelial growth factor, and fms-related tyrosine kinase-1 (flt1) expression that was related to the inhibition of p38 mitogen-activated protein kinase (MAPK) and NF-kB B/Rel DNA-binding activity [71]. Another study in 2014 demonstrated that inflammatory markers interleukin (IL) 1β, vascular endothelial growth factor (VEGF), tumour necrosis factor (TNF)-α, interferon (IFN)-α, inducible protein-10 (IP10), soluble CD40 ligand (sCD40L), and soluble tissue factor (sTF) were all significantly and reversibly reduced in APS patients prescribed fluvastatin 40 mg daily [72].

In summary, preliminary studies which examine the effects of statins on APS outcomes show some promise, pointing toward a down-regulation of pro-thrombotic markers and decreased incidence of pregnancy morbidity. However, clinical data are currently limited to small observational and retrospective studies. Based on this evidence, statins should only be considered for APS patients when there is a standard indication, i.e., hyperlipidemia, or for refractory cases of APS, as an adjunctive therapy. A larger, controlled trial is warranted.

4.2. Hydroxychloroquine

Hydroxychloroquine (HCQ) is an antimalarial with multiple immune modulating, anti-inflammatory, and anti-thrombotic mechanisms, including inhibition of TF, complement, and TLR-4 expression. Hydroxychloroquine is an essential component of lupus therapy [73] and is also used in many other autoimmune conditions including rheumatoid arthritis (RA). Prior to its use in rheumatologic conditions, HCQ was shown to prevent postoperative venous thromboembolism (VTE) following hip arthroplasty [74,75].

There are limited prospective data examining the clinical benefits of HCQ in primary APS. In a small, non-randomized trial published in 2013 [76], twenty patients were treated with HCQ 400 mg daily in addition to anticoagulation, and 20 controls were treated only with oral anticoagulation. The follow up period was three years. Authors do not provide significant detail regarding the variance between each group. Results reveal no thrombotic events in the 20 patients included in the HCQ group, and six VTE in the 20 patients included in the control group (HR 2.4, 95% CI 1.3–4.1; $p < 0.005$). An international randomized controlled trial investigating the prophylactic role of HCQ in the primary thrombosis prophylaxis of aPL-positive patients without systemic autoimmune disease [77] were only able to recruit 20 patients, with no participants experiencing a thrombotic event and therefore no conclusions could be drawn (the trial was terminated early due to logistical reasons).

Available retrospective data include a European multi-center trial published in 2015 [78]. This study compared the obstetrical outcomes of a retrospective cohort of patients with aPL using HCQ and standard treatment, versus standard treatment alone. They included asymptomatic aPL carriers, which should lead to some hesitation in interpretation of the results. However, the authors also analyzed the outcomes of pregnancies before and after the addition of HCQ, observing a significant decrease of pregnancy losses after the addition of hydroxychloroquine, from 16/20 (80%) to 4/20 (20%; $p < 0.05$).

Three studies have been published which examine the antithrombotic effects of HCQ in patients with lupus and APS (secondary APS). These include a prospective observational study, as well as two retrospective studies [73,79–81], with each showing a trend toward lower rates of thrombotic events with use of HCQ. The presence of lupus in these reports creates a confounding factor and caution should be taken when applying results to primary APS patients. Hydroxychloroquine has been shown to be associated with lower odds of persistently positive aPL in SLE patients [82,83], although more recent data are conflicting [77].

Several mechanistic and animal studies support the use of HCQ in both thrombotic and obstetric APS. The most recent study was published by Schrieber et al in 2017 [84] and shows that HCQ significantly reduced sTF levels in patients with aPL. No significant change was observed in AnxA5 activity, anti-domain 1 IgG activity, C-reactive protein (CRP), complement Bb, C3a-des-Arg, or VEGF. All participants received the same dose of HCQ (200 mg daily), regardless of body weight, so some participants may have had sub-therapeutic HCQ levels. In 2016, Bertolaccini et al [85] demonstrated in mouse models that HCQ can inhibit complement and prevent fetal death, central nervous system abnormalities and placental abnormalities. Surprisingly, there was no change in the rate of in vivo aPL binding in APS mouse models as shown with the use of labelled aPL and proton magnetic resonance imaging spectroscopy (SPECT scan), which is in contrast to prior investigations showing decreased rates of aPL binding in vitro with the use of HCQ [86,87]. Earlier studies have also shown that HCQ is able to restore trophoblastic differentiation in mouse models via inhibition of TLR-4 [88], as well as reduce platelet activation, thrombus size, and thrombi duration [89,90].

To summarize, the evidence for use of HCQ for treatment of APS is encouraging. Mechanistic studies show reduced expression of prothrombotic factors and attenuation of obstetric pathology, while preliminary clinical studies reveal decreased rates of thrombosis and pregnancy morbidity. While all SLE patients should be considered for HCQ therapy, there is currently insufficient evidence to recommend this therapy for all primary aPL/APS patients and a larger, controlled trial is warranted. Hydroxychloroquine should, however, be considered in patients who present with refractory APS symptoms given the positive data as outlined above.

4.3. B-cell depleting therapy

Rituximab is an anti-CD20 monoclonal antibody approved for treatment of RA, granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), Non-Hodgkin's lymphoma (NHL), and chronic lymphocytic leukemia (CLL) and has also shown utility for several off-label purposes including SLE [91].

The ability of rituximab to deplete B cells and thus antibody production makes it an appealing potential therapy for APS. Accordingly, there are studies to show that rituximab use is associated with diminution of aPL ELISA titers [92–96], although data are conflicting [97–104]. In fact, a systematic review showed that there are no studies demonstrating that monotherapy with Rituximab renders a negative aPL profile in patients with persistently positive aPL [104]. Notably, clinical response to rituximab was not affected by aPL persistence in several reports [97–99,101–103], pointing to other potential mechanisms of rituximab in APS treatment. Knowledge of these further mechanisms is limited, although it is proposed that immune complexes formed by the binding of rituximab to CD20 act as a decoy, attracting monocytes and macrophages and therefore reducing pathologic inflammation elsewhere [105]. As well, in vivo studies have shown that rituximab can inhibit the expression of inducible co-stimulator (ICOS), which activates T helper cells [106]. This is significant because murine models have shown that CD4+ T cell activation is a necessary step in the development of APS [107].

Evidence for the clinical utility of rituximab consists of case series and observational data. A non-randomized pilot study was published in 2013 [98], which examines the safety and outcome of rituximab in treating non-criteria APS manifestations including cardiac valve disease, aPL-nephropathy, thrombocytopenia, skin ulcers, and cognitive dysfunction. Nineteen patients were involved in the study and show variable responses to treatment, with approximately half of patients experiencing a partial or complete response, and no participants experiencing a major adverse reaction (of note, two patients could not complete the treatment because of infusion reactions). A relatively small number of case studies describe the effects of rituximab on both criteria and non-criteria manifestations in patients with primary and secondary APS. The vast majority of these studies demonstrate complete or near-complete response, although there is inherent bias in which cases are submitted and chosen for publication (also many patients received additional treatments). These case reports include treatment of venous thrombosis [95,99,101,103,108–114], arterial thrombosis [93,95,115], thrombocytopenia [93,95,101,102,109,114,115], hemolytic anemia [115], cutaneous ulcers [99,108,114,115], pulmonary hemorrhage [97], and CAPS [97,110,116–118]. There are also published case studies, which showed a non-favorable outcome. The first was written by Ames et al, who in 2006 [100] reported a case of APS with associated thrombocytopenia, showing only a modest benefit after rituximab administration, with platelets increasing to 30,000. Asherson et al. [119] also reported a death in a patient with CAPS treated with rituximab, and Wig et al. report a lack of response to rituximab treatment in a patient with CAPS [120], with subsequent response to eculizumab.

Multiple studies also described APS patients with concurrent malignancy who were treated successfully with rituximab [96,117,121]. However, in each identified case, the resolution of APS occurred in conjunction with resolution of malignancy. Malignancy is a known precipitating factor for the development of aPL and the resolution of malignancy could have attenuated these symptoms. As well, rituximab was often given in conjunction with chemotherapeutic agents, many of

which could have also contributed to APS recovery.

Limited data suggest that belimumab may also be an effective treatment for APS. Belimumab inhibits B-cell activating factor (BAFF), also known as B lymphocyte stimulator (Blys), and is currently approved for treatment of SLE. Inhibition of this pathway in murine APS models has prevented nephritis and arterial thrombosis and resulted in prolonged survival [122]. B-cell activating factor blockade did not, however, prevent the development of thrombocytopenia. Inhibition of BAFF in murine models led to the depletion B cells, reduced activation of CD4+ cells, reduced expression of adhesion molecules and reduced deposition of macrophages and dendritic cells [122]. Prior murine studies have shown CD4 depletion to contribute to significant improvements in APS manifestations [123]. Two primary APS cases treated with belimumab have been reported [124] for treatment of diffuse alveolar hemorrhage and cutaneous ulceration. In both cases, use of belimumab resulted in clinical improvement although not complete recovery.

Drawing conclusions from the current evidence described above, B cells play an important role in APS pathophysiology. Rituximab is able to deplete CD20+ B cells and diminish other relevant inflammatory pathways including CD4+ activation. There are multiple case reports of partial or complete recovery of aPL manifestations (including skin ulcers, aPL nephropathy, and diffuse alveolar hemorrhage) with the use of rituximab, but controlled data are still lacking. Thus, rituximab should be considered for APS or CAPS patients with hematologic and/or microthrombotic manifestations, especially for those who fail to respond to standard therapy. Belimumab has less supporting data, but could also be considered in refractory APS cases.

4.4. Complement inhibition

As summarized in the *Mechanisms* section above, complement plays a crucial role in APS pathogenesis [32–34,40,41,125] and it is often considered a therapeutic target in refractory CAPS cases. There are two variants of complement inhibitors which are currently FDA approved: plasma protease C1 inhibitors (C1INH), which are primarily used for treatment of angioedema in congenital C1 inhibitor deficiency, and eculizumab. Eculizumab is a humanized monoclonal antibody that binds to C5, preventing the generation of C5a and C5b [126] and thus averting the activation of the membrane attack complex (MAC) and the expression of numerous cytokines [127]. In addition to targeted complement inhibition, other pleotropic medications mentioned earlier in this article have been shown to modestly decrease complement levels and may contribute to favorable outcomes in APS patients. These include hydroxychloroquine [84,85], heparin [44] and rivaroxaban [128].

Eculizumab is currently FDA approved for treatment of atypical hemolytic uremic syndrome (aHUS), paroxysmal nocturnal hemoglobinuria (PNH), and generalized myasthenia gravis (gMG). In addition, eculizumab is being considered for use in multiple other disorders including ANCA-associated vasculitis [129], lupus nephritis [127], reperfusion injury post stroke and myocardial infarction [130], among others. Eculizumab has previously been considered for treatment of RA, but was shown in a double blind, placebo-controlled study that blockade of C5a does not reduce synovitis [131], despite mechanistic studies demonstrating a pathogenic role for C5 in RA patients [132,133], highlighting the importance of concurrent mechanistic and clinical trials. A Phase IIa trial investigating the use of the C5 inhibitor ALXN1007 for treatment of APS was initiated, but was terminated due to slow patient enrollment (clinicaltrials.gov#: NCT02128269). The goal of this study was to determine the effects of complement inhibition on non-criteria APS manifestations including thrombocytopenia, nephropathy, and/or skin ulcers. A further clinical trial is currently being completed to investigate the utility of eculizumab to enable renal transplantation in CAPS patients (clinicaltrials.gov#: NCT01029587), with results expected shortly.

Currently available clinical data supporting the use of eculizumab in APS patients consists of small number of case reports or series. The majority of reported clinical cases involve patients with primary CAPS and show significant [134,135] or complete recovery [120,136] with the addition of eculizumab to the standard therapy. As in the cases reported for rituximab in the treatment of APS, there is significant bias in which cases are submitted and chosen for publication and we expect that cases with negative outcomes may not have been reported. Additional case reports show favorable outcomes with clinically significant [137] or complete response [138] to eculizumab in patients with CAPS associated with SLE, despite prior failure of standard treatment. Further studies have shown that eculizumab can successfully rescue renal allografts after the development of secondary APS microangiopathy [139–141] and may also avert the development of recurrent CAPS in patients undergoing renal transplant [142,143]. One of the aforementioned primary CAPS patient showed persistent recovery from APS symptoms with eculizumab despite a major motor vehicle collision requiring multiple orthopedic surgeries [139] and a further case revealed relapse of CAPS symptoms with eculizumab withdrawal, which were quickly aborted with reinstitution of therapy [136].

There are data regarding the use of eculizumab in pregnancy consisting of case reports with no identified fetal or maternal complications [144,145] and evidence to suggest limited placental transmission [146]. However, the use of eculizumab in pregnant APS patients is limited to one case report. This particular patient was deemed to be at very high for developing CAPS, given her prior history of recurrent arterial thromboses resulting in amputations, development of cutaneous ulcers and ongoing ischemia during her pregnancy, and triple aPL positivity [147]. She was given 600 mg of eculizumab 8 days and 1 day before the delivery at 32 + 4 gestational week; she developed no postpartum thrombosis, the complement activity normalized within a week, and negligible amounts of eculizimab was detected in infant.

Necessary safety considerations in the administration of eculizumab include immunization against Neisseria meningiditis prior to use, as there has been reports of fatal and near fatal of N. meningiditis meningitis [148], rendering an FDA black box warning. As well, patients treated with eculizumab are at higher risk of infection with all encapsulated organisms and should be vaccinated against Streptococcus pneumoniae and Haemophilus influenza as well as receive all routine vaccinations, prior to treatment [149]. Another consideration with use of eculizumab is the extraordinarily high cost, with yearly estimates exceeding $500,000 [150]. This price is substantial, even when considering other related costs, e.g., intensive care admissions (greater than $3500 daily) [151], dialysis ($129,997 to $173,507 annually) [152], or rituximab therapy ($30,000 annually) [153].

To conclude, eculizumab targets the terminal complement cascade, which has been shown to be a critical step in the pathogenesis of APS. The application of eculizumab in APS has been generally limited to CAPS and prevention of recurrent CAPS, with several case reports documenting positive outcomes. This limited use of eculizumab is largely due to its high cost. Clinical trials are pending and have presented numerous challenges, including the rarity of CAPS. Based on the data currently available, eculizumab is a reasonable therapeutic option for CAPS patients who have failed standard therapy and are critically ill.

4.5. Mammalian target of rapamycin blockade

The mammalian target of rapamycin (mTOR) is an intracellular pathway targeted by aPL binding and has been shown to contribute to endothelial proliferation leading to APS vasculopathy and vessel occlusion/end organ damage [35,37,154]. The mammalian target of rapamycin activation also increases the expression of TF, TLR4, and IL-8 [36,155] and leads to B cell proliferation and T cell differentiation and activation [156–159]. Sirolimus, or rapamycin, is a medication that inhibits this pathway by binding the intracellular protein FK, which reduces expression of interleukin-2, causing a cell cycle arrest at the G1-

S phase juncture [156]. Recently, it was also shown that sirolimus may also contribute to lower aPL titers in SLE patients [160]. Currently, sirolimus is FDA approved for use in renal transplant rejection prophylaxis and lymphangioleiomyomatosis.

There has been one combined mechanistic and retrospective clinical study to date which has looked at the use of sirolimus in APS, completed by Canaud and colleagues in 2014. This study was divided into four parts: 1) immunostaining of renal biopsy samples to search for evidence of mTOR activation; 2) in vitro analysis of aPL on human endothelial cells; 3) post-mortem analysis of vessels of CAPS patients, and 4) clinical effect of sirolimus on the outcomes of APS patients undergoing renal transplant [35]. The in vitro component of the study analyzed kidney biopsies from four groups of participants: primary APS, APS associated with SLE, non-APS SLE, and controls (whose tissue was obtained for the purpose of tumor resection). Results show activation of the mTOR pathway as demonstrated by phosphorylation of S6RP and AKT (Ser473) and endothelial proliferation, in APS samples but not in the control samples. Moreover, they demonstrated that in vitro human endothelial cells can mimic these same effects if incubated with polyclonal aPL. Post mortem assessment of CAPS patients showed similar features, with marked intimal proliferation, activation of mTOR as well as severe constriction of the vessel lumens in the carotid and left anterior descending arteries. Given the in vitro findings, authors proceeded to retrospectively analyze the outcomes of APS patients undergoing renal transplant. Ten APS patients at their institution were treated with sirolumus to prevent graft rejection and each developed significantly less vascular proliferation, as shown on post-transplant biopsies, and had no vascular lesions (7/10 versus 3/27 untreated patients). Moreover, the rate of functioning allograft was significantly higher in this group. Interestingly, sirolimus did not increase graft survival for patients without a history of APS. Additional supporting clinical data for the use of sirolimus for APS treatment includes a case report by Mora-Ramirez and colleagues in which they describe successful coronary stenting in a patient with APS, after having refractory coronary disease with a paclitaxel-implanted stent [161].

Mechanistic studies which demonstrate the importance of mTOR activation in the development of APS thrombosis, combined with evidence from the retrospective study outlined above demonstrate significant potential of sirolimus as a therapeutic target in APS. However, controlled data are lacking and the side-effect profile of sirolimus is not benign, which includes potential thrombogenicity [162–164]. These limitations currently preclude the recommendation of sirolimus to patients without another approved indication.

4.6. Adenosine receptor agonists

Defibrotide is an adenosine receptor agonist currently FDA approved for treatment of hepatic sinusoidal obstruction syndrome [165] and functions by inhibiting platelet aggregation and thromboxane [166]. As well, it decreases monocyte expression of TF, TNF, endothelin, thrombin, and interleukin-2 [166,167]. Defibrotide has anti-inflammatory, antithrombotic, and even thrombolytic properties with no clear increased risk of bleeding, making it an appealing potential therapy for APS [47]. However, there has been only one case report to date which has documented use of defibrotide in APS [7]. The response to defibrotide in this case was dramatic, with complete remission of CAPS symptoms despite failure of standard therapy. A recent murine study has further demonstrated the benefits of adenosine receptor agonists in APS, showing a decreased incidence of venous thrombosis in an APS mouse model treated with dipyridamole [168].

Despite the limited clinical data, defibrotide is a potential treatment for APS given the basic science data and recent approval for the venous occlusive disease hepatic sinusoidal obstruction. However, defibroide is contraindicated in patients receiving systemic anticoagulation or fibrinolytic therapy [169], which precludes the use of this agent for many APS patients.

4.7. Peptide therapy

Peptide therapies are considered by the FDA to be small molecule treatments, containing 40 amino acids or fewer [170]. These synthetic, highly targeted treatments are created to bind key molecules that contribute to the pathogenesis of disease [171]. There are several approved peptide therapies for other disease entities, including the glucagon-like peptide-1 (GLP1) receptor agonists approved for use in diabetes mellitus type 2 [172]. There are currently no peptide therapies undergoing human trials for use in APS, although several mechanistic studies have been initiated [173]. Each proposed peptide treatment targets different epitopes of β_2GPI and β_2GPI targets, including DI [174], DV [175–177] and the DV aPL binding site [20,178,179]. Results have been variable and it is not yet clear what unintentional side effects could be produced with use of these peptide therapies. There are also several other limitations to use of peptide therapy, including their limited half-life, although progress has already been made to improve half-life through the addition of polyethylene glycol (PEGylation) [180,181].

5. Summary

Treatment options for APS have expanded considerably over the past decade, although controlled trials are still lacking for each of these novel therapies.

Statin therapy and hydroxychloroquine reduce pro-thrombotic markers and possibly decreased the incidence of aPL-related manifestation; while the lack of controlled studies impedes the recommendation of these agents for all APS patients, they should each be considered when a patient presents with another indication for their use. As well, given the available positive data, it is reasonable to consider these medications in refractory cases.

There are case reports of partial or complete recovery of refractory CAPS as well as thrombocytopenia or hemolytic anemia with use of rituximab. This treatment should be considered for patients with CAPS who fail to respond to standard therapy, or for those mostly presenting with hematologic or microthrombotic aPL manifestations. Belimumab has less supporting data, but could also be considered in refractory APS cases. Eculizumab targets the terminal complement cascade, which has been shown to be a critical step in the pathogenesis of APS clinical events. Based on the data currently available, eculizumab is a therapeutic option for CAPS patients who have failed standard therapy, especially for those with prominent atypical HUS features.

Sirolimus does not currently have enough data to recommend its use in APS; it may be a promising treatment option in the future, especially for graft rejection prophylaxis in APS patients undergoing renal transplantation. Sirolimus-imbedded coronary stents may also be considered in place of paclitaxel stents in APS patients. Adenosine agonists including defibrotide show promise in mechanistic studies; however, the limited clinical data as well as the increased bleeding risk in anticoagulated patients restricts their use in APS. Peptide and targeted antibody therapy have shown potential in murine models, but development of therapy for human use is expected to take several years.

Disclosure statement

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