Is there a role for immunosuppression in antiphospholipid syndrome?

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Antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterized by thrombosis, pregnancy morbidity, or nonthrombotic manifestations in patients with persistently positive antiphospholipid antibodies (aPL). Conventional APS treatment focuses on antithrombotic strategies, which are usually ineffective for the microvascular and nonthrombotic manifestations of aPL. Using a case-based presentation, this review focuses on the role of immunosuppression in nonobstetric APS, including B-cell inhibition (rituximab, belimumab, and bortezomib), complement inhibition (eculizumab), mechanistic target of rapamycin inhibition (sirolimus), vascular endothelial cell modulation (defibrotide), statins, and traditional rheumatologic disease–modifying agents (hydroxychloroquine, mycophenolate mofetil, azathioprine, and cyclophosphamide).

Learning Objectives

- Understand the spectrum of antiphospholipid antibody (aPL)–related clinical manifestations, including microvascular disease
- Better understand the role of immunosuppression in the management of aPL-positive patients

Introduction

Antiphospholipid syndrome (APS) is an autoimmune disease characterized by a variety of clinical phenotypes, including arterial, venous, and small vessel thrombosis and/or pregnancy morbidity in patients with persistently positive antiphospholipid antibodies (aPL), namely lupus anticoagulant (LA) test, anticardiolipin antibodies (aCL), and anti–β_2-glycoprotein I antibodies (aβ_2GPI).[1] aPL-positive patients with only nonthrombotic features (eg, thrombocytopenia) are also included in the APS spectrum. Catastrophic antiphospholipid syndrome (CAPS) is a rare (~1%) life-threatening variant of APS defined by multiple organ thromboses.

Conventional therapy for the prevention and treatment of APS focuses on low-dose aspirin, vitamin K antagonists, and heparin (currently, direct oral anticoagulants are not recommended in APS). However antithrombotic strategies are usually not effective for the microvascular and nonthrombotic manifestations of aPL (Table 1); in fact, APS patients can develop these manifestations while on anticoagulation. Similarly, in addition to heparin, IV immunoglobulin (IVIG) and/or plasma exchange are generally required in CAPS patients to achieve the best clinical outcomes.[2]

In parallel to our increased understanding of the mechanisms of aPL-mediated clinical events, immunosuppression has been increasingly used in aPL-positive patients. This article will review the role of immunosuppression in the management of aPL-positive patients with nonobstetric manifestations.

Clinical case

A 53-year-old white male presented with a 3-month history of worsening shortness of breath, dry cough, and painful leg ulcers. He had a past medical history of APS diagnosed 6 years prior, with an unprovoked deep vein thrombosis (DVT), pulmonary embolism, and persistent triple aPL positivity (LA test and high-titer [>80 U] aCL and aβ_2GPI immunoglobulin G [IgG]). He had been on warfarin with a target international normalized ratio (INR) of 2.5 to 3. Other relevant past medical history included mild chronic renal insufficiency in the setting of diabetes mellitus and hypertension. On admission, he was afebrile, hypoxic, and hypertensive; his physical examination was normal except for livedo racemosa of the upper extremities and 3 painful skin ulcers on bilateral lower extremities with moderate edema. His admission hemoglobin was 8.7 mg/dL with no schistocytes, platelet count $78 \times 10^3/\mu L$, INR 2.1, creatinine 2.9 mg/dL (baseline 1.5 mg/dL), and urine protein-to-creatine ratio (UP/C) 1.75 (baseline 0.5). Bilateral lower extremity Doppler was negative for DVT. Chest radiograph showed extensive patchy bilateral airspace opacities, and chest computer tomography showed diffuse ground glass opacities; infection workup was negative. Bronchoalveolar lavage confirmed alveolar hemorrhage with persistent bloody returns, demonstrating neutrophilic predominance and high percentage of hemosiderin-laden macrophages. Echocardiogram was normal except for 6-mm thickening of the mitral valve. Renal biopsy was deferred because of high risk of thrombosis and bleeding.

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Table 1. Major microvascular and nonthrombotic manifestations of APS

Microvascular manifestations
Renal (aPL nephropathy)
Acute—thrombotic microangiopathy
Chronic (ie, fibrous intimal hyperplasia, focal cortical atrophy, tubular thyroidization, glomerular ischemia, interstitial fibrosis, tubular atrophy, organized thrombi with or without recanalization)
Pulmonary (diffuse alveolar hemorrhage)
Cardiac (microvascular disease)
Dermatologic (livedo with/without skin ulcers)
Nonthrombotic manifestations
Thrombocytopenia
Immune mediated
Thrombotic microangiopathy related
Hemolytic anemia
Immune mediated
With schistocytes and thrombotic microangiopathy
Cardiac valve vegetations or thickening
Neurologic*
Cognitive dysfunction in the absence of stroke
Subcortical white matter changes

*Due to multiple mechanisms, including small vessel ischemic events and the direct pathogenic role of aPL.

The patient initially received IV methylprednisolone 500 mg for 3 days followed by 1 mg/kg daily, IV heparin, IV rituximab 1000 mg (second dose was given 2 weeks later), and hydroxychloroquine (HCQ) 200 mg twice a day. On the third day of his admission, because of declining platelets counts ($48 \times 10^3/\mu L$), he was started on IVIG (140 g over 3 days). Follow-up chest radiograph on day 8 showed clearing of airspace opacification. He was discharged on the 10th day of admission with improved pain of his leg ulcers, normal platelet counts ($212 \times 10^3/\mu L$), creatinine of 2.0, and UP/C of 1.1; IV heparin was switched to warfarin, and he was started on mycophenolate mofetil (MMF) 500 mg twice a day and fluvastatin 10 mg once a day.

Diagnostic considerations

The first diagnostic step in the management of aPL-positive patients is the assessment of the clinical significance of the aPL profile, for which a step-by-step approach is summarized in Table 2. It is important to note that (1) not every positive aPL test is clinically significant and that, (2) similar to that observed in our clinical case, LA test positivity as well as triple-aPL positivity for LA, aCL, and aβ_2GPI, especially with moderate-to-high aPL titers in solid-phase assays, provide better assurance for APS diagnosis and indicate increased risk for events.[3]

The second diagnostic step is the assessment of aPL-related manifestations and the determination of the clinical phenotype(s) of patients (ie, asymptomatic, obstetric APS; nonthrombotic APS; thrombotic APS; microvascular APS; and/or CAPS), which also have therapeutic implications. Our clinical case, with a history of thrombotic APS, presented with nonthrombotic (thrombocytopenia and cardiac valve disease) and microvascular (diffuse alveolar hemorrhage [DAH], possible aPL nephropathy, and livedo racemosa with possible livedoid vasculopathy) manifestations of aPL. Our clinical case did not fulfill the CAPS classification criteria (Table 3) given the relatively chronic nature of the problems and the lack of tissue biopsies demonstrating microthrombosis; however, without early and aggressive treatment, the patient likely would have developed new thrombosis progressing to CAPS.

The last diagnostic step is the assessment of additional venous and cardiovascular disease risk factors given that approximately half of thrombotic APS patients have a non-aPL thrombosis risk factor at the time of their thrombotic events.[4] However, the role additional risk factors in the development of microvascular and nonthrombotic manifestations of aPL, such as in our clinical case, is not well established.

Brief review of APS pathogenesis and the rationale for immunosuppression

A brief review of APS pathogenesis will provide a useful framework for understanding the role of immunosuppression in the management of aPL-positive patients; a detailed discussion can be found elsewhere.[5]

aPL-related clinical events occur as a consequence of the interactions of aPL with antigenic targets, of which β_2-glycoprotein I (β_2GPI) is the most relevant. The structural change within β_2GPI from the circular closed to the open fishhook configuration in response to inflammation or exposure to anionic phospholipids is important for the interaction of aPL with β_2GPI. This conformational change exposes the major B-cell epitope on domain I of β_2GPI and allows binding to autoantibodies followed by subsequent stabilization of this configuration and binding to cellular receptors and other antigenic targets.[6] Various receptors (heparan sulfate, toll-like receptors, apolipoprotein E receptor 2, Annexin II, and glycoprotein Ibα) for β_2GPI are expressed on the cellular surfaces of multiple cell types, including endothelial cells, monocytes, platelets, trophoblasts, decidual and neuronal cells, and fibroblasts. The intracellular signaling pathways activated by aPL depend on the individual receptor(s) engaged and the cell type; however, the activation of nuclear factor-κB (NF-κB) and/or p38/MAPK signaling pathways is common to a majority of aPL-β_2GPI receptor interactions. aPL-mediated events likely occur owing to various signaling mechanisms activated independently by different aPL specificities. These mechanisms (Table 4) are not mutually exclusive and indeed, might act synergistically to induce typical aPL-related clinical outcomes.[7]

Therapeutic considerations

Given the increasing awareness of the mechanisms involved in APS pathogenesis, novel therapies targeting different mechanisms are considered in the management of aPL-positive patients with microvascular disease and/or hematologic manifestations. In this section, after we briefly review the management of CAPS, we will focus on the evidence for these potential targeted treatments.

CAPS management

The combination of anticoagulation, corticosteroids, and IVIG and/or plasma exchange, also known as "triple therapy," is the most commonly used strategy in CAPS.[2,8] The justification for this strategy can be summarized as (1) heparin inhibits complement activation in addition to the anticoagulation effect; (2) corticosteroids inhibit NF-κB and systemic inflammatory response syndrome; (3) IVIG blocks autoantibodies, regulates complement, and suppresses cytokines; and (4) plasma exchange removes aPL, cytokines, and complement products.[9] A detailed discussion of the management of CAPS patients can be found elsewhere[2,9]; the targeted treatments discussed below are also used in CAPS patients refractory to the "triple therapy."

Table 2. Diagnostic steps in the assessment of aPL-positive patients

Step 1. Assessment of aPL tests individually (2 positive tests at least 12 wk apart are important to rule out transient positivity during infections)	
LA test	The LA test is associated with highest risk for clinical events (compared with aCL and $a\beta_2$GPI) The LA test should be interpreted with caution in anticoagulated patients because of false positive results
aCL and $a\beta_2$GPI antibodies	Moderate-to-high titers* of aCL or $a\beta_2$GPI IgG or IgM have higher association with clinical events (compared with lower titers) IgG positivity has a stronger association with clinical events (compared with IgM) Isolated moderate- to high-titer aCL or $a\beta_2$GPI IgA is rare with unknown clinical significance
Step 2. Assessment of aPL profile (clinical judgement is needed if the LA test is performed during anticoagulation, the aPL profile is low risk, the aPL is tested only once, and the only positive aPL is aCL and/or $a\beta_2$GPI IgA)	
High-risk aPL profile	Positive LA and/or moderate- to high-titer* aCL or $a\beta_2$GPI IgG or IgM
Moderate-risk aPL profile	Negative LA and moderate- to high-titer* aCL or $a\beta_2$GPI IgG or IgM
Low-risk aPL profile	Negative LA and low titer* of aCL or $a\beta_2$GPI IgG or IgM

Adapted from Garcia D, Erkan D. Diagnosis and management of the antiphospholipid syndrome. *N Engl J Med*. 378, 2010-2021, Copyright © 2018 Massachusetts Medical Society.

*Our definition of moderate-to-high titer is ≥40 GPL/MPL units, and our definition for low titer is 20-39 GPL/MPL units. GPL, IgG phospholipid units; MPL, IgM phospholipid units.

B-cell inhibition

B cells, particularly CD5+ B cells (also referred to as B1 cells), have numerous functions in the pathogenesis of APS. Other than altering T-cell differentiation and regulating cytokines, in vitro studies indicate that activated B cells contribute to fetal loss (via decreased interleukin-3 [IL-3] production).[10] Blocking B cell–activating factor (BAFF) prevents disease onset and prolongs survival in APS mouse models.[11] In contrast, although cytotoxic T-lymphocyte antigen 4 immunoglobulin may limit pathogenic B-cell development in early disease stages, it does not prevent development of APS in the NZW × BXSB F1 APS mouse model after aPLs are produced.[12] Other T cell–targeted therapies have proven equally ineffective in this respect. Furthermore, primary APS patients with venous thromboembolism (VTE) have disturbed B-cell subset distribution with increased B1 and naïve B cells compared with aPL-negative VTE patients.[13]

Several case reports described rituximab use in APS patients with severe thrombocytopenia, hemolytic anemia, skin ulcers or necrosis, nephropathy, DAH, and CAPS with variable responses.[14] A pilot study of 19 APS patients suggested that, despite causing no substantial change in aPL profiles, rituximab is effective for aPL-related skin ulcers, kidney disease, and cognitive dysfunction.[15] Based on the analysis of the international web-based CAPS Registry,[16] rituximab-treated CAPS patients (n = 20) had a 75% chance of recovery, and it is generally used in combination with other medications. Data regarding the effect of rituximab on aPL titers are conflicting; in fact, a systematic review showed that there are no studies demonstrating that monotherapy with rituximab renders a negative aPL profile (LA, aCL, and $a\beta_2$GPI) in patients with persistently positive aPL (LA and/or moderate-to-high titer aPL enzyme-linked immunosorbent assay [ELISA]).[17]

Belimumab, which inhibits BAFF, is also a potential treatment target in APS. Two primary APS patients treated with belimumab, one with DAH and the other with recurrent skin ulcers, had clinical improvement with discontinuation of corticosteroids after belimumab.[18] Sciascia et al[19] reported aPL titers before and after belimumab in 3 patients with APS and systemic lupus erythematosus (SLE): 2 patients were persistently LA positive despite belimumab, and low-titer aPL ELISA in 2 patients became negative postbelimumab (but not the high-titer aPL ELISA in the third patient).[19] Similarly, a recent small study monitored aCL and $a\beta_2$GPI levels in 12 persistently aPL-positive SLE patients (7 with APS) treated with belimumab for a median of 13 months. In HCQ-naïve SLE patients, mean aCL IgG level decreased from 232.5 to 136.5, aCL IgM decreased from 95.5 to 44.3, and $a\beta_2$GPI decreased from 60.5 to 25.5 (patient characteristics and LA test were not reported; the clinical significance of these findings is unknown).[20]

Bortezomib inhibits the ubiquitin-proteasome proteolytic pathway, which controls intracellular protein turnover, and also results in significant B-cell function impairment via decreased proliferation and reduced immunoglobulin production.[21] One case report documented bortezomib use in a triple aPL-positive (LA, aCL, and $a\beta_2$GPI) SLE patient with a history of venous thrombosis. This patient had autoimmune hemolytic anemia, thrombocytopenia, and skin ulcers responsive to corticosteroids but worsening during corticosteroid tapering despite rituximab, cyclophosphamide, and cyclosporine. After 6 cycles of IV bortezomib (1.3 mg/m^2 twice weekly) in addition to 3 cycles of plasma exchange and cyclosporine, anemia and thrombocytopenia improved in 6 weeks, and skin lesions regressed with no relapse of hemolysis or thrombosis at 1 year follow-up while still on bortezomib every 3 weeks.[22]

In summary, despite limited basic science and clinical experience, B-cell inhibition is an option for aPL-positive patients with prominent hematologic and microvascular manifestations. Given that B cells have a role in disease pathogenesis not limited to antibody production, it is highly likely that the clinical response seen in some aPL-positive patients is independent of a substantial change in aPL profile.

Complement inhibition

aPL can induce complement activation; most importantly, the generation of complement 5 (C5a), which subsequently activates endothelial cells, neutrophils, and monocytes, leads to tissue factor (TF) expression and the release of other proinflammatory mediators. The consequence is vascular inflammation, endothelial damage, and pregnancy morbidity; in fact, the blockage of complement system prevents aPL-induced inflammation and pregnancy loss in mouse models.[23,24] Similarly, complement C3 and C5 inhibition limited aPL-mediated thrombosis in APS animal models.[25]

Case reports documented positive outcomes with eculizumab, an anti-C5 monoclonal antibody, especially in the treatment of postrenal

Table 3. CAPS classification criteria[54]

Classification	Criteria
Definite CAPS	1. Evidence of involvement of 3 or more organs, systems, and/or tissues
	2. Development of manifestations simultaneously or in <1 wk
	3. Confirmation by histopathology of small vessel occlusion in at least 1 organ or tissue
	4. Laboratory confirmation of persistent aPL
Probable CAPS	All 4 criteria except for only 2 organs, systems, and/or tissues involved
	All 4 criteria except for the absence of laboratory confirmation of aPL
	All 4 criteria except for the absence of histopathologic confirmation of small vessel occlusion
	All 4 criteria except for the development of a third event in >1 wk but <1 mo despite anticoagulation

transplantation thrombotic microangiopathy (TMA) in CAPS patients.[26] However, publication bias as well as the lack of systematic clinical studies are a concern. Two recent case series of SLE and/or APS patients (9 [6 with APS] and 11 [3 with APS] patients, respectively) presenting with TMA syndrome demonstrated that the majority of these patients respond to eculizumab with improvement in platelet counts and renal function.[27,28] Only one of these case series[28] investigated complement-related protein mutations, which is an important consideration given additional reports of positive mutations in APS and/or SLE patients presenting with a TMA syndrome.[29,30] For instance, a rare heterozygous mutation in exon 13 of the C3 gene was detected in a CAPS patient presenting with acute renal failure (renal TMA confirmed by biopsy), myocardial ischemia, severe thrombocytopenia, hemolytic anemia, and subsequently, DAH.[30]

In summary, eculizumab, which is Food and Drug Administration (FDA) approved for complement-mediated TMA (ie, atypical hemolytic uremic syndrome [HUS]), may have a role in the management of aPL-positive patients, especially those with prominent features of renal TMA or an atypical HUS–like presentation.

Mammalian target of rapamycin inhibition

The mammalian target of rapamycin (mTOR) is a kinase that integrates with a variety of cell signaling pathways to regulate cellular growth, proliferation, and survival.[31] In vitro studies indicate mTOR involvement in regulating aPL-induced TF and IL-8 expression in monocytes as well as platelet activation/aggregation.[32,33]

Polyclonal aCL and aβ_2GPI from APS patients, but not normal human IgG autoantibodies, increase S6 ribosomal protein (S6RP) and protein kinase B (protein kinase B [AKT] [via Ser473]) phosphorylation, indicating mTOR activation in endothelial cells, which also correlates with AKT phosphorylation and aPL titers. In addition, immunohistochemical (IHC) staining analysis of vascular specimens of CAPS patients with autopsies shows increased S6RP and AKT phosphorylation.[34]

Based on preliminary results of an ongoing cross-sectional study, mTOR activity in the basal layer of the epidermis was increased (IHC staining of the skin biopsies from the center of livedoid lesions with S6RP) in 3 aPL-positive patients with SLE compared with an aPL-negative SLE patient.[35] Given the vascular stenosis occurring in arterioles located in the center leading to livedo at the periphery, these findings were consistent with the pathophysiology of livedoid lesions. In addition, 3 aPL-positive patients with microvascular manifestations of aPL demonstrated mTOR pathway activation by flow cytometry analysis.[36]

Sirolimus, also known as rapamycin, has potent immunosuppressive and antiproliferative properties owing to its ability to inhibit the mTOR complex. Kidney transplant recipients with APS who were treated with sirolimus had better outcomes compared with aPL-positive patients who were not treated with sirolimus (70% and 11% graft survival at a mean follow-up of 144 months, respectively).[34] More recently, a primary APS patient with microvascular disease despite warfarin (indicated by magnetic resonance imaging and positron emission tomography [PET]; eventually confirmed by endomyocardial biopsy) received corticosteroids followed by sirolimus with significant clinical improvement during the 12-month follow-up (although PET findings were unchanged).[37]

In summary, the mTOR pathway plays a role in the endothelial proliferation, which is a key finding in aPL-positive patients with

Table 4. Major mechanisms involved in the etiopathogenesis of aPL-mediated clinical events[4,55]

Mechanisms and examples of aPL-induced proinflammatory/thrombotic changes
Cell activation
Endothelial cells
↑ TF production
↑ E-selectin, P-selectin, VCAM-1, and I-CAM-1 expression
↑ MCP-1 expression
↑ Leukocyte-endothelium interaction
↑ mTOR pathway activity
↓ eNOS production
↑ Release of microparticles
Platelets
↑ Expression of TxA2/B2
↑ Expression of GPIIb/IIIa
Monocytes
↑ TF production
↑ TNF-α and IL-1β expression
↑ VEGF and its receptor expression
Neutrophils
↑ TF production
↑ IL-8 production
↑ Release of neutrophil extracellular traps
↑ Oxidative stress
↑ Levels of circulating LDGs
Complement activation
↑ "Classical" and "alternative" complement pathway activity
↑ TF production
Coagulation system activation
↑ TF activation
↓ TF pathway inhibition
↓ Annexin A5 anticoagulation shield
↑ Prothrombin binding
↓ Antithrombin activity
↑ Activated protein C resistance
↓ Fibrinolysis

eNOS, endothelial nitric oxide synthetase; GPIIb/IIIa, glycoprotein IIb/IIIa; I-CAM-1, intracellular adhesion molecule 1; IL-8, interleukin-8; LDG, low-density granulocyte; MCP-1, monocyte chemoattractant protein 1; mTOR, mammalian target of rapamycin; TF, tissue factor; TNF-α, tumor necrosis factor-α; TxA2/B2, thromboxane A2/B2; VCAM-1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor.

microvascular disease (ie, aPL vasculopathy). Although the number of studies is very limited and more data are needed, sirolimus is an option in aPL-positive patients with microvascular disease resistant to standard treatments.

Vascular endothelial cell modulation

aPL-induced vascular endothelial cell activation is important in the pathogenesis of APS as are neutrophil extracellular traps (NETs), which are networks of extracellular fibers primarily composed of DNA from neutrophils.[38] Defibrotide is an adenosine receptor (A1 and A2) agonist with antithrombotic, anti-ischemic, anti-inflammatory, and thrombolytic properties. Defibrotide functions by inhibiting platelet aggregation and thromboxane biosynthesis[39]; however, it lacks systemic anticoagulant effect with no increased risk of bleeding.[40] Defibrotide modulates tissue necrosis factor, endothelin, thrombin, and IL-2 as well as TF secretion from monocytes.[41]

Ali et al[42] recently studied the role of surface adenosine receptors that trigger cyclic adenosine monophosphate formation in neutrophils. They reported that a specific adenosine receptor (A2) agonist suppresses aPL-induced NETs formation in vitro and reduces the incidence, weight, and length of thrombus in mice along with decreased plasma NET levels. The follow-up experiments with dipyridamole showed similar results.[42] Of note, only 1 case report exists describing a CAPS patient who achieved a complete remission with defibrotide after a limited response to anticoagulant/antiplatelet therapy.[43]

Given that APS patients with microvascular disease have concurrent impairment of vascular endothelial cell functions, defibrotide or other adenosine receptor agonists can be a potential treatment of APS patients in the future. With its recent FDA approval for hepatic veno-occlusive disease, additional mechanistic and controlled studies are needed to evaluate defibrotide in APS.

Statins

In vitro studies with human umbilical vein endothelial cells demonstrate that fluvastatin reduces aPL-mediated TF, IL-6 messenger RNA, cell adhesion molecule expression, and NF-κB transcription factor activation as well as monocyte adhesion to endothelial cells.[44]

Two prospective mechanistic studies in APS patients were promising to further support the role of statins in APS patients. In the first study, inflammatory proteins were reversed with 1 month of fluvastatin (20 mg/d), which downregulated TF and other prothrombotic markers.[45] The second study showed significant reduction of inflammatory markers (IL-1β, vascular endothelial growth factor, tumor necrosis factor-α, interferon-α, inducible protein-10, soluble CD40L, and soluble TF) after 3 months of fluvastatin treatment (40 mg/d).[46]

In summary, statins exert anti-inflammatory and antithrombotic effects in aPL-positive patients. Despite the lack of controlled clinical data, statins may have a role as an add-on treatment in APS patients when anticoagulation alone is not sufficient.

"Traditional" immunosuppressive medications

HCQ is an antimalarial agent with anti-inflammatory and antithrombotic effects via the inhibition of complement, TF, and toll-like receptor activation. Furthermore, HCQ reduces thrombus size in APS mouse models, decreases aPL binding to phospholipids, and protects Annexin A5 anticoagulant shield from disruption by aPL.[47] HCQ decreases the risk of thrombosis in lupus patients, a multifactorial effect not specific for aPL. In a small, nonrandomized study of 20 primary APS patients treated with HCQ in addition to anticoagulation (vs 20 controls treated only with oral anticoagulation), there were more recurrent thrombotic events in the latter group during the 3-year follow-up (hazard ratio, 2.4; 95% confidence interval, 1.3-4.1; $P < .005$).[48]

MMF and azathioprine suppress B- and T-lymphocyte proliferation, autoantibody production, and adhesion molecules' glycosylation via inhibiting de novo synthesis of purine nucleotides.[49,50] Despite the lack of strong clinical studies, MMF has been used in aPL nephropathy, and azathioprine has been used in thrombocytopenia and hemolytic anemia with variable success.[3] Cyclophosphamide, an alkylating agent, selectively suppresses regulatory T cells. There is anecdotal positive experience in APS patients with DAH and CAPS patients with accompanying lupus or other vasculitis flares. Of note, based on a logistic regression analysis of the international CAPS registry, cyclophosphamide use was associated with improved survival in SLE-CAPS patients but not in primary CAPS patients.[51]

In summary, HCQ is a relatively safe medication that can be considered an add-on treatment in APS patients when anticoagulation alone is not sufficient. Other traditional immunosuppressive medications are effective for some of the aPL-related nonthrombotic or microthrombotic manifestations based on anecdotal experience.

Clinical case discussion—when to consider immunosuppression in APS

APS patients with isolated moderate-to-large vessel thrombosis are managed by anticoagulation in the short and long term; currently, there are no clinical data supporting the use of corticosteroids or immunosuppression in these patients. However, our clinical case with microvascular and nonthrombotic aPL-related clinical problems required a treatment strategy beyond anticoagulation. Given the lack of hemoptysis and severe thrombocytopenia during admission, our decision was not to stop anticoagulation; however, the decision to continue or discontinue anticoagulation was assessed carefully on a daily basis. We believe that the discontinuation of anticoagulation would have worsened the prognosis owing to challenges of managing APS patients with simultaneous bleeding and thrombosis.[52]

The first-line treatment of our case was IV corticosteroids, which is a standard approach for several microvascular and nonthrombotic manifestations of aPL (eg, DAH, severe thrombocytopenia, or severe hemolytic anemia). Given the lack of dosing studies on "pulse corticosteroids," we generally use doses between 250 and 1000 mg/d for 3 days.

The justifications for the second-line immunosuppressives were as follows. (1) Cyclophosphamide- or rituximab-based regimens provide better outcomes in DAH patients compared with other immunosuppressives[53] (we preferred rituximab because of a better safety profile and accompanying thrombocytopenia and possible aPL nephropathy). (2) Although patients with platelet counts >50 000/mm^3 usually require no therapy, in aPL-positive patients with microvascular involvement (or CAPS), worsening platelet count is generally a poor prognostic sign, and thus, we added IVIG. (3) Chronic aPL nephropathy is usually slowly progressive, with no proven treatment; however, there are anecdotal reports of succesful rituximab or MMF use in these patients, and thus, we added MMF. Lastly, add-on treatment with a statin and HCQ (doses discussed above) completed the comprehensive management of our clinical case.

Conclusion

In parallel with our better understanding of the heterogenous clinical phenotypes of aPL-positive patients, it is clear that treatment options are different for different aPL manifestations. There is a role for immunosuppression in APS and the microvascular and non-thrombotic manifestations of aPL independent of concomitant lupus or another systemic autoimmune disease diagnosis. One of the unmet needs of APS is the investigation of additional immunosuppressive pathways that can be potential treatment targets that more consistently improve outcomes in APS patients.

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