ANTIPHOSPHOLIPID SYNDROME NOVEL THERAPIES

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ABSTRACT

Antiphospholipid syndrome (APS) is an autoimmune disease characterised by arterial and/or venous thrombosis, recurrent pregnancy loss, and persistently positive antiphospholipid antibodies (aPLs). It could be life-threatening as in the case of catastrophic APS where multi-organ failure is observed. APS morbidities are thought to be the result of a combination of thrombotic and inflammatory processes. Over the past decades, the mainstay of therapy of APS has been anticoagulation. As new mechanisms of pathogenesis are being unravelled with time, novel targeted immunomodulatory therapies are being proposed as promising agents in the treatment of APS. In this article, we present an overview of new pathogenetic mechanisms in APS as well as novel antithrombotic and immunomodulatory therapies.

Keywords: Antiphospholipid syndrome, thrombosis, antiphospholipid antibodies, seronegative antiphospholipid syndrome, thromboprophylaxis, immunomodulatory, new oral anticoagulants.

INTRODUCTION

Antiphospholipid syndrome (APS) is an autoimmune disease characterised by clinical thrombotic events associated with the presence of antiphospholipid antibodies (aPLs) in patient plasma.[1-3] It was first described in 1983 by Graham R.V. Hughes.[4] APS is recognised as one of the common causes of acquired thrombophilia and can be classified as primary or secondary depending on its association with other autoimmune diseases.[5] Up to 40% of patients with systemic lupus erythematosus (SLE) test positive for aPLs, but only half of these patients go on to develop overt thrombosis or miscarriages.[6] Over the past 30 years, the mainstay of treatment was antithrombotic medications. As we continue to unravel the pathophysiology of the disease, some promising novel immunomodulatory therapies are being introduced. In this article, we will review the pathogenesis of the disease, its clinical manifestations, diagnostic criteria, and advances made in therapy.

PATHOGENESIS

Although several mechanisms were described as the cause of thrombosis in APS, the ultimate means by which clinical manifestations occur is still not fully understood. aPLs are autoantibodies directed against phospholipid-bound proteins, particularly the β_2-glycoprotein I (β_2GPI). It is believed that thrombosis in APS follows a 'two-hit' hypothesis where the first hit disrupts the endothelium and the second hit potentiates thrombus formation.[7-13] One of the many proposed mechanisms that constitute the first hit is increased oxidative stress. Studies in APS patients showed increased lipid peroxidation by-products as well as an increase in intracellular reactive oxygen species (ROS). These were reflected in animal models where ROS contributed to the pathogenesis of murine thrombosis.[14] Another proposed mechanism is impaired endothelial nitric oxide synthase (eNOS) function; some APS patients were found to have decreased plasma nitrite levels and diminished NO-dependent vascular relaxation accordingly, thus, enhancing thrombosis.[15] Disruption of the annexin A5 (AnxA5) shield is also believed to play a role in promoting thrombosis. AnxA5 forms a shield when binding

to phosphatidylserine surfaces; this shield inhibits the formation of procoagulant complexes.[16] Domain I anti-β_2GPI autoantibodies disrupts this shield when combined to β_2 glycoprotein 1 (β_2GPI), thus exposing procoagulant phosphatidylserine and predisposing to thrombosis.[17] An increased expression and activation of tissue factor (TF) was also seen in APS patients where aPLs caused upregulation of the TF in monocytes, neutrophils, and on endothelial cells. TF was thought to play a role in APS-associated thrombotic microangiopathy.[18,19] The second hit is thought to be any triggering event that can cause thrombosis, i.e. local endothelial damage or infection.[7]

Obstetric APS and recurrent pregnancy losses were believed to be the result of different mechanisms acting on placental cells and endometrial tissues.[20] Thrombosis, inflammation, and immunomodulations are thought to affect placental cells. Histological analysis of placenta collected from APS patients showed more thrombotic characteristics than those collected from controls.[20] Complement system activation is also thought to play a role where biopsies from the placental tissue of mice treated with aPLs showed greater deposition of complement components 3 (C3) and 4 (C4) accompanied with a reduction in membrane attack complex (MAC).[21] Recently, immunomodulation was introduced as a possible mechanism in APS-related pregnancy loss. Toll-like receptors (TLRs) have been implicated in the pathological activation of endothelial cells, monocytes, and platelets, thus leading to uncontrolled inflammation and apoptosis.[22] Pathologic mechanisms may also occur at the level of endometrial tissue where some studies showed that aPLs may inhibit endometrial angiogenesis, decrease vascular endothelial growth factor secretion, and inhibit NFκB activation.[23,24] Catastrophic antiphospholipid syndrome (CAPS) was believed to be the result of combined pathogenic mechanisms that involve cellular activation, inhibition of anticoagulants, including the protein C pathway, inhibition of fibrinolysis, and complement activation.[25]

CLINICAL MANIFESTATIONS

APS usually manifests itself as a thrombotic disorder where patients experience vascular events or pregnancy morbidities. The most common presentation is venous thromboembolism (VTE) where up to 70% of patients can acquire deep vein thrombosis, pulmonary emboli, or develop clots anywhere in the axillary, retinal, or hepatic vascular networks.[26,27] Although arterial bed thrombosis is less common, it is more serious and life-threatening as it affects most generally the central nervous system (CNS) and presents as strokes or transient ischaemic attacks. Obstetric APS appears clinically as recurrent pregnancy losses or premature births due to eclampsia, preeclampsia, or placental insufficiency. Other less common manifestations are listed in Table 1.[28,29]

DIAGNOSIS

APS is diagnosed by the presence of at least one clinical criterion in addition to one laboratory criterion. Classification criteria were updated in 2006 where some laboratory criteria were modified. Clinical criteria remained unchanged. The revised classification criteria for APS are listed in Table 2.[30]

Seronegative APS

Hughes and Khamashta[31] were among the first to introduce the term 'Seronegative Antiphospholipid Syndrome' (SNAPS) for patients with clinical manifestations highly suggestive of APS but with persistently negative serologies (lupus anticoagulant [LAC], anticardiolipin antibody [aCL], and anti-β_2GPI).[23] Although still not widely accepted, some studies showed that

Table 1: Other less common clinical manifestations.

Thrombocytopaenia	Transverse myelitis
Haemolytic anaemia	Leg ulcers
Livedo reticularis	Adrenal haemorrhage
Cardiac valvular vegetations	Antiphospholipid syndrome nephropathy
Myocardial ischaemia/coronary artery disease	Budd-Chiari syndrome
Amaurosis fugax	

SNAPS involve several other antigens than those mentioned in the revised criteria, and new non-criteria antibodies were described that can be utilised in the future as potential diagnostic laboratory markers.[32,33] A list of the non-criteria aPLs is found in Table 3.[34]

Catastrophic APS

<1% of APS patients tend to develop a severe life-threatening entity called CAPS, which has a 30% mortality rate in the absence of treatment.[35] CAPS was first introduced by Asherson et al.[36] after reporting several patients with accelerated thrombosis and acute organ failure. In 2003, diagnostic criteria for CAPS were proposed and published.[37] A diagnosis of definite CAPS is met when there is evidence of multisystem (≥3) organ involvement over 7 days associated with small vessel occlusion evidence on histopathology and the presence of aPLs in the serum.[37]

Table 2: Revised classification criteria for APS.

Clinical criteria	Laboratory criteria
Vascular thrombosis • One or more clinical episodes of arterial, venous, or small vessel thrombosis. It has to be supported by objective validated criteria i.e. unequivocal findings of appropriate imaging studies or histopathology. In histopathology, no evidence of inflammation in the vessel wall shall be present.	• LAC present in plasma, on two or more occasions at least 12 weeks apart. LAC is detected according to the guidelines of the International Society on Thrombosis and Haemostasis. • IgG &/or IgM isotypes of aCL present in serum or plasma, in medium or high titres (i.e. >40 GPL or MPL, or greater than the 99th percentile) on two or more occasions, at least 12 weeks apart. aCL is measured by a standardised ELISA. • IgG &/or IgM isotypes of anti-β_2GPI present in serum or plasma (in titres greater than the 99th percentile) on two or more occasions at least 12 weeks apart. anti-β_2GPI is measured by a standardised ELISA according to recommended procedures.
Obstetric morbidity • One or more unexplained deaths of a morphologically normal foetus at or beyond the 10th week of gestation. Healthy foetal morphology has to be documented by ultrasound or by direct examination of the foetus. OR • One or more premature births of a morphologically normal newborn baby before the 34th week of gestation due to eclampsia, severe preeclampsia or placental insufficiency. OR • Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation. Maternal anatomical or hormonal abnormalities and paternal and maternal chromosomal causes must be excluded.	

APS: antiphospholipid syndrome; LAC: lupus anticoagulant; IgG &/or IgM: immunoglobulin G/M; aCL: anticardiolipin antibody; GPL: units for IgG [1 GPL unit = 1 μg of affinity-purified IgG]; MPL: units for IgM [1 MPL unit =1 μg of affinity-purified IgM]; ELISA: enzyme-linked immunosorbent assay; anti-β_2GPI: anti-$\beta_2$glycoprotein 1 antibody.

Table 3: Non-criteria antiphospholipid antibodies.

aPE antibodies
Antibodies to negatively charged phospholipids other than cardiolipin: PA, PS, and PI
Anti-domain I antibodies of β_2GPI
Antibodies to vimentin/cardiolipin complex
Anti-PT: aPT-A and aPS-PT
IgA, aCL, and IgA anti-β_2GPI antibodies

aPE: anti-phosphatidylethanolamine; PA: phosphatidic acid; PS: phosphatidylserine; PI: phosphatidylinositol; β_2GPI: β_2-glycoprotein I; aPT: anti-prothrombin; aPS/PT: anti-phosphatidylserine/prothrombin.

MANAGEMENT

The management of APS thrombosis constitutes either primary thromboprophylaxis or secondary thromboprophylaxis. Primary thromboprophylaxis represents treating aPL-positive patients with no previous thrombosis, while secondary thromboprophylaxis represents treating APS patients with previous thrombotic events. The mainstay of treatment is currently anticoagulation, though multiple novel immunomodulatory therapies are on the rise.

Before initiating any primary prevention, one must exclude the co-existence of autoimmune diseases (such as SLE) and target any other thrombotic risk factors. If any is present, it has to be addressed according to the standards of care. Once the patient is labelled as asymptomatic, testing positive for aPLs, it is not recommended to initiate thromboprophylaxis as per The Antiphospholipid Antibody Acetylsalicylic Acid (APLASA) study which showed no advantage between placebo and low-dose aspirin.[38] If the patient has a high-risk profile (triple positivity - positive LAC, aCL, and anti-β_2GP1 antibodies), therapy with aspirin should be considered to prevent further vascular events as triple positivity showed to increase the risk of thrombosis.[39]

Secondary thromboprophylaxis depends on the first presentation of the thrombotic event, whether venous or arterial in nature. Randomised controlled trials (RCTs) in patients with previous venous thrombosis indicated the use of warfarin with target international normalised ratio (INR) of 2.0–3.0 as an ideal anticoagulant therapy.[40] If a patient has transient risk factors and a low-risk profile, anticoagulation could be stopped after 3-6 months, otherwise lifelong anticoagulation is recommended.[41-43] Arterial thrombosis presenting mostly as strokes shows a high incidence of mortality and thus, must be managed aggressively. Studies showed that 70% of patients with APS had arterial events with INR <2.5.[44,45] This observation necessitated high intensity anticoagulation to a target INR >3.0 as per Khamashta et al.[46] In the light of increased bleeding complications associated with high intensity anticoagulation, Okuma et al.[47] demonstrated that combination therapy (aspirin and warfarin) had significantly lower stroke recurrence rates with lower bleeding complications than warfarin alone. Anticoagulation is lifelong in the case of arterial events, with no data suggesting that stopping the medications is ever possible.[48]

Rodríguez Garcia et al.[49] concluded that long-term treatment with low molecular weight heparin (LMWH) at anticoagulant dosages could be an option in refractory APS patients, or in those who are contraindicated for oral anticoagulants. This conclusion was based on the results of two studies that observed a total of 47 APS patients treated with LMWH and followed them up for an average of 24 months.[50,51] Both studies showed high rates of clinical improvement with very low incidence of rethrombosis. Keeping in mind that LMWH can cause haemorrhage, osteoporosis, and thrombocytopaenia as a complication of treatment,[52] its use may be an effective and safe alternative for subjects who cannot tolerate oral anticoagulants. Future clinical trials are needed to assess its efficacy and safety when used to treat APS patients.

Warfarin is considered category X in pregnancy; it is associated with several birth defects when given during the first trimester[53] and may cause CNS disorders and eye defects if used in late pregnancy.[54] As warfarin and vitamin K antagonists are harmful during pregnancy, it was concluded by Derksen et al.[55] that combined therapy of heparin and aspirin is the recommended therapy for obstetric APS. This recommendation was based on a meta-analysis which concluded that aspirin alone is ineffective and that low live-birth rate was observed in patients treated with aspirin alone compared to combined therapy.[56] Aspirin should be initiated before conception or at the time of positive pregnancy test, while warfarin must be shifted to heparin or LMWH which has a more predictable dose and has the advantage of easy administration once daily.[57,58] Warfarin can be resumed postpartum after therapeutic INR has been reached.[57]

As CAPS is associated with high mortality rate, recommendations are to treat it aggressively with therapeutic doses of anticoagulation, corticosteroids, plasma exchange, intravenous immunoglobulins (IVIG), and rituximab (anti CD20 monoclonal antibody).[59,60] The 14th International Congress on Antiphospholipid Antibodies Task Force Report on CAPS concluded that anticoagulation and corticosteroids should be the backbone of therapy with Grade B recommendation.[61] Adding plasma exchange to the aforementioned regimen is also recommended, with IVIG added in the case of ongoing infection.[61]

Patients with concomitant autoimmune diseases such as SLE may benefit from extra immunosuppression (i.e. cyclophosphamide).[61] Rituximab may have a role as an initial adjuvant therapy or may be used as a second-line therapy when standard triple therapy (anticoagulation + glucocorticoids + plasma exchange) fails.[61]

NOVEL THERAPIES

Over the past decade, intensive research in APS field unleashed new pathogenic mechanisms that gave a hope for future targeted therapies. Below we discuss new oral anticoagulants as well as novel immunomodulatory regimens.

New Oral Anticoagulants

Long-term anticoagulation with oral vitamin K antagonists such as warfarin has been associated with certain limitations as well as undesirable side-effects. It is limited by a narrow therapeutic range, requires frequent laboratory monitoring, has slow onset/offset of action, and interacts with food, drugs, and alcohol. Thus, new agents are being tested currently. These agents include direct anti-Xanthium inhibitors (rivaroxaban, apixaban) and direct thrombin inhibitors (dabigatran etexilate). These agents demonstrated a better safety profile with fewer dietary and drug interactions along with a predictable anticoagulant effect omitting the need of frequent monitoring.[62,63] They are currently FDA approved to be used in the treatment of different conditions based on Phase III prospective RCTs (Table 4).[62,64-69] Although these trials showed superiority of new oral anticoagulants over warfarin when dealing with VTE, its role in managing APS patients is still unknown as aPL status was not documented in any of these trials.[64,65,68] Prospective studies on APS patients are needed as the use of these agents would result in a major improvement in quality of life if proven efficacious.

One trial comparing warfarin versus rivaroxaban in APS patients (Rivaroxaban in Antiphospholipid Syndrome – RAPS) is currently undertaken in the UK.[70]

Immunomodulatory Regimens

As we continue to understand the different mechanisms underlying APS, new targeted therapies are being explored.

Statins

Statins are lipid lowering agents that function by inhibiting the enzyme hydroxymethylglutaryl-coenzyme A (HMG-CoA), and are used widely as a measure to prevent cardiovascular disease in high-risk patients. Along with its lipid lowering role, it was shown that statins have antithrombotic and anti-inflammatory characteristics due to its ability to modify endothelial functions, inflammatory responses, plaque stability, and thrombus formation.[71] Experiments on different statins revealed that fluvastatin and simvastatin[72,73] were able to inhibit aPL-induced endothelial cell activation and TF upregulation *in vitro*, while others showed that fluvastatin and pravastatin[74-76] prevented aPL-mediated thrombosis and inflammation and pregnancy loss *in vivo*. Data are limited in human subjects although its dual action on tumour necrosis factor-alpha (TNF-α) and TF makes it beneficial for use against the inflammatory and thrombotic features present in APS.[77]

Hydroxychloroquine (HCQ)

HCQ is an antimalarial agent used in SLE to prevent thromboembolic events. HCQ has different immunologic effects and acts by inhibiting inflammatory cytokines (Interleukin [IL]-1,2,6, TNF-α), T cell antigen receptor (TCR) and B cell antigen receptor (BCR) induced calcium signalling, and TLR activation.[78] HCQ was also shown to inhibit

Table 4: FDA approved treatments of various conditions.

Medication	Indication
Rivaroxaban	VTE prevention after orthopaedic surgery, stroke prevention in non-valvular AF, VTE treatment
Apixaban	VTE prevention after orthopaedic surgery, stroke prevention in non-valvular AF
Dabigatran	VTE prevention after orthopaedic surgery, stroke prevention in non-valvular AF

VTE: venous thromboembolism; AF: atrial fibrillation.

aPL-mediated thrombosis in mice by restoring the anticoagulant action of AnxA5 and reducing the binding of anti-β_2GPI antibodies to the phospholipid bilayer.[79,80] It is currently recommended to combine HCQ with LMWH when attempting to treat recurrent APS.[81] No consensus regarding the use of HCQ for primary thromboprophylaxis in APS patients is currently present. We are currently undertaking a clinical trial to study the efficacy of HCQ as primary thromboprophylaxis in asymptomatic aPL-positive patients, as part of the Antiphospholipid Syndrome Alliance for Clinical Trials and International Networking (APS ACTION).

B cell directed therapies

B cells play a pivotal role in the pathogenesis of APS. Targeting B cells is believed to be beneficial in both treating APS manifestations and preventing the onset of thrombotic events. Rituximab (an anti-CD20 chimeric monoclonal antibody) has proven to be efficacious in treating refractory APS mainly when dealing with haematological manifestations such as persistent thrombocytopaenia and autoimmune haemolytic anaemia.[60] Certain reports also mentioned that rituximab is beneficial in treating diffuse alveolar haemorrhage, skin ulcers, and cognitive dysfunction.[82,83] Rituximab was also tested in CAPS patients where improvement was noticed in six out of seven cases.[84-86] Another promising agent is belimumab (BlyS-specific inhibitor) which acts by inhibiting B cell activating factor (BAFF). Belimumab is currently approved for the treatment of SLE patients.[87] It was tested on murine models with APS where it was able to prevent the onset of the disease and showed an increase in survival rates.[88] Current data on humans are lacking.

Miscellaneous

Defibrotide, an adenosine receptor agonist, was shown to be successful when used to treat refractory CAPS.[89,90] It acts by blocking monocyte TF expression. Eculizumab (anti-C5) is another agent that demonstrated efficacy in improving the manifestations of APS and preventing aPL-induced thrombosis.[91] It is a humanised monoclonal antibody that acts by inhibiting the cleavage of C5a and C5b and thus, preventing the formation of MAC. It is the first therapy approved for the treatment of paroxysmal nocturnal haemoglobinuria (PNH). Abciximab and dilazep are two antiplatelet agents that exert their action by inhibiting GPIIb/IIIa receptor and blocking TF expression in endothelial cells and monocytes, respectively. Some data support that these agents are effective when used for secondary arterial thromboprophylaxis in APS patients.[92,93] While abatacept (CTLA4-Ig) is currently approved for the treatment of refractory rheumatoid arthritis, it is suggested that by selectively blocking the co-stimulation of T cells, it can prevent B cell activation and aPL production.[88] Thus, it is believed that abatacept may play a role in preventing disease onset although efficacy in APS patients is not yet reported.[94]

As APS is known to be associated with an increase in proinflammatory cytokines, TNF-α blockers were proven to be advantageous when used in patients with recurrent pregnancy loss but not in secondary APS cases (i.e. SLE-related).[95] Several proteins and intracellular pathways are involved in aPL-induced thrombotic mechanisms. By selectively inhibiting these pathways, one can reduce monocyte and endothelial cell activation as well as TF upregulation. Proteins that need to be blocked in order to address the underlying thrombotic state include p38 MAP kinase, NFκB, and apolipoprotein E receptor cell-surface receptor among others.[96-98] Some of the previously mentioned new therapies were discussed briefly as studies assessing their efficacy in APS are still lacking.

CONCLUSION

APS is a systemic autoimmune disease characterised mainly by thromboembolic events. It can affect multiple organs and tissues and may lead to a life-threatening form called CAPS. New molecular mechanisms of the disease are being revealed as research advances; this will open the door for exploring novel targeted therapies. Although immunomodulatory approach is gaining more importance in the treatment of APS patients, anticoagulation remains the mainstay of therapy. More studies addressing the use of immunomodulatory therapies in humans are needed as most of the data we currently have are extracted from experiments done on murine models.

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