Viewpoint:

Management of anticoagulant-refractory thrombotic antiphospholipid syndrome

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Summary

Anticoagulant-refractory thrombotic APS can be broadly defined as breakthrough thrombosis on standard treatment with oral anticoagulation, namely warfarin or an alternative vitamin K antagonist (VKA). The management of anticoagulant-refractory thrombotic antiphospholipid syndrome is a major challenge, given the serious nature of the thrombotic capacity observed, which has become refractory to standard-intensity anticoagulation. The factors (genetic and cellular) which conspire to cause anticoagulant-refractory thrombotic antiphospholipid syndrome are better understood. However, efforts to utilise this better understanding have not yet transformed our capacity to treat it successfully in many cases. In this Viewpoint we review the factors likely to be contributing to its cause and consider how they might be modified or inhibited. We also discuss current management, including general strategies to minimise thrombotic risk, escalation of anticoagulation, adjunctive treatment for thrombosis, immunomodulatory agents, complement inhibition, vascular options and future potential therapeutic targets.

Introduction

Antiphospholipid syndrome (APS) is an autoimmune thrombophilia that causes an increased risk of thrombosis. Anticoagulant-refractory APS is breakthrough thrombosis on standard treatment with oral anticoagulation, namely warfarin or an alternative vitamin K antagonist (VKA). It has potential major impact on patients' quality of life and health. Definitions of recurrent thrombosis and anticoagulant-refractory thrombosis are provided in Panel 1.

Thrombosis and pregnancy morbidity in association with persistent antiphospholipid antibodies (aPL; one or more of lupus anticoagulant [LA], IgG and/or IgM anti-beta 2 glycoprotein I [aβ2GPI] and anticardiolipin antibodies [aCL]) are cardinal features of antiphospholipid syndrome (APS).[1] APS-associated thrombosis can affect any blood vessel (venous, arterial or microvascular), with lower limb deep venous thrombosis and pulmonary embolism accounting for approximately 50% of events, strokes and transient ischaemic attack (TIA) around 30%, in the Euro-phospholipid prospective cohort study.[2] The frequency of venous thromboembolism (VTE) or stroke in APS varies in different populations, e.g. there is a higher prevalence of arterial thrombosis compared with VTE in APS patients in Japan.[3] Approximately 15% of patients with systemic lupus erythematosus (SLE) have

thrombotic APS, a major predictor of organ damage.[4] The standard treatment for thrombotic APS is life-long anticoagulation with a vitamin K antagonist (VKA).[5-7]

The overall prevalence of APS is estimated to be 40 to 50 per 100,000 people,[8] with a female-to-male ratio of approximately 5:1.[2] Catastrophic antiphospholipid syndrome (CAPS) is defined by the presence of aPL in a patient with rapidly developing thromboses in three or more organ systems in less than one week. CAPS is rare, developing in 1% of APS patients and has an overall mortality of 37%.[9]

The laboratory diagnosis of APS, based on the Sapporo/Sydney international consensus classification criteria, requires the presence of persistent antiphospholipid antibodies (aPL), i.e. present on at least two occasions at least 12 weeks apart.[1] APS classification criteria (being updated under the auspices of the American College of Rheumatology and the European League Against Rheumatism (EULAR)), were designed for scientific clinical studies rather than for routine diagnosis in clinical practice. Many other clinical manifestations are associated with persistent aPL, including immune thrombocytopenia, livedo reticularis, migraine, valvular heart disease and cognitive impairment.[1] Patients with these noncriteria APS manifestations also require clinical consideration.

Search strategy and selection criteria

References for this article were identified through searches of PubMed with the search terms "antiphospholipid syndrome", "recurrent thrombosis", "vitamin K antagonists", "direct oral anticoagulants", "low-molecular-weight-heparin", "fondaparinux", "anticoagulant-refractory", "antiplatelets", "hydroxychloroquine", "statins", "vitamin D", "immunomodulation", "complement", vasodilators" and "vascular intervention" from 1995 until November, 2019. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this Viewpoint.

Understanding the pathophysiology of APS provides a basis to explain why anticoagulation alone may not control thrombotic manifestations and identifies potential therapeutic targets. A unified mechanism for thrombosis remains elusive but various pathways are likely to contribute (Table 1). A key initiating pathogenic process in cell activation is binding of β2GPI to exposed, negatively charged phospholipid. This changes its conformation, with exposure of a cryptic domain 1 Arg39-Arg43 epitope recognised by pathologic aPL. The Arg39-Arg43-aβ2GPI

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complex subsequently interacts with surface receptors, with activation of endothelial cells, monocytes, neutrophils and platelets, causing prothrombotic and proinflammatory haemostatic changes.[10] Here, we focus on therapeutic strategies for APS patients with recurrent thrombosis while on anticoagulation, anticoagulant-refractory thrombotic APS and future potential therapeutic targets.

Risk of recurrent thrombosis while on oral anticoagulation

Vitamin K antagonists

Annualised recurrent thrombosis rates on VKA in previous studies were 1.3–4.0%,[11,12] 4.3%[13] and 4.8%.[14] More recent annualised recurrent thrombosis rates in two RCTs were 0% in the warfarin arm in the TRAPS (Rivaroxaban in Thrombotic APS) trial[15] and 2.1% in the VKA arm.[16] All patients in the former and 60.5% (115/190) in the latter RCTs were considered to be 'high risk' due to triple positivity (i.e. presence of LA, aβ2GPI and aCL). Notably, in the latter RCT, 14.7% (28/190) of patients in the trial had been on high-intensity VKA, target INR 3.1-4.0 (generally undertaken when patients have had recurrent thrombosis on standard-intensity VKA), yet were randomised to high-intensity VKA versus rivaroxaban 20mg once daily. This rivaroxaban dose has comparable efficacy to standard-intensity warfarin in the phase 3 trials of rivaroxaban in the general population (for VTE or atrial fibrillation), however, it may not protect against recurrent thrombosis in patients who have had breakthrough thrombosis while on standard-intensity VKA.

Direct oral anticoagulants

The recurrent VTE rate in the large phase 3 RCTs of direct oral anticoagulants (DOACs) versus warfarin, in patients with a first VTE after up to a year's follow-up, showed no significant difference at 2.2% and 2.0%, respectively.[17] No recurrent thrombosis was observed in thrombotic APS patients on rivaroxaban 20mg once daily versus standard-intensity warfarin over seven months follow-up in the RAPS (Rivaroxaban in APS) RCT, in which 28% of patients (24.6% [14/57] and 32.2% [19/59] in the rivaroxaban and warfarin arms, respectively) were triple positive.[24] Notably, the clinical phenotype of the RAPS trial patients was 'low risk', i.e. a single VTE or recurrent VTE while on subtherapeutic or no anticoagulation, with patients who had APS-related arterial thrombosis excluded.[18] In contrast, the annual recurrent thrombosis rate in the TRAPS RCT was 9%, all arterial, in the rivaroxaban arm versus 0% in the warfarin arm.[15] The Ordi-Ros *et al* RCT reported an annualised recurrent thrombosis rate in 3.9% and 2.1% in the rivaroxaban and warfarin arms, respectively, with a preponderance of

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recurrent strokes. *Post hoc* analysis suggested an increased risk for recurrent thrombosis in rivaroxaban–treated patients with previous arterial thrombosis, livedo racemosa or APS-related cardiac valvular disease.[16]

The ASTRO-APS (Apixaban for the Secondary Prevention of Thrombosis Among Patients With Antiphospholipid Syndrome) RCT protocol (apixaban 2.5 mg twice daily (bd) versus warfarin INR 2.0-3.0 in thrombotic APS patients (clinicaltrials.gov registration number: NCT022954) was modified twice due to a higher rate of thrombosis in patients with a history of arterial thrombosis. The protocol was modified after recruitment of 25 patients, to use apixaban 5 mg bd. Subsequently, five patients were enrolled during which there was a possibly higher than expected rate of stroke among patients randomized to apixaban. The protocol was further modified to enrol APS patients with prior VTE and exclude those with prior stroke or white matter changes disproportionate for patient age on brain MRI. The ASTRO-APS trial is active (follow up of included patients) but not recruiting, with results anticipated in 2020.

In a systematic review of 728 APS patients treated with DOACs, almost 50% triple aPL-positive, the annualised recurrent thrombosis was 11%.[19] The risk of recurrent thrombosis was associated with, amongst other factors, a higher mean number of prior thrombotic events and history of combined arterial and venous thrombosis, previous treatment with low-molecular-weight heparin (LMWH) and patient choice.[19] Risk factors for thrombosis were identified in a meta-analysis of 447 APS patients treated with DOACs, with an overall annual thrombosis recurrence rate of 11.7%. These were triple-positivity and a higher number of clinical criteria for APS classification; and n patients on anti-Xa inhibitors, prior arterial thrombosis. Of the 73 patients who had recurrent thrombosis, 31 had arterial events. Of these, three had prior arterial thrombosis alone, 10 had arterial plus venous thrombosis; and 18, VTE alone.[20]

Concerns have been raised about DOAC use for APS. The European Medicines Agency (EMA) has recommended against the use of DOACs, especially in APS patients with triple positive aPL.[21] This recommendation followed a risk assessment triggered by the TRAPS RCT. The EMA recommendation has been incorporated into the DOAC manufacturers' summary of product characteristics. The United Kingdom's Medicines and Healthcare products Regulatory Agency issued the following advice to healthcare professionals: "Review whether continued treatment with a DOAC is appropriate for patients diagnosed with antiphospholipid syndrome, particularly high-risk patients, and consider switching to a vitamin K antagonist such as warfarin."[22] The European League Against

Rheumatism (EULAR) advises against the use of DOACs in triple positive or those with arterial events.[7] The use of DOACs in single and double aPL-positive APS patients appears to be less concerning, and DOACs may be suitable for such patients following a single VTE. Importantly, a patient who is switched from a DOAC to warfarin may also experience recurrent thrombosis. Overall, there is no clarity about the use of DOACs in APS.

General strategies to minimise thrombotic risk

Prothrombotic situations

Factors contributing to VTE are summarised in Table 2. In contrast, a meta-analysis reported that progestogen-only contraception (POC; oral or the Mirena intrauterine device) appear to be unassociated with increased thrombotic risk. Thus, these options are suitable for contraception from a thrombotic perspective, although the study suggested that injectable POC use might increase the risk of VTE.[23] Notably, therapeutic doses of progestogen are associated with increased thrombotic risk,[24] and , individualised specialist assessment should be undertaken.

Other prothrombotic states

Other conditions that are associated with increased thrombotic risk are detailed in Table 2. The importance of active management of conventional cardiovascular risk factors was highlighted in a cross-sectional study of 379 APS patients who presented with arterial and/or venous thrombosis. Overall, significantly higher adjusted global antiphospholipid syndrome scores (aGAPSS; hyperlipidemia, arterial hypertension, and aCL, aβ2GPI and LA positivity) were seen in patients with recurrent arterial thrombosis, who had had higher aGAPSS (8.1 $\pm$ SD 2.9 vs. 6 $\pm$ 3.9; p<0.05).[25] An observational study suggested that, in asymptomatic patients with persistently aPL, thrombosis was associated with concomitant conventional cardiovascular risk factors or autoimmune disease.[26]

Anticoagulation for recurrent thrombosis in APS patients while on anticoagulation

The management of APS patients with recurrent thrombosis on oral anticoagulation is largely empirical. Figure 1 summarises our approach to anticoagulation for recurrent thrombosis. A checklist for the initial assessment of suspected VTE recurrence while on standard-intensity VKA is provided in Panel 2.

Vitamin K antagonists: considerations about anticoagulation intensity

The standard treatment following recurrent thrombosis while at standard-intensity VKA within the therapeutic range, is to increase anticoagulation to high-intensity, target INR 3.5, after an initial period of LMWH. Limited support for this pragmatic approach comes from a systematic review of 16 studies concluding that of 49/180 (27%) recurrences on VKA, only 7/49 (14%; four arterial and one venous were specified) occurred at an INR >3.0.[27] Although two RCTs showed no benefit of high- versus standard-intensity warfarin, six of eight recurrences in the high-intensity arm in one of these studies occurred at an INR <3.0,[11] with information on the INR associated with recurrence not reported in the other.[12] Uncertainty regarding the optimal anticoagulation intensity in APS patients with a first arterial thrombosis is reflected in the EULAR guidelines that recommend either standard-intensity VKA, with/without low dose aspirin (LDA), or high-intensity VKA (target INR 3.0, range 3.0-4.0), considering the individual's risk of bleeding and recurrent thrombosis.[7] When recurrent thrombosis occurs despite standard-intensity VKA, the main anticoagulant options are intermediate/high-intensity VKA, LMWH or fondaparinux.

Anticoagulation for anticoagulant-refractory APS

Figure 2 summarises the progression of management options for anticoagulant-refractory thrombotic APS. Continuation of anticoagulation remains integral to the treatment of these patients.

Low-molecular-weight heparin (LMWH)

If the patient is adherent and the INR therapeutic after increasing to high-intensity VKA, limited data and clinical experience support switching to LMWH. A study of LMWH in 24 APS patients, 16 having 'failed adequate warfarin therapy', showed no rethrombosis recurrence after approximately 10 months' follow-up.[28] A review of LMWH in APS patients with intolerance or "warfarin failure" (nine patients), median follow-up 36 months, reported recurrent thrombosis in up to three patients, suggesting that LMWH may be effective in patients who have had recurrent thrombosis while on warfarin.[29]

A reasonable approach, in patients who have thrombosed while on high-intensity VKA, is LMWH at approximately 25% above standard dose (i.e. high-intensity),[30] using split-dose. Further dose escalation to about 33% above standard dose[30] is suggested for recurrent thrombosis while on high-intensity LMWH, with

consideration of monitoring anti-factor Xa levels. Heparin induced thrombocytopenia (HIT) should be excluded in those developing recurrent thrombosis on LMWH.[31] A systematic review and meta-analysis showed the use of LMWH between 6-24 months was associated with a decrease in bone mineral densitometry (BMD).[32] Monitoring of BMD and optimisation of vitamin D and calcium intakes in patients on prolonged LMWH is prudent.

Other anticoagulant options

Fondaparinux, a synthetic analogue of heparin pentasaccharide, used mainly for the treatment of HIT,[31] has specific anti-factor Xa activity seven-fold higher than LMWH.[33] Its use was reported in two patients in combination with mycophenolate mofetil (MMF) with no recurrent events after four years of follow-up.[34] Fondaparinux shows no significant inhibitory effect on osteoblast proliferation or activity *in vitro*,[35] although clinical data supporting these findings are lacking.

Antiplatelet agents

The use of VKA over LDA is supported by observational studies showing a lower risk of recurrent thrombosis among APS patients with prior arterial thrombosis, mainly stroke, treated with VKA versus LDA alone, as reported by Verro et al.[36] The APASS (Antiphospholipid Antibodies and Stroke Study), a prospective cohort study within WARSS (Warfarin versus Aspirin Recurrent Stroke Study) in older patients with stroke reported no difference in event recurrences between LDA and warfarin,[37] but aPL testing did not fulfil international classification criteria.[1] There is a lack of consensus regarding the use of LDA for thrombotic APS. EULAR guidelines recommend consideration of LDA plus standard-intensity VKA following a first arterial thrombosis and, in APS patients with recurrent arterial or venous thrombosis, addition of LDA, increase of INR target to 3–4 or change to LMWH.[7]

Adjunctive treatment for thrombosis

The 15th International Congress on Antiphospholipid Antibodies (ICAPA) Treatment Trends Task Forces recommend that hydroxychloroquine be considered as adjunctive treatment in refractory APS; statins, for APS patients with hyperlipidaemia; and vitamin D deficiency corrected, based on general population guidelines.[6]

Hydroxychloroquine

Ruiz-Irastorza et al showed a protective effect of antimalarials against thrombus formation and increased survival in SLE patients.[38] Hydroxychloroquine reduces the risk of thrombosis in SLE patients and may decrease titres of aPL.[39] In a retrospective study, reduced titres of aPL (p<0.002) and a decreased incidence of arterial thrombosis recurrence occurred in primary APS patients treated with hydroxychloroquine.[40]

Statins

Statins have proven benefit in the primary and secondary prevention of coronary heart disease. As well as a lipid-lowering effect, statins have immunomodulatory, anti-inflammatory and antithrombotic properties.[41] A prospective open-label pilot study of fluvastatin use for three months in 24 APS patients showed reduction in proinflammatory and prothrombotic biomarkers, including interleukin-1 beta (IL1β), vascular endothelial growth factor (VEGF), tumour necrosis factor alpha (TNFα) and soluble TF.[42]

Vitamin D

Vitamin D may protect against thrombosis in APS through inhibition of angiogenic factors in endothelial cells and immunomodulatory effects on inflammatory activity.[43] *In vitro* models have shown that vitamin D inhibits the expression of TF in monocytes stimulated by aβ2GPI from APS patients, suggesting a potential role of vitamin D in the pathogenesis of APS.[44] Low vitamin D levels correlate with arterial/venous thrombosis in APS patients.[44]

Immunomodulatory agents

Standard immunosuppressive drugs often reduce, but not remove, autoantibodies completely. it is likely that the efficient removal of antibodies, capable of inducing the activation of different pathways, such as coagulation or neutrophil extracellular traps (NETS), requires more than one mechanism to be blocked. This suggests why anticoagulation alone may not suffice and why a single immunomodulatory agent may also appear to be associated with apparent resistance to treatment. The role of immunomodulation in APS is uncertain as agents are often given with multiple other therapies. The main modalities where clinical use is evident in anticoagulant-refractory thrombotic APS are described below.

B-cell depletion

The evidence for the use of rituximab, an anti-CD20 monoclonal antibody, for anticoagulant-refractory thrombotic APS is scarce, few cases having recurrent thrombosis as a primary indication. The largest case series includes five APS with SLE patients with recurrent thrombosis despite appropriate anticoagulation on warfarin. Four out of five (80%) had no further thrombotic events after its use.[45] In primary APS, only sporadic reports of successful treatment with rituximab for thrombotic events are available.[46,47] The RITuximab in APS (RITAPS) phase 2 open-label prospective pilot study of rituximab for APS patients with non-criteria manifestations suggested rituximab was safe in aPL-positive patients, consistent with its safety profile.[48] This study also suggested that despite causing no substantial change in aPL profiles, rituximab may be effective in controlling some, but not all, non-criteria manifestations of APS.[48] Ioannou et al reported a significant fall in aCL titres in SLE patients following rituximab.[49]

Mycophenolate mofetil

Mycophenolate mofetil (MMF) use in APS is limited to case reports describing two thrombotic APS patients that presented with ischaemia and necrosis of distal lower extremities secondary to microvascular thrombosis. Both were given plasma exchange and MMF, with the addition of IV MP in one, and maintained on MMF plus fondaparinux. No microvascular thrombotic recurrence was observed after four years' follow-up.[34]

Intravenous immunoglobulin

Intravenous immunoglobulin (IVIG) might have beneficial effects in thrombotic APS as a result of direct action, through the Fc receptor, blocking pathological antibodies and increasing their clearance; and indirect effects via immunomodulation and inhibition of complement system activation. A review of 35 studies, reporting the effects of IVIG in APS patients, suggested that it could be useful, in addition to standard therapy, to prevent recurrent thrombosis in APS patients refractory to conventional anticoagulant treatment.[50]

Complement inhibition

The coagulation and complement pathways are closely linked, with activation of the latter increasingly recognized as a possibly significant cofactor in the pathogenesis of APS. Thrombotic APS patients have raised levels of complement activation markers.[51] Eculizumab is a humanised monoclonal antibody that binds the complement protein C5, preventing generation of the membrane attack complex which leads to tissue injury. Its licensed

indications include atypical haemolytic uraemic syndrome, which is complement-driven. The largest case series reported improvement in thrombocytopenia and renal function in nine patients with SLE and/or APS with secondary thrombotic microangiopathy (TMA) who failed standard care, suggesting that eculizumab may be a potential treatment option .[52] Another study reported complement activation in thrombotic APS patients using a functional modified HAM (mHAM) assay, patient-derived aβ2GPI-induced complement activation *in vitro* shown by a functional assay (mHam) and increased C5b-9 deposition on the cell surface, suggesting a rationale for complement inhibition as a therapeutic strategy in patients with refractory thrombotic APS.[53]

Vascular options for management of thrombosis in antiphospholipid syndrome

Arterial thrombosis

APS can mimic peripheral vascular disease causing both large vessel and microvascular thrombosis leading to digital ischaemia or critical limb ischaemia. There is a little evidence to guide the use of vascular intervention in APS-associated large and small vessel arterial disease; thus, vascular interventions are largely extrapolated from other conditions with similar clinical manifestations. Acute management by intra-arterial catheter directed thrombolysis with tissue plasminogen activator, to improve arterial inflow to the limb, can be used in those presenting without neurovascular compromise.[54] Surgical intervention by thrombectomy is normally accompanied by adjunct arterial stenting or bypass, and should be reserved for patients with limb threatening ischaemia. Management of microvascular thrombosis is dependent on adjunctive therapies for local vasodilation to improve capillary blood supply and improve distal ischaemia.

i)   Vasodilators

Most vasodilators produce a variable response. Benefit with sildenafil, a selective phosphodiesterase-5 (PDE5) inhibitor, was noted in two case reports of cutaneous APS-related thrombotic vasculopathy which did not respond to previous therapeutic regimes.[55,56] Iloprost is a prostacyclin analogue acting via vasodilation and inhibition of platelet aggregation. It also interferes with leukocyte chemotaxis and endothelial and phagocytes adhesion. Iloprost was reported to be useful for the treatment of Raynaud's phenomenon with digital ulcers and digital ischemia in two small case series, one that involved two patients with primary APS already on anticoagulation

therapy[57] and the other three APS patients, two with SLE.[58] Most of these examples were already on calcium channel blockers therapy that did not seem to ameliorate the ischaemic complications of the patients. Thus, the potential benefit of sildenafil and iloprost in APS may go beyond their vasodilatory effect, possibly mediated by platelet function inhibition and endothelium-stabilising properties.

ii)   Surgical interventions to achieve vasodilation

The principle is to block/reduce sympathetic mediated vasoconstriction of arterioles permanently, thereby increasing blood flow to the lower limb by inducing vasodilation of the collateral circulation and shunting of blood through cutaneous arteriovenous anastomoses. Most clinical trials have focused on end stage peripheral vascular disease with the endpoint of amputation prevention or in some cases pain reduction.

- *Lumbar sympathectomy* can be performed surgically by cutting the sympathetic nerve fibres or via chemical ablation. Data are limited and it remains unclear whether any subgroups may have improved pain control or ulcer healing.[59]

- *Digital sympathectomy* is a local microsurgical technique to denervate the digital arteries predominantly in the fingers that has successfully been used in case series for patients with severe Raynaud's syndrome and scleroderma.[60]

- *Sacral nerve stimulation* works by implantable electrodes in the lumbar epidural space that supress sympathetic nerve fibres and gate sensory return. It improves limb salvage in end stage peripheral vascular disease.[59]

Hyperbaric oxygen therapy (HBOT)

HBOT involves placing the patient in a compression chamber breathing 100% oxygen to deliver a greatly increased partial pressure of oxygen to the tissues. A Cochrane review of 12 trials of chronic wounds suggested that HBOT improved wound healing in the short term without long term benefit or reduction in amputation.[61] In the chronic stable situation of cutaneous leg ulceration secondary to cutaneous thrombosis, HBOT is an option for patients with ulceration or tissue loss secondary to ischaemic APS.

Venous thrombosis: Inferior vena cava (IVC) filters

The use of IVC filters has fallen from favour as mounting evidence shows little benefit. Current guidelines advise that there is no role for IVC filters in cancer patients.[30] In patients at high risk of PE with a contraindication to anticoagulation, a role for IVC filter placement may remain. IVC filter removal should be undertaken as soon as the contraindication has resolved.[62] The same approach applies to APS patients, who are also very prothrombotic.

Future potential treatment options

Potential therapeutic options that may hold promise include the following:

B-cell depletion: The introduction of fully humanised B cell depleting agents (e.g. ofatumumab, ocrelizumab) either alone or possibly in combination with belimumab potentially offers an effective and safe way to remove aPL. This approach may be a useful adjunct in the treatment of anticoagulant-refractory APS.

Peptide therapy: Therapies that target either Domain I or V of β2GP1 are being developed, but chemical modification such as polyethylene glycosylation are needed to improve pharmacological properties.[10]

Mammalian target of rapamycin complex (mTORC) pathway inhibitors: Sirolimus, an mTORC inhibitor, which leads to the inhibition of T cells and B cell activation, reduced vascular changes contributory to nephropathy in APS post renal allograft.[63]

Suppression of neutrophil extracellular traps: A selective agonism of the adenosine A_{2A} receptor, CGS21680, suppressed aPL-mediated NETosis and thrombosis in murine models.[64]

Anti-CD38: As CD38-targeting antibodies are promising in the treatment of heavily pretreated multiple myeloma patients, and as aPL are likely produced by plasmablasts and/or plasma cells, anti-CD38 have potential for the treatment of APS.[65]

Anti-FcRn targeted therapies are being used in various autoimmune IgG driven diseases, such as immune thrombocytopenia, and may be potentially useful in APS.[66]

Ubiquonol (reduced Coenzyme Q10): Studies highlight the potential of Ubiquonol to modulate overexpression of inflammatory and thrombotic risk markers in APS.[67]

Conclusions

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The complex and individually variable pathophysiology of thrombotic APS provides therapeutic challenges, particularly when patients are refractory to standard treatment. The dearth of clinical trials and the tendency to treat many of these patients empirically with multiple therapies makes it hard to determine optimal management. As reviewed here, patients with anticoagulant-refractory thrombotic APS will invariably require a switch from standard to high-intensity VKA. If this alone does not control the situation, LMWH (which itself may need to be dose escalated or possibly switched to fondaparinux), may be required, often accompanied by a variable combination of antiplatelet agents, immunomodulation and adjunctive options. There is a need for prospective cohort studies, with standardised management, and randomised controlled clinical trials to help determine optimal therapy for anticoagulant-refractory thrombotic APS. The development of robust outcomes measures, including an internationally agreed disease activity index and specific quality of life index would facilitate the success of these studies.

Authors' contributions

HC, ZS, ME, PG, TR and DI drafted and revised the manuscript and contributed to the literature review. All authors approved the final version.

Conflict of interest statements

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Table 1

Pathophysiological mechanisms in thrombotic antiphospholipid syndrome (for further information, see reviews[10,68-71])

Pathophysiological mechanism	Proposed Pathways involved
Genetic predisposition	-Human leucocyte antigen (HLA)-related: HLA-DR4 and HLA-DRw53 genes -Non HLA-related: IRF5 (interferon regulatory factor 5), STAT4 (encoding signal transducer and activator transcription 4) genes and beta 2 glycoprotein I (β2GPI) valine/leucine247 mutation
Cell activation leading to prothrombotic and proinflammatory effects	-β2GPI binding to exposed, negatively charged phospholipids on the surface of endothelial cells, monocytes/macrophages, neutrophils, and platelets -Induction of a prothrombotic and proinflammatory phenotype via activation of toll-like receptor (TLR2), TLR4, annexin A2 or low density lipoprotein receptor-related protein 8 (LRP8) and activation of their signal transduction pathway, leading to induction of nuclear factor kappa-B (NFkB)-dependent genes
Interference with haemostatic mechanisms	-Increased expression of tissue factor (TF) on monocytes/macrophages -Activation of platelets leading to increased expression of glycoprotein IIb/IIIa receptors and thromboxane A2 -Interference with activated protein C pathway, leading to acquired resistance to activated protein C -Inhibition of fibrinolysis via: i) anti-tissue plasminogen activator antibodies; ii) direct binding to plasmin -Disruption of the Annexin A5 protective shield by aβ2GPI/β2GPI complexes, leading to exposure of the procoagulant anionic phosphatidylserine membrane surface of the placenta, enabling assembly of coagulation and other active complexes that predispose to thrombosis
Complement activation	-Complement activation by aPL generates C5a, which induces neutrophil tissue factor-dependent procoagulant activity through TF expression; C5a also induces tissue factor expression on monocytes and endothelial cells -β2GPI has a complement regulatory role: when bound to a surface, β2GPI undergoes a conformational change from a circular to an elongated form that can bind C3. Subsequently C3 undergoes a conformational change exposing binding sites that make it susceptible to degradation by complement factor H and factor I -Autoantibodies against complement factor H may increase the risk of thrombosis
Induction of proinflammatory signalling	-Increased expression of cell surface adhesion molecules; increased secretion of proinflammatory cytokines -aβ2GP1 binding to β2GP1 on the neutrophil surface leads to cell activation and release of neutrophil extracellular traps (NETs) that enhance thrombosis[72]

Table 2

General strategies to minimise thrombotic risk

Prothrombotic situations **-** the presence of aPL in individuals asymptomatic for thrombosis supports a "two hit" hypothesis,[73] with the following prothrombotic situations contributing[30]

1. Surgery: specialist advice should be sought for bridging anticoagulation

2. Immobilisation

3. Exogenous oestrogen and pregnancy: oestrogen-containing combined contraception was reported to not be associated with increased recurrent VTE risk in 1888 women receiving rivaroxaban or enoxaparin/VKA for confirmed VTE and concomitant hormonal therapy.[74]

4. Multifactorial situations: causes of VTE are multifactorial and anticoagulation may be interrupted, such as for surgery, or there may be coexistent risk factors such as other autoimmune disease.

Other prothrombotic states

1. These include SLE or other autoimmune diseases and myeloproliferative neoplasms, which should be managed optimally to minimise thrombotic risk.

2. Conventional cardiovascular risk factors, including hypertension and hyper/dyslipidaemia, which should be actively managed.

Panel 1

Recurrent and anticoagulant-refractory thrombosis

- Recurrent thrombosis may occur while on standard-intensity VKA, target INR 2.5 (range 2.0-3.0), due to a subtherapeutic INR. This could be related to non-adherence or where the use of standard rather than high-intensity VKA, target INR 3.5 (range 3.0-4.0) is not established, e.g. in APS-related stroke, with recommendations a target INR of 2.5, with or without low dose aspirin, or target INR 3.5[7]

- Anticoagulant-refractory thrombotic APS implies breakthrough thrombosis on standard-intensity anticoagulation in the absence of the above factors. APS patients with recurrent thrombosis while on standard-intensity VKAs and, subsequently, also on high-intensity VKAs, have reached the stage of anticoagulant-refractory APS.

- Prevalence figures for anticoagulant-refractory thrombotic APS are lacking, although clinical experience suggests that it is rare.

- Limited data are available to guide the management of anticoagulant-refractory thrombotic APS patients.

- Management is largely empirical and merits consideration of additional treatment modalities, extrapolated from similar clinical situations associated with other prothrombotic disorders.

Panel 2

Initial assessment of suspected VTE recurrence on standard-intensity VKA – the following checklist should apply

- Confirmation of new thrombosis or thrombosis extension by imaging

- Review of INR in the weeks preceding and at the time of the thrombosis

- Assessment of patient adherence to anticoagulation with patient education

- Checking that the patient's INR assessment has been performed with an assay that has been shown to be reliable in the patient*

- Consideration of additional risk factors for thrombosis e.g. malignancy

- Consideration of bleeding risk factors, e.g. gastrointestinal or uterine, or thrombocytopenia. As such factors may limit anticoagulation intensity, they require active management to optimise clinical outcomes.

*The INR result may not be representative in occasional APS patients due to an effect of LA on the thromboplastin reagent. The majority of commercial thromboplastins can be safely used in LA positive patients, although it is important to use a thromboplastin insensitive to LA to monitor the INR. The prothrombin time, on which the INR is based, should be checked before starting a VKA wherever possible. Point-of-care INRs are variably affected by LA; the results should therefore be interpreted with caution. Chromogenic factor X levels provide an LA-independent assessment of VKA intensity, however, are not validated or practicable for routine use.[75]

Legends to Figures

Figure 1

Approach to anticoagulation for recurrent thrombosis in thrombotic antiphospholipid syndrome

Abbreviations: INR: International normalised ratio; LMWH: low-molecular-weight-heparin

Figure 2

Anticoagulant-refractory thrombotic antiphospholipid syndrome: management flow chart

Abbreviations: VKA: Vitamin K antagonist; INR: International normalised ratio; LMWH: low-molecular-weight-heparin; IVIG: Intravenous immunoglobulin

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Venous thromboembolism
Target INR 2.5 (range 2-3)

Target INR 2.5 +/- antiplatelet agent

Arterial thrombosis

Arterial or microvascular thrombosis – switch to VKA

Venous thromboembolism

Start bridging LMWH and check adherence to DOAC and consider switch to VKA, target INR 3-4
(DOAC level may be helpful)

High-intensity LMWH, split dose; approximately 25% increase over standard therapeutic dose

Recurrent thrombosis while at INR 3-4

thromboplastin insensitive to LA

Escalated high intensity LMWH, split dose; approximately 33% increase over standard dose

Fondaparinux

Figure 2

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┌──────────────────────────────────────────────────────────────┐
│         Limited evidence to guide management, largely empirical │
│                    Multidisciplinary approach                  │
└──────────────────────────────────────────────────────────────┘
                              ⬇
┌──────────────────────────────────────────────────────────────┐
│         Switch from standard-intensity to high-intensity VKA   │
│   Check INR monitoring; Check for coexistent prothrombotic conditions │
└──────────────────────────────────────────────────────────────┘
                              ⬇
            ┌──────────────────────────────────────┐
            │  Consider statin, hydroxychloroquine, vitamin D  │
            └──────────────────────────────────────┘
                              ⬇
                ┌──────────────────────────────┐
                │   High-intensity LMWH (split dose)   │
                └──────────────────────────────┘
                              ⬇
        ┌──────────────────────────────────────────────┐
        │ Consider escalated dose high-intensity LMWH, then fondaparinux │
        └──────────────────────────────────────────────┘
                              ⬇
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│ Consider antiplatelet agent, rituximab, IVIG, complement inhibition, vascular options │
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