Evolution of Antiphospholipid Syndrome

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Abstract

Antiphospholipid syndrome (APS) is an autoimmune prothrombotic disease characterized by thrombosis and/or pregnancy complications caused by antiphospholipid antibodies (aPL). The history of APS can be traced back to observations made during screening programs for syphilis conducted in the mid-20th century, with identification of patients with the so-called biological false-positive serological reactions for syphilis. Initial observation linking aPL with recurrent miscarriages was first reported more than 40 years ago. Since then, our understanding of the pathogenesis and management of APS has evolved markedly. Although APS is an autoimmune disease, anticoagulation mainly with vitamin K antagonists (VKAs) rather than immunomodulation, is the treatment of choice for thrombotic APS. Direct acting oral anticoagulants are inferior to VKAs, especially those with triple-positive APS and arterial thrombosis. Inflammation, complement activation, and thrombosis in the placenta may contribute to pathogenesis of obstetric APS. Heparin, mainly low-molecular-weight heparin, and low-dose aspirin represent the treatments of choice for women with obstetric complications. Increasingly, immunomodulatory agents such as hydroxychloroquine for thrombotic and obstetric APS are being used, especially in patients who are refractory to present standard treatment.

Keywords

- antiphospholipid syndrome
- antiphospholipid antibodies
- thrombosis
- obstetric complications
- anticoagulation

Antiphospholipid syndrome (APS) is an autoimmune prothrombotic disease characterized by thrombosis and/or pregnancy complications caused by antiphospholipid antibodies (aPL). Thrombosis can affect the venous, arterial, or microvascular circulation in virtually any organ or tissue, with some patients developing multiple thromboses, leading to fatal or life-changing outcomes. Characterization of APS requires only persistent presence of $\geq$1 of the three different aPL tests included in the International Consensus Criteria (ICC: Sydney; updated Sapporo),[1] namely, lupus anticoagulant (LA), IgG or IgM anticardiolipin (aCL), and anti-β2-glycoprotein I (anti-β2GPI) antibodies; however, there are a multitude of autoantibodies against various targets present in patients with APS that may contribute to pathogenesis. APS is a highly prothrombotic disease, leading to recurrent thrombosis in some patients, despite adequate anticoagulation. A reported recurrence rate of approximately 30% within 10 years of diagnosis of the index events underlines this risk, particularly in triple positive patients (presence of LA, anti-β2GPI, and aCL).[2] Importantly, unlike non-APS patients with venous thrombosis in whom direct acting oral anticoagulants (DOACs) are the first choice of anticoagulant for the prevention of recurrence, DOACs are inferior to vitamin K antagonists (VKAs) in thrombotic APS, at least for those with triple positive aPL and/or a history of arterial thrombosis. Patients with obstetric APS are generally treated with low-molecular-weight heparin (LMWH) and low-dose aspirin (LDA) during pregnancy. However, these treatments are suboptimal in some women. The role of anti-inflammatory drugs such as

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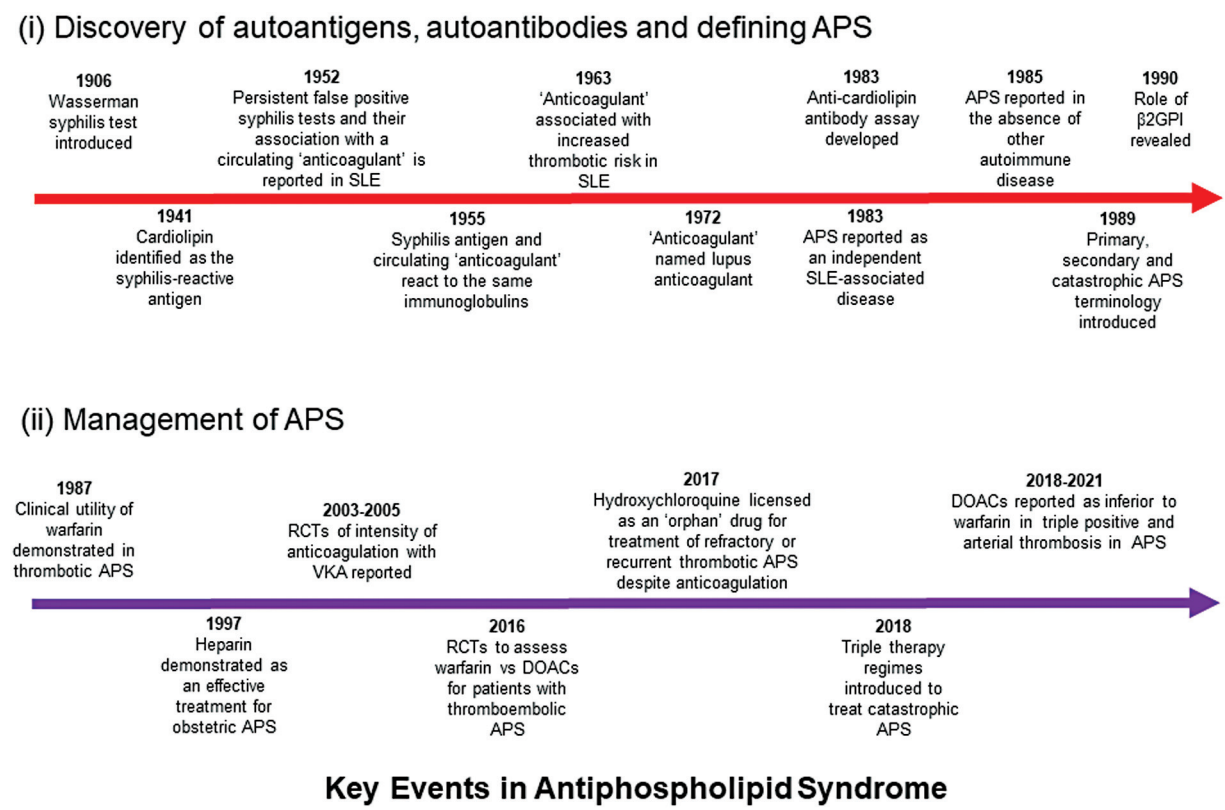

Fig. 1 Key events in the evolution of antiphospholipid syndrome. APS, antiphospholipid syndrome; β2GPI, beta 2 glycoprotein I; DOACs, direct acting oral anticoagulants; RCTs, randomized controlled trials; SLE, systemic lupus erythematosus; VKA, vitamin K antagonists.

hydroxychloroquine (HCQ) in obstetric APS as well as thrombotic APS is under evaluation.

The history of APS can be traced back to observations made during screening programs for syphilis conducted in the mid-20th century. In this review, we aim to appraise the evolution of our understanding of the disease pathogenesis and treatment in both thrombotic and obstetric APS. The main events over the course of the syndrome's evolution are summarized in ►**Fig. 1**.

Identification of Cardiolipin as an Autoantigen

In 1906, August Paul von Wassermann used an immunological test based on complement fixation and syphilis-infected human tissue lysate, to identify an antibody that binds *Treponema pallidum*, the causative organism for syphilis.[3] Soon after, it became apparent that syphilis-infected human tissue could be replaced with lysate from noninfected beef heart.[4] However, the sensitivity and specificity of the test remained problematic, mainly due to the lack of a standardized antigen. In 1941, Mary Pangborn purified the syphilis antigen responsible for the positive Wassermann test, termed cardiolipin (Greek cardia = heart).[5,6] Cardiolipin was identified as an anionic phospholipid found in the inner mitochondrial membrane of cells within the heart as well as other organs. Following this discovery, a further syphilis test known as the venereal disease research laboratory (VDRL) test was subsequently developed.

Unexpectedly, the syphilis-reactive antibodies identified in Wasserman's and VDRL tests were also found in patients who did not have syphilis (biological false-positive, BFP). In some instances, such as following infectious mononucleosis, these antibodies were transient, and the syphilis test became negative over time. Persistent BFP more than 6 months was reported in systemic lupus erythematosus (SLE) and other related autoimmune diseases[7] suggesting that the BFP was a signal of autoimmunity. The relationship between BFP and SLE, as well as rheumatoid arthritis (RA), was described further[8–10] and eventually led to observations that positive tests sometimes preceded clinical manifestations of the collectively described "collagen diseases."[11] Approximately 40 years later, this key syphilis antigen—cardiolipin—became central to the description of APS.

Lupus Anticoagulant, Anticardiolipin Antibodies, and Their Association with Thrombosis and Pregnancy Morbidity

In the mid-1940's, a report from the University of California Medical School described a young man with a fatal condition manifesting as moderate thrombocytopenia and prolonged whole blood clotting time with a hemorrhagic diathesis, intracranial and peripheral venous thrombosis. The prolonged clotting time was attributed to "hypothromboplastinemia" and the crude tests available did not demonstrate a coagulation inhibitor.[12] A second report in 1951 described a young man with abnormal bleeding, arthralgias, and possible lower limb

venous thrombosis. Again, prolonged blood clotting time and prothrombin time were attributed to hypoprothrombinemia. At postmortem and via tissue bleeds, renal changes reminiscent of SLE were evident as well as cerebral infarcts.[13]

In 1952, a "circulating anticoagulant" that prolonged prothrombin time *in vitro* was reported in the sera of patients with SLE[14,15] who were BFP for syphilis. The anticoagulant was deemed responsible for these false-positive syphilis tests. Using serum electrophoresis, the anticoagulant and cardiolipin were shown to recognize the same region of gamma globulins[16,17]; these studies provided the first real evidence that the yet unidentified anticoagulant and cardiolipin interacted with the same group of antibodies. In 1972, the term "lupus anticoagulant" was coined by Feinstein and Rapaport.[18] In 1980, the mechanism of LA was described by Thiagarajan et al who showed that purified IgM from the serum of a patient with high LA was able to inhibit coagulation *in vitro* only in the presence of anionic phospholipid.[19] In 1986, the dilute Russell viper venom test (dRVVT) and other phospholipid-based coagulation assays were introduced for LA detection.[20]

Because lipids were known to be immunogenic,[21] Smolarsky developed a radioimmunoassay that identifies antilipid antibodies.[22] In 1983, Nigel Harris, a pioneer in the APS field, used radioimmunoassay[23] and later enzyme-linked immunosorbent assay (ELISA)[24] to measure anti-cardiolipin antibodies (aCL) as an alternative and more specific assay to the cumbersome LA test that required specialized reagents, fresh plasma, and was proving difficult to standardize. At that time, it was thought that aCL and LA were equivalent. We now know that LA is represented by a class of heterogenous prothrombotic antibodies that prolong phospholipid-dependent clotting times including aCL, anti-β2GPI, and antiphosphatidylserine/prothrombin antibodies (anti-PS/PT; discussed later in this article).

Defining Antiphospholipid Syndrome

Initially, LA positivity in SLE was thought to cause hemorrhage but was later appreciated to associate with a tendency to thrombose rather than bleed.[25–28] Years after, LA was described in the absence of SLE or other connective tissue disease background, once again associating with thrombosis.[29] The importance of LA positivity in pregnancy morbidity was first presented in a study that reported an association with recurrent miscarriage[17] followed by multiple reports of LA in patients with pregnancy complications.[30–32]

Shortly after the first description of the aCL test by Harris et al,[23] APS was described by Graham Hughes who, together with Harris and Azzudin Gharavi, led an international effort to standardize the aCL test. In 1983, APS was reported as an SLE-associated syndrome characterized by aCL presence and recurrent thrombosis.[33] Pregnancy morbidity[33–35] and neurological[33] abnormalities were also common in aCL-positive individuals with SLE. In 1985, the Hughes group discussed APS in the absence of SLE,[36] and in 1989, the terms "primary"[37,38] and "secondary"[39] APS were established to distinguish between APS existing alone compared to APS associated with SLE or another related condition. The term "catastrophic" was initially used to describe a devastating form of a primarily microvascular thrombotic disease or vasculopathy in the presence of aCL[40–43] now termed "catastrophic APS (CAPS)."[44]

Identification of Anti-β2GPI and Domain-Specific Antibodies

In the early 1990s, several independent seminal studies showed that some aCLs were not directed to anionic phospholipid but to a plasma cofactor.[45–48] McNeil et al showed that aCL purified from patient sera could not bind cardiolipin, but the addition of normal plasma restored their binding ability, suggesting that a plasma cofactor was required for aCL to bind its antigen. Further analysis identified β2GPI as the primary serum cofactor.[45] Galli et al showed that purified aCL from patient sera only bound liposomes containing negative phospholipid in the presence of plasma or serum and identified a serum cofactor with properties closely resembling those of β2GPI.[46] The same findings were reported by Matsuura et al who identified the same serum cofactor for enabling aCL binding to liposomes.[47]

β2GPI is a member of the complement control protein superfamily and considered a natural anticoagulant. The importance of β2GPI and its antibodies, as well as the role of β2GPI in health and disease, has been the subject of many studies.[49–51] Abundant in serum (~200 μg/mL),[52,53] β2GPI can switch conformation from a closed, circular structure to an open fishhook form. Induction of anti-β2GPI is largely considered to be primed by infection via a process known as molecular mimicry—whereby an infectious antigen shares similarities with a self-antigen—leading to breakdown of immunological tolerance. Antibodies against all five domains of β2GPI may develop, but in APS the pathogenic groups of anti-β2GPI are thought to primarily recognize the first domain (domain I, DI), which becomes exposed upon closed-to-open conformational change.[54–56] In contrast, domain V (DV) is exposed in both conformations and contains regions that interact with cell surface molecules such as phospholipid and receptors.[51,55,56] Antibodies to domain V are considered nonpathogenic[57] and may be more common in people with transient aPL positivity following infection and clearance,[58,59] whereas anti-DI antibodies cause thrombosis[60,61] and pregnancy loss in mouse models of APS.[60] Studies of anti-DI in patient sera show definitive associations with the syndrome[62] and predominantly vascular complications in primary and SLE-associated APS.[62–67] Fewer studies have focused on anti-DI in patients with obstetric complications.[68] Anti-DI antibodies primarily recognize conformational immunogenic regions, or epitopes, specific to DI.[69–71] However, DI shares some sequence homology with domains II–IV, as all four domains are known as complement control protein or "sushi" domains. Thus, antibodies to other regions of DI may cross-react with domains II–IV or anti-domain II–IV antibodies may cross-react with DI.[72] The role of antibodies against DII–IV in pathogenesis has not been established.

Role of Antibodies against the Phosphatidylserine/Prothrombin Complex

Following improved understanding of the importance of cardiolipin–β2GPI complexes, a second autoantigenic complex was described between phosphatidylserine and prothrombin (PS/PT).[73] Also associated with clinical features of APS, anti-PS/PT are increasingly recognized as a key aPL population responsible for LA positivity.[74–77] The strong correlation between LA and anti-PS/PT has been extensively noted[78–80] including in a multicenter study conducted by Sciascia et al.[81] This observation has major clinical significance, as anti-PS/PT can be used in situations where detection of LA is problematic, the most significant being patients on anticoagulation therapy, which can lead to false-positive LA results.[82]

Pathogenesis of Thrombosis

Thrombotic APS is classified by the presence of persistently positive aPL (at least one of LA, IgG, or IgM aCL, or anti-β2GPI, on at least two occasions ≥12 weeks apart) *and* at least one clinical episode of arterial, venous, or small-vessel thrombosis.[1] These classification criteria have also become default diagnostic criteria. Estimated to account for 1 in 6 strokes in patients younger than 50 years,[83] 1 in 9 heart attacks,[84] and 1 in 11 deep vein thromboses overall,[84] APS is recognized as the most common cause of acquired hypercoagulability in the general population and responsible for a significant proportion of ischemic strokes in young people. Thrombotic events in APS are a "two-hit" phenomenon.[49,50] The first hit is provided by aPL that persistently attack the vessel wall (endothelium) and can activate circulating immune cells (neutrophils, monocytes) and platelets. aPL lowers the threshold for thrombosis that occurs upon exposure to a second hit, such as infection or injury. Despite adequate and often aggressive antithrombotic treatment, recurrent thrombosis develops in 25% of patients,[85] further underlining the strong prothrombotic risk associated with aPL and APS.

Animal models have provided invaluable mechanistic insight of aPL thrombogenicity, enabling researchers to prove the two-hit hypothesis of thrombosis and allowing molecular investigations to identify the prothrombotic and proinflammatory biological processes that support aPL-mediated thrombosis.[49] The first venous thrombosis model reported by Pierangeli and Harris in the early 1990s[86] formed the basis for multiple models via passive transfer of human monoclonal or polyclonal aPL isolated from patients followed by induction of thrombosis, most commonly by localized vessel injury. "Chronic" *in vivo* models, whereby animals are immunized with β2GPI to induce mouse antihuman aPL, are also used to study thrombotic APS.[86] *In vitro* studies employing different cellular sources such as endothelial and immune cells have been equally critical in demonstrating aPL pathogenicity.[49]

Pathogenesis of Obstetric Complications

Initial observations linking aPL with recurrent miscarriages were first reported more than 40 years ago.[30,31] The presence of aPL is probably the single most recognizable risk factor for recurrent pregnancy loss and late placenta-mediated obstetric complications. Obstetric complications in APS include the following: (1) recurrent miscarriages (≥3 unexplained consecutive spontaneous miscarriages before the 10th week of gestation) with no maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes; (2) one or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation with normal fetal morphology; (3) one or more premature births of a morphologically normal neonate before the 34th week of gestation due to eclampsia, severe preeclampsia, or placental insufficiency.[1] Placental thrombosis, inflammation, and complement activation all play major roles in the pathogenesis of obstetric APS.[87] The pathogenesis of obstetric APS probably differs from that of thrombotic APS, at least with recurrent early miscarriages as the placenta is not well formed at this stage. Therefore, thrombosis is unlikely to be the leading cause for this complication.[88] Complement activation may play a major role in early pregnancy loss, evident in mouse models where injection of purified IgG from patients with APS and recurrent miscarriage caused a marked increase in fetal death and low birth weight of the survived pups compared to those injected with IgG from women without APS. Inhibition of the complement cascade using a C3 convertase inhibitor or by antibodies or peptides that block C5a–C5a receptor interactions blocked these detrimental aPL effects in early pregnancy. Additionally, aPL failed to demonstrate the same effect in mice deficient in C3.[89,90] This observation was further strengthened by the finding that heparins prevent early obstetrical complications by blocking aPL-induced complement activation rather than by their anticoagulant effects.[91] However, placental thrombosis is a major contributor of late pregnancy complications as evident by histopathology findings of the placenta from women with late pregnancy complications showing features of thrombosis or infarction.[88]

Catastrophic Antiphospholipid Syndrome

CAPS is a rare (<1% of APS cases) but potentially life-threatening variant of APS characterized by multiple microvascular thromboses leading to multiorgan failure.[92] The most affected organs include the kidney, lung, central nervous system, heart, and skin. In 1992, Ronald Asherson of Cape Town, South Africa, first defined the term CAPS to describe such cases.[44] CAPS shares features with thrombotic thrombocytopenic purpura (TTP), disseminated intravascular coagulation (DIC), and systemic inflammatory response syndrome (SIRS) as seen in sepsis. Therefore, it is possible to cause both under- and overdiagnosis of CAPS. CAPS may be the first presentation of APS or may develop as a complication of previously diagnosed APS. There is often a trigger for the acute episode such as infection, surgery, or anticoagulant withdrawal.[93]

Progress in the Management of Thrombosis in Antiphospholipid Syndrome

Although APS is an autoimmune antibody-mediated disease, the initial management of acute thrombosis has been with

heparin and VKAs rather than immunosuppressive therapy. In early 1987, Bingley and Hoffbrand reported two patients with recurrent arterial thrombosis treated with warfarin who initially received steroids and azathioprine with no reduction in aCL levels.[94] Of the VKAs, warfarin is the predominant agent used and continues to be the mainstay of thrombotic APS treatment. In the 1990s, following observational data from case series that rethrombosis rate was particularly high in patients with APS compared to patients with other thrombotic diseases,[95,96] high intensity oral anticoagulation for the prevention of thrombosis in APS was promoted (i.e., achieving a target INR greater than moderate intensity INR [set at 2.0–3.0]). However, this was changed after two randomized controlled trials (RCTs) demonstrated that high-intensity warfarin (INR: 3.0–4.0) was not superior to moderate-intensity warfarin (INR: 2.0–3.0) for the prevention of recurrent thrombosis.[97,98] Nevertheless, there are some important limitations on these trials; for example, patients with arterial events were underrepresented.[97,98] A meta-analysis of the results from the two above RCTs showed a significantly higher rate of minor bleeding in patients allocated to high-intensity warfarin.[98] The Antiphospholipid Antibodies and Stroke Study (APASS) was a prospective cohort study comparing warfarin anticoagulation (target INR: 1.4–2.8) over aspirin (325 mg/day) in stroke prevention in patients with APS. This study found no benefit of anticoagulation with warfarin over aspirin.[99] However, major limitations of this study were testing aPL only at study entry, including IgA antibodies as laboratory diagnostic criteria, and the average age of the study cohort was higher than previous studies. All these limitations raise the possibility that some recruits may not have had APS. Therefore, it is not surprising that the optimal intensity of anticoagulation following arterial, as opposed to venous, thrombosis in patients with APS remains controversial. Practice to date can vary from VKAs with target INR of 2.0 to 3.0 or 3.0 to 4.0, single or dual antiplatelet agents, or a combination of VKAs and antiplatelet treatment.

Direct Acting Oral Anticoagulants

Direct factor Xa (rivaroxaban, apixaban, and edoxaban) and thrombin (dabigatran) inhibitors have become the standard anticoagulant over VKAs for patients with venous thromboembolism (but not APS) due to their fewer drug and food interactions, lower rate of intracranial bleeding, and more importantly no need for regular monitoring. The first successful RCT comparing DOAC (rivaroxaban) versus warfarin had its primary outcome as laboratory based rather than a clinical end-point; nonetheless, at 6-month follow-up, there was no recurrent thrombosis or major bleeding events were reported in either of the two arms.[100] However, data from three RCTs, systematic review, and meta-analysis of several case series and cohort studies reported inferiority of DOACs to warfarin in those with triple positive aPL.[101–105] Two clinical trials compared rivaroxaban versus warfarin,[101,105] while another compared apixaban versus warfarin.[102] Two of these three trials were terminated early due to excess of arterial thrombosis in patients treated with DOACs.[101,102] The uniform finding from all three trials was that patients treated with DOACs had a significantly higher rate of recurrent thrombosis, especially those with triple positive aPL. Recurrent events occurring in the arterial circulation included ischemic strokes and myocardial infarctions.

Following the findings from the TRAPS trial and its early termination in 2018,[101] the European Medicines Agency (EMA) and the Medicines and Healthcare Products Regulatory Agency (MHRA) recommended against the use of DOACs in thrombotic APS, especially those with triple positive aPL. The British Society for Haematology adopted a similar approach and recommended that DOACs should not be used for APS patients with triple positive aPL or a history of arterial thrombosis. Although there is insufficient evidence to make a strong recommendation for patients with non-triple positive (single or dual positive) APS with venous thrombosis, guidelines suggest using VKAs over DOACs in these patients as well.[106] A systematic review and meta-analysis of RCTs that compared DOACs versus VKAs including 4 open-label RCTs involving 472 patients demonstrated that DOAC treatment was associated with increased risk of arterial thrombosis (odds ratio [OR]: 5.43, 95% confidence interval [CI]: 1.87–15.75, $p < 0.001$, $I^2 = 0\%$), especially stroke, compared to VKA treatment.[107] However, there was no difference in the risk of subsequent venous thrombotic events between the two anticoagulants (OR: 1.20, 95% CI: 0.31–4.55, $p = 0.79$, $I^2 = 0\%$) or major bleeding (OR: 1.02, 95% CI: 0.42–2.47, $p = 0.97$, $I^2 = 0\%$).[107]

Management of Recurrent Thrombosis and Immunomodulation in APS

Despite standard anticoagulation with VKAs, a proportion of patients with APS develop recurrent thrombosis. For these patients, either increasing target INR from 2.5 (2.0–3.0) to 3.5 (3.0–4.0) or adding antiplatelet treatment to standard intensity warfarin is generally recommended. For a small proportion who develop recurrence with high-intensity INR or VKAs plus antiplatelet treatment, there are only limited alternative therapeutic options. These include changing to LMWH, including high-intensity LMWH (maintaining peak anti-Xa levels of 1.6–2.0 IU/mL for once-daily dosing and peak of 0.8–1.0 IU/mL for twice-daily dosing) or a combination of anticoagulation with immunosuppression and/or immunomodulation. Modalities including rituximab, HCQ, statins, rituximab, complement inhibitors, and mTOR inhibitors such as sirolimus have been used.[108] Out of these non-anticoagulant options, HCQ is the main interest at present. Its pleiotropic anti-inflammatory, anticoagulant, and antiplatelet effects support the hypothesis that it may act as successful adjunctive treatment in the prevention of recurrent thrombosis or pregnancy complications in APS.

In a prospective nonrandomized small study of 40 patients with primary APS, equal numbers were assigned to receive VKAs with HCQ 400 mg daily versus VKAs alone. Reduction in recurrent thrombosis was reported in patients treated with HCQ.[109] The two groups had comparable aPL profiles. Six recurrent venous thromboses (30%) were

detected in APS patients treated with VKAs alone, while none of the patients receiving VKAs and HCQ developed recurrent thrombosis during the follow-up period (up to 36 months) and none of patients became negative for aPL.[109] Currently, HCQ is used in patients with APS and refractory or recurrent thrombosis despite adequate anticoagulation and the European Medicines Agency has licensed its use for the treatment of APS as orphan medicinal product.[110]

Progress in the Management of Pregnancy Complications in the Antiphospholipid Syndrome

Based on early studies, if left untreated more than 90% pregnancies in women with APS can end up as miscarriage.[111] Immunomodulatory therapies including corticosteroids and intravenous immunoglobulin were tested for improving pregnancy outcomes in women with APS.[112,113] However, treatment with prednisone and aspirin was not effective in improving live birth rare but increased the risk of prematurity.[112] In 1997, Rai and colleagues published an RCT comparing aspirin alone with aspirin and subcutaneous unfractionated heparin (UFH) in women with recurrent miscarriage and persistently positive aPL. Treatment with aspirin and heparin resulted in a significantly higher rate of live births compared to aspirin alone.[114] This leads to assumption that the pathogenesis of pregnancy failure is also likely to involve a thrombotic process. However, early miscarriages occur prior to placentation; thus, heparin effects on improving live birth rates is potentially multifactorial, including its anticomplement and anti-inflammatory effects. This was later shown by observations made by Girardi et al that complement activation is important in recurrent early miscarriage and that heparin may be effective through inhibition of complement rather than its anticoagulant properties.[91]

A subsequent clinical trial studied 98 women with aPL and recurrent miscarriages, assigned to receive LDA (75 mg daily, 47 women) or LDA and LMWH (5,000 units subcutaneously daily, 51 women) throughout pregnancy. The live-birth rate was 72% in women received aspirin alone compared to 78% in women received combined treatment (OR: 1.39, 95% CI: 0.55, 3.47), indicating the addition of LMWH did not have significant effect in improving pregnancy outcome.[115] However, the use of heparin with LDA has become the standard of care in women with recurrent miscarriages or late pregnancy complications and LMWH is used instead of UFH due to its low risk of causing heparin-induced thrombocytopenia or osteopenia compared to UFH.[116]

Management of CAPS

As CAPS is a very rare presentation of APS, management is based on experience from case reports, case series, and expert opinions rather than evidence from clinical trials. Due to its high mortality despite aggressive treatment, a combination of treatments including parental anticoagulation (mainly UFH with monitoring of the anticoagulant effect by heparin anti-Xa levels rather activated partial thromboplastin time [APTT]), intravenous immunoglobulin, plasma exchange, immunosuppressive therapy with rituximab, prostacyclin, fibrinolytics, complement inhibitors, and defibrotide have all been used with variable success rates.[116,117] The CAPS Registry, an international registry for CAPS, was created in 2000 by the European Forum on Antiphospholipid Antibodies to collect clinical, laboratory, and therapeutic data from patients with CAPS. Analysis of data from 500 CAPS patients on the CAPS Registry showed that anticoagulation with heparin was associated with higher recovery rate (63%) versus no anticoagulation (22%, $p < 0.0001$). However, combination treatment with anticoagulation, high-dose steroids, plasma exchange, and/or intravenous immunoglobulins achieved the highest survival rate (71.4%).[118]

Management of Asymptomatic Carriers of aPL

There is evidence to suggest that individuals with aPL with no history of thrombosis should receive treatment toward primary thromboprophylaxis. A prospective observational study of 258 asymptomatic individuals with aPL determined the incidence and risk factors for a first vascular event. At median follow-up of 35 months, the annual incidence of thrombosis was 1.86% compared to 0.1% in the general population.[119] Hypertension and the presence of LA were independent risk factors for the development of thrombosis.[119] Another study included 104 individuals with triple aPL and reported an annual thrombotic rate of 5.3% with a cumulative incidence of 37.1% (95% CI: 19.9–54.3%) at 10 years. In this study, prophylaxis with aspirin had no significant benefit in reducing the incidence of thromboembolic events.[120] The Antiphospholipid Antibody Acetylsalicyclic Acid (APLASA) was a randomized controlled study with 98 individuals with aPL and no history of thrombosis allocated to receive aspirin (48 individuals) or placebo (50 individuals). There was no difference in the acute thrombosis incidence rates (2.75 per 100 patient-years for aspirin-treated vs. 0 per 100 patient-years for the placebo-treated subjects (hazard ratio: 1.04, 95% CI: 0.69–1.56; $p = 0.83$).[121]

An important question of whether individuals with triple positive aPL should receive primary thromboprophylaxis remains to be answered. It is our current local practice to give HCQ for triple positive aPL with no contraindication to receive such treatment. Irrespective of the aPL profile, all individuals should be given advice to improve the modifiable risk factors for thrombosis, such as smoking, hypertension, and diabetes which should be addressed adequately in all patients. Hypercholesterolemia should be treated with statins and dietary modifications.

Concluding Remarks

APS is an autoimmune prothrombotic disease mediated by heterogeneous group of aPL. Although there is a clear association between aPL with thrombotic and pregnancy complications with multiple pathogenic mechanisms involving several pathways, there are still many unknown areas in disease

pathogenesis. Despite the autoimmune nature of the disease, anticoagulation remains the mainstay of treatment for both thrombotic and obstetric APS. VKAs are the oral anticoagulant of choice for patients with thrombotic APS, especially those with triple positive aPL and arterial thrombosis, while LMWH and LDA are given to women with history of obstetric complications. Increasingly, benefit is reported with other agents such as the immunosuppressive HCQ for thrombotic and obstetric APS or biologics in CAPS. More recently, the first phase II, prospective open label trial for the biologic belimumab, a B cell inhibiting agent recently approved in SLE, has been launched for patients with refractory APS and/or those showing non-criteria manifestations such as livedo reticularis.[122] Such efforts to introduce novel agents in our treatment artillery are promising and will undoubtedly spearhead additional studies toward advancing APS management.

Authors' Contributions

D.J.A. designed the manuscript. Both D.J.A. and C.P. wrote, reviewed, and approved the final manuscript.

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