Review
Antiphospholipid syndrome

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Abstract

Antiphospholipid syndrome is diagnosed when arterial or venous thrombosis or recurrent miscarriages occur in a person in whom laboratory tests for antiphospholipid antibodies (anticardiolipin antibodies and/or lupus anticoagulant and/or anti-beta 2-glycoprotein I) are positive. Despite the strong association between antiphospholipid antibodies and thrombosis, their pathogenic role in the development of thrombosis has not been fully elucidated. Novel mechanisms involving both the complement pathway and microparticles have been described. The knowledge of these new pathogenic approaches might identify novel therapeutic targets and therefore may improve the management of these patients.

Introduction

Antiphospholipid syndrome (APS) is characterized by venous or arterial thromboses, fetal losses and thrombocytopenia, in the presence of antiphospholipid antibodies (aPL) (namely lupus anticoagulant (LA)), anticardiolipin antibodies (aCL) or antibodies directed to various proteins, mainly beta 2-glycoprotein I (β_2GPI), or in the presence of all three [1].

Despite the strong association between aPL and thrombosis, the pathogenic role of aPL in the development of thrombosis has not been fully elucidated. The aPL have been implicated in reactions that interfere with almost all known hemostatic and endothelial cell reactions [2]. Some evidence regarding the effect of aPL on the complement has been described recently, and related to pregnancy complications and thrombosis [3]. Given the heterogeneity of clinical manifestations in APS it is likely that more than one pathophysiological process may play a role.

Regarding the clinical spectrum of APS, any combination of vascular occlusive events may occur in the same individual and the time interval between the events also varies considerably from weeks to months or even years. Deep vein thrombosis is the most frequently reported manifestation in this syndrome, whereas cerebrovascular accidents are the most common arterial thrombotic manifestations. Early and late fetal losses, premature births and pre-eclampsia are the most frequent fetal and obstetric manifestations [4]. Additionally, several other clinical features such as thrombocytopenia, *livedo reticularis*, and heart valve lesions are relatively common in these patients. Finally, a large variety of unusual clinical manifestations, with prevalence <5%, have been described in APS patients. These unusual manifestations include, among others, large peripheral artery occlusions, chorea, transverse myelopathy, adult respiratory distress syndrome, and avascular necrosis of the bone [5].

With respect to the treatment of APS, there is consensus in treating patients with APS and first venous thrombosis with oral anticoagulation to a target International Normalized Ratio of 2.0 to 3.0 [6]. A recent systematic review recommended a target International Normalized Ratio >3.0 in the group of patients with APS and arterial thrombosis [7]. The approach for women with obstetric manifestations of APS is based on the use of aspirin plus heparin [8].

The aim of the present review is focused on some recent aspects of pathogenesis, clinical manifestations, and treatment of APS.

Pathogenetic mechanisms in APS
Induction of antiphospholipid antibodies

Which are the factors involved in the production of aPL? The aPL are not directed against phospholipids, but against a wide variety of phospholipid-binding proteins (also named cofactors). β_2GPI is the most important antigenic target of aPL [9]. Moreover, it seems that only aPL with high affinity for β_2GPI are pathologically relevant.

Infectious agents have been related with the production of aPL. Many infections may be accompanied by increases in aPL and, in some cases, by clinical manifestations of APS. It has been shown that aPL may be synthesized by B-cell clones cross-reacting with epitopes expressed on infectious

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aCL = anticardiolipin antibodies; aPL = antiphospholipid antibodies; APS = antiphospholipid syndrome; β_2GPI = beta 2-glycoprotein I; LA = lupus anticoagulant; NF = nuclear factor; TLR = Toll-like receptor; TNF = tumor necrosis factor.

agents as the result of a molecular mimicry between exogenous molecules and β_2GPI [10]. Anti-β_2GPI antibodies have been shown to recognize β_2GPI peptides displaying molecular mimicry with common bacteria and viruses, both at the level of the amino acid sequence and of the conformational structure. Such a homology was suggested to represent the rationale for the possible infectious origin of the syndrome.

It could be possible that other environmental factors, such as drugs or neoplasms, might be responsible for inducing aPL. In cancer, the accumulation of many cells is a result of excessive cell proliferation and/or insufficient apoptosis. One of the earliest changes in cells undergoing apoptosis is the exposure of phosphatidylserine on the outer membrane leaflet. A key link between apoptosis and the onset of autoimmunity is provided by autoantibodies that bind apoptotic cells and recognize surface epitopes that include complexes of phospholipid and β_2GPI. It is possible that autoantibodies to malignant cells arise secondary to changes in the cell membrane inducing exposure of certain antigens that are normally facing the intracellular compartment [11].

Moreover, the presence of aPL is linked to genetic predisposition, which may be associated, at least in part, with genes of the major histocompatibility complex (HLA system) [12]. Regarding the genetics of β_2GPI, there is evidence that the Val247 allele may be one of the genetic risk factors for development of APS – although the results are contradictory. Yasuda and colleagues found that the Val247 β_2GPI allele was associated with both a high frequency of anti-β_2GPI antibodies and stronger reactivity with anti-β_2GPI antibodies [13]. On the other hand, Camilleri and colleagues found no association between the Val/Leu247 polymorphism and the presence of anti-β_2GPI in a white population [14]. Exposure to one or more environmental agents, such as infections, in a genetically susceptible individual, through a molecular mimicry, can result in the production of pathogenic aPL that can induce thrombosis and pregnancy loss.

Another hypothesis explains the existence of natural autoantibodies that develop for a good purpose (infectious theory) but may evolve to become pathogenic under certain adverse conditions such as oxidant stress. Antiphospholipid antibodies have been found in approximately 12% of elderly populations and in some 2% of younger populations. Some evidence favors natural autoantibodies perhaps having specific regulatory functions in the immune system. In accordance with these observations, it may be possible that autoantibodies are not pathological forms of immunity but, under aberrant vascular conditions such as oxidant stress, they lose their normal functions, leading to autoimmunity [15].

Pathogenic role of β_2GPI–antibody complex
β_2GPI is a highly glycosylated single-chain protein that is present in plasma without known physiological function. The protein avidly binds to negatively charged phospholipids such

as cardiolipin, phosphatidylserine, or phosphatidylinositol. Upon phospholipid binding, β_2GPI changes conformation and exposes a cryptic epitope to which high-affinity antibodies can bind [16]. β_2GPI is subsequently dimerized by the autoantibodies and is probably fixed in an activated conformation. Furthermore, this complex integrated by the anionic phospholipid, β_2GPI, and antibody is able to interact with hemostatic reactions and several cellular receptors [17] (Figure 1). Several animal models immunized with the cofactor β_2GPI developed clinical manifestations of APS, including fetal loss, thrombocytopenia, and neurological and behavioral dysfunction [18].

*Effect of β_2GPI–antibody complex on hemostatic reactions*
The aPL may alter the kinetics of the normal procoagulant and anticoagulant reactions by cross-linking membrane-bound proteins, by blocking protein–protein interactions, and/or by blocking the access of other proteins to the phospholipid membrane. In this sense, interference has been described in the form of inhibition of aPL on the anticoagulant reactions, such as inhibition of the protein C pathway, of protein S activity, or of antithrombin activity.

Furthermore, aPL may present with impaired fibrinolysis, as indicated by increased plasma levels of plasminogen activator inhibitor 1 and tissue-type plasminogen activator antigens [3]. Thrombin, tissue-type plasminogen activator, and activated protein C, which are involved in hemostasis, belong to the serine protease superfamily. Some aCL were recently demonstrated to bind to their homologous catalytic domains, suggesting that some aCL recognize a conformational epitope shared by β_2GPI and the homologous catalytic domain of several serine proteases [19].

Cellular activation by β_2GPI–antibody complex in APS
β_2GPI–antibody complex is able to bind several cell types, such as endothelial cells, monocytes, and platelets. Annexin A_2, a potent fibrinolytic receptor, has been suggested as the receptor of β_2GPI on the membrane of endothelial cells. This receptor is able to bind monomer β_2GPI, without the need for the presence of anti-β_2GPI antibodies [20]. Taking into account that annexin A_2 is a membrane-bound protein without a transmembrane domain, it could not transmit signals across the cell membrane. Other unknown receptors must therefore be involved in the activation of endothelial cells.

There is evidence that Toll-like receptor (TLR) signaling pathways are involved in endothelial activation by β_2GPI–antibody complex. Because common microbial structures do represent the natural ligand for TLRs, it has been speculated that β_2GPI might interact with TLRs and that β_2GPI–antibody complex – recognizing the molecule – might cross-link it together with TLRs. In this sense, endothelial activation in APS has been described to be mediated through TLR4, resulting in a prothrombotic (upregulation of tissue factor) and proinflammatory phenotype (synthesis and secretion of

Figure 1
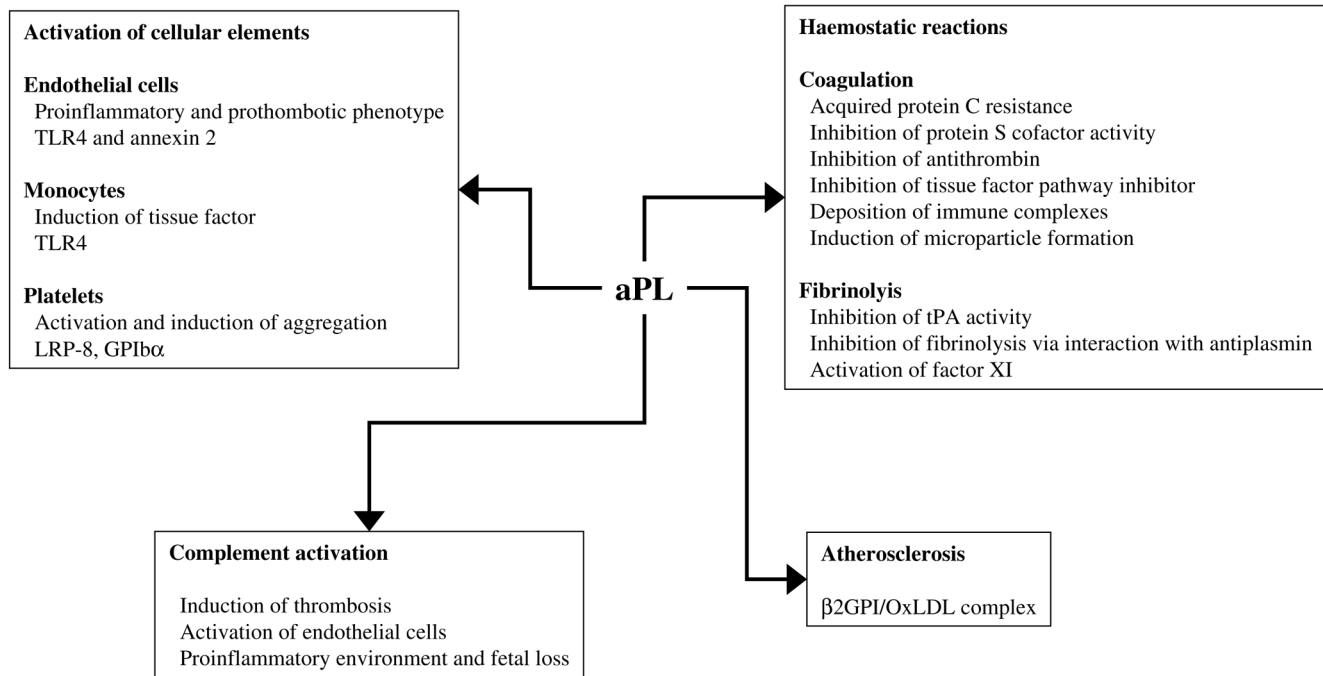
Main current pathogenetic views of antiphospholipid antibodies. aPL, antiphospholipid antibodies; β_2GPI/OxLDL, beta 2-glycoprotein I/oxidized low-density lipoprotein; GPIbα, glycoprotein Ibα; LRP-8, low-density lipoprotein receptor-related protein 8; tPA, tissue-type plasminogen activator; TLR4, Toll-like receptor 4.

adhesion molecules and proinflammatory cytokines) [21]. Moreover, APS can be mediated through pathways involving activation of NF$\kappa\beta$ and phosphorylation of p38 mitogen-activated protein kinase [21]. In this sense, Raschi and colleagues have demonstrated the involvement of MyD88 and TRAF6, molecules depending on TLR4, in this endothelial activation [22].

Monocytes have also been activated by β_2GPI–antibody complex. The activation of monocytes allows the tissue factor upregulation in APS [23]. Lopez-Pedrera and colleagues suggested that the intracellular signaling involved the simultaneous activation of NF$\kappa\beta$/Rel proteins via the p38 mitogen-activated protein kinase pathway and of the MEK-1/ERK pathway [24]. More recently, Sorice and colleagues demonstrated an interaction between β_2GPI, annexin A$_2$, and TLR4 in lipid rafts in the human monocyte plasma membrane [25]. In addition, they illustrated the role of the NF$\kappa\beta$-dependent signaling involving TLR4 and interleukin-1 receptor-associated kinase, similar to the situation in endothelial cells.

Platelet activation in APS is mediated by at least two receptors, the low-density lipoprotein receptor-related protein 8 (also known as apolipoprotein E receptor 2′) and the platelet adhesive receptor glycoprotein Ibα [26]. It is unclear why two receptors are necessary for the platelet activation by

β_2GPI–antibody complex. Subsequently, in the presence of subactivating doses of thrombin, β_2GPI–antibody complex induces the production of thromboxane B$_2$ mainly through the activation of p38 mitogen-activated protein kinase and subsequent phosphorylation of cytosolic phospholipase A$_2$ [27].

The wide distribution of thrombosis in APS may be explained by the widespread distribution of the membrane receptors involved in the cellular activation.

Effect of β_2GPI–antibody complex on trophoblast cells
Not all placentae from women with fetal losses and aPL have signs of thrombosis or infarction. This finding allows the hypothesis that aPL have a direct effect on human placental trophoblast. In this sense, aPL have demonstrated *in vitro* their effect on the trophoblast. Specifically, aPL may interfere in trophoblast binding, reduce their proliferation and invasiveness and the human chorionic gonadotrophin release, and increase apoptosis. In addition, expression of β_2GPI on trophoblast cell membranes has been demonstrated, explaining the aPL placental trophism. The reactivity between aPL and trophoblasts induces a proinflammatory state with cytokine secretion and complement activation (see below) [28]. As a consequence, aPL-mediated inflammatory processes may induce a defective placentation without thrombosis.

Is there inflammation in APS?

There is some evidence supporting the existence of a proinflammatory environment in APS [29]. The aPL-induced endothelial proinflammatory response is characterized by adhesion molecule (vascular cell adhesion molecule 1 and E-selectin) upregulation and by proinflammatory cytokine and chemokine synthesis and secretion. In addition, an increased adhesion of leukocytes to activated endothelium has been demonstrated [30]. Taking into account that leukocytes are important sources of tissue factor, this inflammatory response could play a role in the pathology of APS. However, no histological signs of vascular inflammation can usually be found in APS patients. In fact, the absence of inflammation in the vessel wall is required for APS diagnosis [1]. At present, the precise role of this inflammatory response has not been fully elucidated.

Role of complement in APS

The complement system has been recently involved in the development of thrombosis and fetal loss in APS [31]. Tissue injury in APS might be caused by a complement-mediated inflammatory process, rather than by thrombosis alone. Complement activation may supply the thrombophilia features of APS. As C5a is an important mediator of the inflammatory response, it is possible that inflammation is involved in the pathogenic mechanisms of β_2GPI–antibody complex. Some data support this relationship. Activated complement fragments themselves have the capacity to bind and activate inflammatory and endothelial cells, either directly through C5b–9 (membrane attack complex) or through C5a receptor-mediated effects. In addition, endothelial cells can release tissue factor in response to C5a activation [32]. In this sense, Pierangeli and colleagues demonstrated that complement activation mediated two important effectors of aPL: induction of thrombosis and activation of endothelial cells [33]. Oku and colleagues demonstrated recently that hypocomplementemia is frequent in patients with primary APS, reflecting complement activation and consumption, and was correlated with anticoagulant activity [34]. Taken together, these findings suggest that aPL may activate monocytes and macrophages via anaphylatoxins produced in complement activation.

The other very important point is the role of complement activation in the pathogenesis of fetal losses in APS. In this field, data from *in vitro* studies performed by the group of Salmon and colleagues are of capital value [35,36]. According to their work, β_2GPI–antibody complexes are preferentially targeted to the placenta where they activate complement via the classical pathway. The complement cascade is initiated, leading to generation of C5a and C3a, recruitment and activation of neutrophils, monocytes and platelet cells, and release of inflammatory mediators, including reactive oxidants, tissue factor, proteolytic enzymes, cytokines such as TNFα, and complement factors. This proinflammatory environment enhances oxidative burst, causing trophoblast injury and pregnancy loss. Depending on

the extent of the damage, either death *in utero* or fetal growth restriction ensues. Moreover, the same group demonstrated that heparins prevent obstetric complications caused by β_2GPI–antibody complex because they block activation of complement [37].

Relationship between atherosclerosis and APS

The issue of the association between β_2GPI–antibody complex and atherosclerosis remains unresolved [38]. Whereas *in vitro* studies have shown that β_2GPI–antibody complex is associated with endothelial perturbation, and cross-reaction with oxidized low-density lipoproteins [39], evidence for this association from clinical studies is scarce [40]. Furthermore, β_2GPI–antibody complex was not related to the presence of atherosclerosis in patients with systemic lupus erythematosus [41].

Microparticles as pathogenic mechanism of thombosis in APS

In response to activation or apoptosis, remodeling of the membrane phospholipid bilayer of all eukaryotic cells is associated with the release of microparticles – defined as small vesicles that are membrane-coated and released from the plasma membrane by exocytic budding. These vesicles express negatively charged phospholipids and cell surface antigens characteristic of the cells of origin [42]. Surface exposure of phosphatidylserine or tissue factor activity provides a catalytic surface that supports the assembly of clotting enzymes complexes, leading to thrombin generation.

Numerous studies have found elevated levels of micro-particles associated with prothrombotic or proinflammatory disorders. Indeed, the levels of endothelial cell microparticles in patients with LA were increased compared with those of healthy control individuals. Moreover, the microparticle count was higher in patients with thrombotic complications than in those without [43]. Pereira and colleagues, however, did not find an association of circulating microparticles in plasma of systemic lupus erythematosus patients with disease activity or an association with the presence of aPL [44]. The role of generation of procoagulant endothelial microparticles in the pathogenesis of thrombosis in APS therefore remains unknown.

Clinical aspects of APS

The classical clinical picture of APS is characterized by venous, arterial or small vessel thrombosis, fetal losses, and thrombocytopenia, in the presence of aPL. Deep vein thrombosis is the most frequently reported manifestation in this syndrome. Conversely, cerebrovascular accidents are the most common arterial thrombotic manifestations. Early fetal loss, late fetal loss, premature births, and pre-eclampsia are the most frequent fetal and obstetric manifestations [45].

In spite of the persistence of aPL, clinical manifestations of APS only appear occasionally. The aPL are not able to

produce their effects by themselves, and they need a priming factor. This fact has been demonstrated *in vitro* by Fischetti and colleagues [31]. They showed a growing thrombus after infusion of aPL in rats only after a prior stimulation with intra-peritoneal lipopolysaccharide. *In vivo*, Vega-Ostertag and colleagues demonstrated platelet aggregation induced by aPL only in the presence of suboptimal doses of thrombin [46]. These priming factors might be the initial step in inducing cellular activation by aPL.

Nonthrombotic manifestations of APS

Other clinical manifestations, not directly associated with the presence of underlying thrombotic lesions, have been less frequently described in patients with APS. For instance, some neurologic manifestations such as cognitive dysfunction or demyelinization might be related to aPL–cellular interactions, possibly because of a disrupted blood–brain barrier or an increased intrathecal synthesis of aPL [47]. Experimental studies have demonstrated the inhibition of astrocyte proliferation and the nonspecific permeabilization and depolarization of synaptoneurosomes induced by aPL. Furthermore, not only thrombotic occlusion of capillaries but also a combination with mild inflammation were the main findings in mouse brain tissue examination.

The exact etiologic role of aPL in APS-associated transverse myelitis remains to be established. A direct interaction between aPL and cellular elements of the central nervous system, rather than aPL-associated thrombosis, seems to be a more plausible mechanism. Patients with an APS-related transverse myelitis, especially those with recurrent episodes, may have an unrecognized myelin-specific antibody.

Pulmonary capillaritis, not thrombosis, appears to be the predominant pathology of the APS patients with diffuse alveolar hemorrhage. Deane and West provide a speculative hypothesis to explain the development of vasculitis as the etiology of this entity [48]. In accordance with their hypothesis, aPL-induced upregulation of endothelial cell adhesion molecules with subsequent neutrophil recruitment and migration into the alveolar septae may induce tissue destruction and hemorrhage. The C5a-mediated neutrophil activation may contribute to this tissue injury [3].

Another example of inflammation as a basis of pathogenic mechanisms of aPL is the abovementioned role of complement in fetal losses in APS patients [49]. In short, complement activation products may cause an imbalance of angiogenic factors required for normal pregnancies. Insufficient placental vasculature has been associated with obstetric problems [3].

Catastrophic APS

A small number of patients suffer from a potential life-threatening variant of APS – catastrophic APS, characterized by multiple small vessel thromboses that can lead to multiorgan failure [50]. Catastrophic APS is an unusual form of presentation that represents <1% of APS cases. Patients with catastrophic APS, however, usually end-up in a life-threatening situation [51].

In the recent paper from Bucciarelli and colleagues, the mortality has clearly fallen by some 20% [52] – due, in all probability, to energetic and early therapies such as plasma exchange, intravenous immunoglobulin, full anticoagulation, and parenteral steroids (Figure 2). The disorder is characterized by a diffuse thrombotic microvasculopathy, with micro-thrombosis being the main finding of necropsy studies [52].

The mechanisms of causation and pathogenesis of catastrophic APS are not completely understood. A possible mechanism for catastrophic APS is the systemic inflammatory response syndrome, which is presumed to be due to excessive cytokine release from affected and necrotic tissues. Catastrophic APS is characterized by multiple microvascular thrombotic events, of rapid onset, causing multiorgan failure – a picture suggestive of septic shock in which there is a massive, acute inflammatory response. At present, this hypothesis remains theoretical.

Microangiopathic APS

The term microangiopathic APS has been introduced recently to refer patients with aPL and clinical features of thrombotic microangiopathy, such as thrombotic thrombocytopenic purpura or hemolysis, elevated liver enzymes, and low platelet count syndrome [53]. There is usually accompanying hemolytic anemia, often severe thrombocytopenia, and the presence of schistocytes. At present, it is suggested that the aPL detected in this group of patients may be generated by endothelial cell perturbation and damage.

Therapeutic aspects of APS

In accordance with a recent systematic review, patients with definite APS with first venous thrombosis have to be treated with prolonged oral anticoagulation at a target International Normalized Ratio of 2.0 to 3.0 and >3.0 for those with recurrent and/or arterial events [7]. The approach for women with obstetric manifestations of APS is based on the use of aspirin plus heparin [8]. Aspirin in monotherapy, however – best started before conception – still has a role to play in particular patients such as those with recurrent early miscarriages [54].
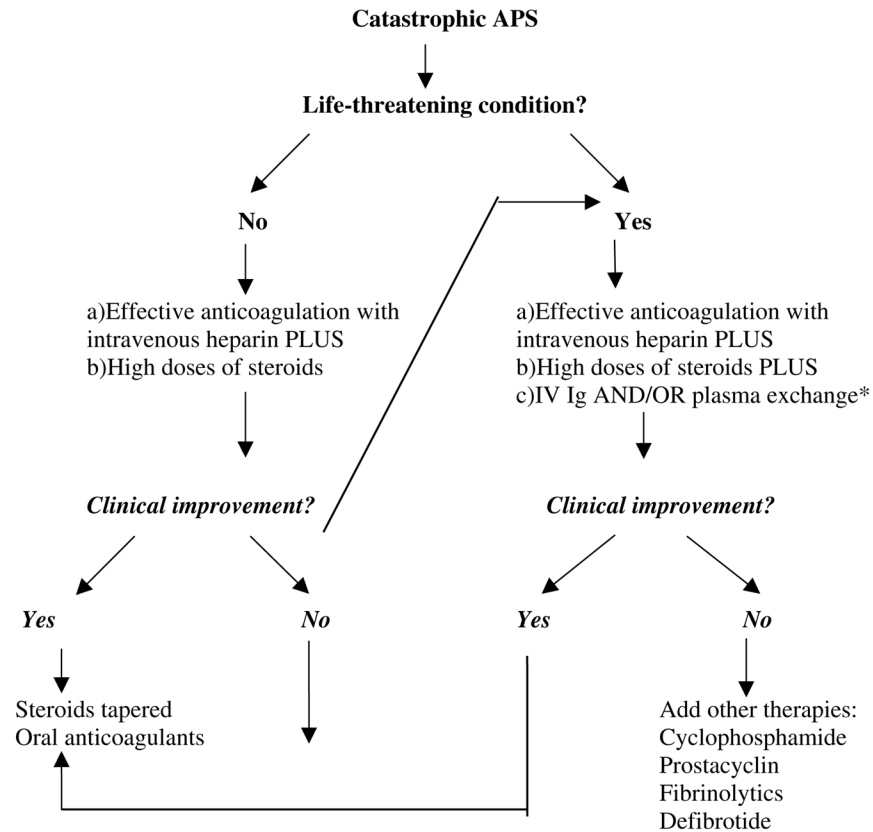
How can the treatment of APS patients be improved?

One important and novel aspect of APS is that patients should be stratified and treated according to some clinical and immunologic characteristics in addition to the aPL positivity [1].

Additional vascular risk factors
It is advisable to categorize APS patients according to the presence or not of classic thrombophilic risk factors such as hypertension, diabetes mellitus, hypercholesterolemia, or tobacco use because they may contribute to modifications in

Figure 2

Catastrophic APS

↓

Life-threatening condition?

No

a)Effective anticoagulation with intravenous heparin PLUS
b)High doses of steroids

↓

Clinical improvement?

Yes   *No*

↓

Steroids tapered
Oral anticoagulants

Yes

a)Effective anticoagulation with intravenous heparin PLUS
b)High doses of steroids PLUS
c)IV Ig AND/OR plasma exchange*

↓

Clinical improvement?

Yes   *No*

Add other therapies:
Cyclophosphamide
Prostacyclin
Fibrinolytics
Defibrotide

Treatment algorithm of catastrophic antiphospholipid syndrome. *Specially indicated if schistocytes are present. APS, antiphospholipid syndrome; IV Ig, intravenous immunoglobulins.

the eventual risk factor profile [55]. Close control of these factors has to be an important clue in the management of patients with APS and thrombosis. In addition, it is also important to take into account whether the patient has an inherited thombophilia.

Profile of antiphospholipid antibodies
Patients with LA, aCL IgG at high titers, or anti-β_2GPI antibodies plus LA or aCL have the highest thrombotic risk [9]. Closer clinical and therapeutic monitoring (to ensure a correct International Normalized Ratio) is advisable in patients with thrombosis and any of these immunological profiles. In the newly revised classification criteria for APS, it is advisable to classify APS patients into different categories according to their aPL profile [1]. There is no evidence, however, for the effectiveness of more intensive therapy in these patients.

Persistence of antiphospholipid antibody positivity
Another point to bear in mind is the profile and the persistence of aPL positivity with time. At present, there is no evidence for the usefulness of repeat aPL testing on patients who meet the criteria for APS. A recent prospective study in

patients with systemic lupus erythematosus, however, has demonstrated that LA-positive patients had a highly increased risk of thrombosis, both at the arterial and venous levels. Interestingly, LA-negative patients with persistently positive aCL (defined as positive in more than two-thirds of the determinations) had increased risk of thrombosis at the expense of arterial events, whereas in LA-negative and transiently aCL-positive patients (defined as positive on at least two occasions but on less than two-thirds of the determinations) the risk of thrombosis – both arterial and venous – was no different from that in aPL-negative systemic lupus erythematosus patients [56]. Similar results were obtained by our group in patients with APS [57]. The adjusted risk for recurrent thrombosis during follow-up was increased in persistently positive aPL patients (defined as >75% of the aPL determinations positive during follow-up) compared with transiently positive aPL patients. The profile of persistently positive aPL related with the appearance of thrombosis during follow-up was the combination of aCL IgG plus LA. The role of high aCL titers (≥40 GPL or MPL), a laboratory criterion for APS diagnosis, in the recurrent thrombosis risk was not performed in these two studies.

These findings open the door to identify a subset of APS patients in which the aPL test turns repeatedly negative and who possibly are no longer at increased risk for thrombosis. Although the anticoagulation withdrawal may be safe in APS patients when aCL antibodies become negative [58], further evidence describing the clinical importance of a disappearance of aPL is needed to recommend this approach.

The dark zone
Although a set of classification criteria has been established to stratify the thrombotic risk of APS, some patients present diagnostic and therapeutic dilemmas. One example of this is the patient with thrombosis and repeated low titers of aCL or anti-β_2GPI antibodies and negative LA. In this case, the diagnostic problem is due to the absence of data to establish the threshold between moderate–high levels and low levels. From the therapeutic point of view, commonsense dictates the need for anticoagulation in a similar manner to a patient who follows the laboratory criterion of APS. Another important diagnostic problem is to know the sensitivity and the specificity of some clinical features such as *livedo reticularis*, nonbacterial thrombotic endocarditis, seizures, or nephropathy. The recently updated classification criteria for APS indicate that these clinical characteristics are frequently related with aPL. Their inclusion as classification criteria for definite APS, however, may decrease the diagnostic specificity [1]. Using commonsense, faced with a patient with renal thrombotic microangiopathy and persistent positivity for aPL, we have to act as is suitable for classic APS; that is, initiate long-term anticoagulation.

Another interesting group of patients who represent diagnostic problems is constituted of those with classic features of APS whose tests remain persistently negative. These patients suffer from the named seronegative APS, and anticoagulation is required [59].

Apart from these diagnostic controversies, the second dark point is the therapeutic approach in asymptomatic carriers of aPL. Based on current evidence, it seems very important to stratify these individuals according to the presence of traditional congenital or acquired procoagulant risk factors, the coexistence of an underlying autoimmune disease (systemic lupus erythematosus in particular), and the profile of aPL (persistently positive aCL and/or anti-β_2GPI antibodies at moderate/high titers and/or unequivocal LA) to consider a primary prophylactic therapy with low-dose aspirin (75 to 100 mg daily) [60]. In addition, cessation of estrogen-containing oral contraceptive use, treatment of vascular risk factors if present, and the avoidance of smoking are all additional recommended therapeutic measures. Prophylaxis with heparin administered subcutaneously should certainly be given to cover higher-risk situations, such as surgery. Moreover, hydroxychloroquine may be protective against the development of thrombosis in aPL-positive patients with systemic lupus erythematosus.

The future
The extensive knowledge of new pathogenic mechanisms of aPL allows the identification of potential therapeutic targets in APS patients [61]. In this sense, statins that have shown anti-inflammatory properties inhibiting the aPL-mediated increase of tissue factor in cultured human endothelial cells and angiotensin-converting enzyme inhibitors that inhibit the monocyte tissue factor expression might have a role in the armamentarium of APS in the future. The inhibition of complement, NF$\kappa\beta$, and p38 mitogen-activated protein kinase will probably open new therapeutic possibilities in these patients.

The molecular mimicry between bacterial or viral antigens and certain regions of the β_2GPI structure to explain the induction of aPL from infectious agents is the basis for using synthetic peptides to inhibit the thrombogenic properties of aPL [62]. A similar method is performed by β_2GPI toleragen. In this case, a polyvalent conjugate of recombinant domain I of human β_2GPI cross-links with specific surface immunoglobulins to target and induce tolerance in B cells to β_2GPI.

Competing interests
The authors declare that they have no competing interests.

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