Management of antiphospholipid syndrome

Nicoletta Del Papa and Nikoleta Vaso

Abstract: The antiphospholipid syndrome (APS) is an autoimmune disorder presenting with tissue injury in various organs related to large- or small-vessel thrombosis associated with antiphospholipid and antiprotein/phospholipid complex antibodies. Although the pathophysiology, diagnosis, and clinical scenario may seem clear and straightforward, a more detailed examination reveals a more complex and uncertain picture related to the management of APS. This article reviews the current situation relating to APS therapy by evaluating the different clinical features of the syndrome ranging from thrombosis to pregnancy complications together with new strategies and pharmacological approaches.

Keywords: anti-phospholipid syndrome, anti-phospholipid antibodies, anti-phospholipid therapy

Introduction

The antiphospholipid syndrome (APS) is an acquired autoimmune thrombophilic disorder characterized by vascular thrombosis and/or pregnancy failure in the presence of a persistent detection of antiphospholipid (aPL) antibodies. The syndrome may occur alone (primary APS) or in the presence of other autoimmune rheumatic diseases, most commonly systemic lupus erythematosus (SLE). Single-vessel involvement or multiple vascular occlusions may give rise to a wide variety of clinical presentations. In addition, it has often been assumed that recurrent thrombotic events occur in the same distribution of arterial or venous events, but any combination of vascular occlusive events may occur in the same patient at any point in the clinical history [Miyakis *et al.* 2006]. Preliminary, recently revised, classification criteria are a widely used consensus definition of APS (Table 1) [Miyakis *et al.* 2006]. These criteria were not meant to supplant the physician's clinical judgment in making a diagnosis in any particular patient, but to define the essential features of APS in order to facilitate studies on the pathogenesis and therapy.

The management of aPL-positive patients is focused on antithrombotic therapies and the acute management of thrombosis in APS patients is no different to the management of thrombosis in the general population. However, the variety of clinical presentations together with the heterogeneity of the aPL antibodies (and related assays)

make it difficult to give definite therapeutic guidelines for the treatment of APS. All these features and the difficulties in recruiting large numbers of patients undermine the conclusions of randomized controlled trials (RCTs). Likewise, observational studies have methodological limits that make it difficult to use them to develop a correct formula for the management of APS.

Management of thrombosis

After a first episode of thrombosis, patients with aPL antibodies have a higher risk of recurrent thrombosis than patients without the antibodies. Retrospective studies suggest that patients with aPL antibodies have a lower risk of recurrent thrombosis with an unusually high intensity of anticoagulant therapy (i.e. international normalized ratio (INR) 3.1–4.5) [Khamashta *et al.* 1995]. However, RCTs did not confirm this conclusion showing that the use of moderate-intensity warfarin (target INR 2.5, range 2–3) is at least as safe and efficacious as higher intensity anticoagulation, at least after an aPL antibody-related venous event [Finazzi *et al.* 2005; Crowther *et al.* 2003]. The optimal regimen for arterial thrombosis is less clear. Only, the Antiphospholipid Antibodies and Stroke Study [APAS Foundation Writing Committee, 2004], a prospective cohort study that focused on arterial cerebral events and compared warfarin (INR 1.4–2.8) and aspirin (325 mg/day) for the prevention of recurrent stroke, showed that both are useful in patients with first ischemic stroke and a single positive aPL detection. [Lim, 2004].

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Table 1. Updated clinical and laboratory criteria.

Clinical criteria

Vascular thrombosis

- One or more clinical episodes of arterial, venous, or small vessel thrombosis in any tissue or organ confirmed by imaging studies, Doppler studies, or histopathology (without significant vessel wall inflammation).
- Pregnancy morbidity (normal morphology on ultrasonography or direct examination findings)
- One or more unexplained fetal deaths at more than 10 weeks gestation.
- One or more premature births at less than 34 weeks gestation due to severe pre-eclampsia, eclampsia, or placental insufficiency.
- Three or more unexplained consecutive spontaneous abortions at less than 10 weeks gestation, excluding maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes.
- In research studies of patient populations that contain more than one type of pregnancy morbidity, investigators are strongly encouraged to stratify subjects according to the three groups above.

Laboratory criteria

- Anticardiolipin antibody of the immunoglobulin G (IgG)/immunoglobulin M (IgM) isotype in medium/high titer (>40 IgG phospholipid units [GPL], >40 IgM phospholipid units [MPL], or >99th percentile) on two or more occasions at least 12 weeks apart (measured by a beta2-GPI-dependent enzyme-linked immunosorbent assay).
- Lupus anticoagulant on two or more occasions at least 12 weeks apart, according to the guidelines set out by the International Society of Thrombosis and Hemostasis Scientific Subcommittee on Lupus Anticoagulants/Phospholipid-dependent Antibodies.
- Prolonged phospholipid-dependent coagulation (e.g. activated partial thromboplastin time, Kaolin clotting time, dilute Russell viper venom test, dilute PT test).
- Failure to correct the prolonged coagulation time by a mix with platelet-poor plasma.
- Shortening or correction of the prolonged coagulation time with excess phospholipids.
- Exclusion of other coagulopathies (e.g. factor VIII inhibitor, heparin).

All the available studies regarding the prevention of thrombotic events in aPL-positive patients contain important restrictions mostly related to the characteristics of the patients recruited (venous thromboembolism together with stroke) and the methods and time for aPL antibody determination (i.e. single detection, low titers of anticardiolipin (aCL), isotype of aCL considered, lupus anticoagulant (LA) treatment not performed according to international recommendations). Thus, the right therapeutic choice in a patient with aPL antibody-related thrombosis is often difficult and gives rise to uncertainty. A recent systematic review by Ruiz-Irastorza and colleagues [2007a] made some important points by reviewing published data on the secondary prophylaxis of thrombosis in APS. This review, even if limited by the heterogeneity of the selected studies (i.e. small numbers of patients, type of patients included, uncontrolled therapeutic choices, interpretation of results, no control groups), included both observational studies and RCTs, and indicates some important clinical conclusions:

- (1) patients with APS and a venous thromboembolic event should be treated with indefinite warfarin therapy to an INR of 2–3;
- (2) patients with definite APS and arterial thrombosis and/or recurrent venous events should be treated with indefinite warfarin therapy to an INR >3;

- (3) patients with venous thromboembolism or arterial thrombosis and a single positive aPL detection, not confirmed by following determinations, should be treated no differently to the general population (warfarin therapy to an INR of 2–3 and aspirin, respectively).

The association of aspirin in the patients with recurrent thromboembolic events while on anticoagulant therapy is still a matter of some controversy and there are no consistent data to recommend it.

Finally, in the management of APS, we should consider both the individual thrombotic risk related to the aPL-antibody profile and the presence of traditional vascular risk factors for thrombosis. Regarding the immunological subset, LA-positive patients have the highest risk of thrombosis [Galli *et al.* 2003] and the risk is further increased by the concomitant positivity for aCL or anti-b2glycoprotein I antibodies [Martinez-Berriotxo *et al.* 2007; Forastiero *et al.* 2005]. The transient positivity for aCL antibodies does not increase the thrombotic risk [Martinez-Berriotxo *et al.* 2007].

Management of pregnancy

Women with the APS are at increased risk for miscarriages and recurrent fetal loss, especially after 10 weeks of gestation [Ruiz-Irastorza,

2007]. In addition, there is an increased risk of maternal complications (i.e. hypertension/pre-eclampsia, thrombosis) during pregnancy and puerperium. Prior to pregnancy, a complete aPL-antibody profile should be performed. Pregnancy should be discouraged when patients have experienced a thrombotic event in the previous 6 months or in women with untreated hypertension or pulmonary hypertension. During pregnancy, close maternal and fetal monitoring with a multidisciplinary team comprising an obstetrician, rheumatologist and neonatologist are indicated to allow timely intervention in the case of complications and to reduce the possible consequences of premature delivery. In women with APS visits every 2 weeks are recommended until midgestation and weekly thereafter, also monitoring of blood pressure and urine protein, and frequent ultrasounds to check fetal growth and well being.

Several management protocols have been proposed to prevent maternal thrombotic complications and improve pregnancy outcome in women with APS [Empson *et al.* 2002]. However, interpretation of studies in this area is difficult due to a lack of well-designed trials and the clinical complexity of the syndrome, so treatment decisions should be made on an individual basis.

For prevention of fetal loss in women with APS, administration of low-dose aspirin alone has been associated with an increased frequency of successful pregnancy outcome in some studies, but was no better than supportive care in others [Empson *et al.* 2002; Farquarson *et al.* 2002; Pattison *et al.* 2000].

At present, for the management of women with APS, a systematic review of treatments came to the conclusion that heparin, with or without aspirin, is the recommended intervention in APS pregnancy [Bates *et al.* 2008; Empson, 2005; Lassere and Empson, 2004]. Low-molecular-weight heparin (LMWH) is now widely used as it is as effective as unfractionated heparin and is associated with fewer side effects such as thrombocytopenia and osteoporosis.

Women with laboratory criteria for aPL antibodies and a prior history of arterial or venous thrombosis are at high risk of recurrence and are generally on lifelong anticoagulation with warfarin. Thus, women receiving warfarin before pregnancy should discontinue this therapy

because of its teratogenic properties between 6 and 14 weeks of gestation and switch to LMWH at conception. For patients with particularly severe recurrent thromboses, particularly stroke, warfarin can be restarted after the period of organogenesis is complete [Pauzner *et al.* 2001]. It is recommended that oral anticoagulation postpartum be resumed by women who received heparin or LMWH antepartum [Bates *et al.* 2008; ACOG, 2005].

Over 50% of women carrying aPL antibodies will have a successful pregnancy without medical treatment [Lockshin *et al.* 1989; Lockwood *et al.* 1989]. The majority of the Advisory Board of the 10th International Congress on aPL antibodies suggested using low-dose aspirin only in pregnant women with the incidental finding of a persistent presence of aCL or LA, without previous pregnancy morbidity or thrombosis [Tincani *et al.* 2003].

There are no consistent data to guide the postpartum management of women with aPL but no history of prior thrombosis. The American College of Chest Physicians evidence-based clinical practice guidelines concluded that these women are probably at increased risk of developing pregnancy-related venous thrombosis and suggested that they receive postpartum anticoagulation [Bates *et al.* 2008].

Intravenous gamma globulin is an alternative treatment that has been proposed; however, the efficacy of this approach has not been demonstrated [Triolo *et al.* 2003; Branch *et al.* 2000; Scott *et al.* 1988].

There is no support for the efficacy of glucocorticoids in reducing the risk of adverse pregnancy outcomes. In addition, an increased risk of adverse obstetrical and maternal consequences of steroid therapy including the premature rupture of membranes, preterm delivery, fetal growth restriction, infection, pre-eclampsia, gestational diabetes, maternal osteopenia, and avascular necrosis have been demonstrated consistently [Laskin *et al.* 1997; Silver *et al.* 1993; Cowchock *et al.* 1992; Lockshin *et al.* 1989]. Their use should be restricted in secondary APS such as SLE.

Plasmapheresis is used to remove aPL antibodies in an attempt to avoid spontaneous abortion in women with multiple previous miscarriages [Frampton *et al.* 1987; Fulcher *et al.* 1989], but

the usefulness of this procedure needs to be confirmed.

The antimalarial drug, hydroxychloroquine, appears to reverse platelet activation induced by human immunoglobulin aPL antibodies and decrease the thrombogenic properties of aPL antibodies in mice [Espinola *et al.* 2002; Edwards *et al.* 1997]. This agent also appears to decrease aCL levels in humans [Toubi *et al.* 2003]. No teratogenicity has been described with the use of hydroxychloroquine in pregnant women with SLE [Motta *et al.* 2005; Khamashta *et al.* 1996; Parke and West, 1996]; however, the safety and efficacy of this drug in pregnant women with APS have not been examined in large clinical trials.

During *in vitro* fertilization (IVF) procedures, as established at the 5th International Conference: Sex Hormones, Pregnancy and Rheumatic Disease (Florence, Italy, April 2007), the use of heparin is mandatory only in woman with classic APS undergoing IVF, while no consensus was obtained for heparin treatment in asymptomatic aPL-positive woman [Erkan *et al.* 2008]

Therapeutic dilemmas

Although the available literature suggests that patients with definite APS with first venous thrombosis should be treated with warfarin to an INR 2.0–3.0 and >3.0 for those with recurrent and/or arterial events [Ruiz-Irastorza, 2007a], some patients present some diagnostic and therapeutic uncertainties, for example, a patient with low titers of aPL antibodies and thrombosis or a patient with clinical manifestations other than thrombosis (i.e. livedo reticularis, thrombotic microangiopathy, seizures, nonbacterial thrombotic endocarditis) and persistent positivity for aPL antibodies. In both these situations, in the absence of precise guidelines, we suggest the patient be treated with warfarin in a similar manner to a patient who follows the clinical and laboratory criteria for APS. The overall risk of thrombosis is increased in patients with aPL antibodies [Levine *et al.* 2002], but unfortunately the diagnosis of APS is made after the first thrombotic event. Thus, it is very difficult to discuss primary thromboprophylaxis in asymptomatic aPL carriers. The APLASA (AntiPhosphoLipid Antibody Acetylsalicylic Acid) study, a multicenter, double-blind, placebo-controlled RCT, compared a low dose of aspirin daily with placebo in asymptomatic

aPL-positive patients, and concluded that aspirin was not useful in preventing thrombosis [Erkan *et al.* 2007]. However, there are some limitations that influence the conclusions of the APLASA study, that is, the small number of patients included, the recruitment of patients with primary and secondary APS, and the inclusion of patients with a lower risk immunological profile. Therefore, the existing data are not sufficiently exhaustive to suggest the optimal preventive therapy in aPL carriers. It is not possible to predict which patients will have thromboembolic events but it is important not to underestimate the higher thrombotic risk inherent in some situations in which factors other than aPL antibodies are effective (e.g. postoperative time, a long period of immobilization, hormone replacement or estrogen-containing oral contraceptives, hyperlipidemia).

Treatments under investigation

Current treatment for APS is only partially effective and new therapies are urgently needed. Therapies being investigated for APS include autologous hematopoietic stem cell transplantation (HSCT) and rituximab. To date, insufficient data on the use of these approaches exist to guide therapeutic recommendations.

Autologous HSCT is currently being evaluated as a new treatment for autoimmune diseases, including SLE, that are associated with a very severe prognosis. The rationale for autologous HSCT in autoimmune diseases lies in the hypothesis that vigorous immunoablation can induce profound alterations of the immune system affecting B and T cells, monocytes, and natural killer and dendritic cells, resulting in the elimination of autoantibody-producing plasma cells and the induction of regulatory T cells. Statkute and colleagues [Statkute *et al.* 2005] showed that in 46 patients with primary and secondary APS high-dose chemotherapy and autologous HSCT are effective in eliminating aPL antibodies and preventing thrombotic complications: 10 out of 22 patients discontinued anticoagulation therapy and 78% have had no further thrombotic events.

Rituximab is a genetically engineered chimeric murine/human anti-CD20 monoclonal antibody cell-surface protein believed to function in B-cell cycle initiation and differentiation. The anti-CD20 antigen represents an ideal target for the immunotherapy of B-cell lymphomas and B-cell-mediated autoimmune diseases such as

idiopathic thrombocytopenic purpura, rheumatoid arthritis, and SLE [Shaw *et al.* 2003; Silverman and Wiseman, 2003; McLaughlin *et al.* 1999]. B cells may also be key contributors in the immunopathogenesis of APS: these cells may either act as antigen-presenting cells that initiate inflammation by the production of cytokines, or have a direct influence on T cells [Tsokos 2004; Edwards *et al.* 1999]. The depletion of these immunologic B cells may decrease or even halt the continuing cascade of inflammatory mediators signaling thrombocytopenia, bleeding, and/or thrombosis.

A review of the literature revealed that only 12 case reports on the use of rituximab in patients with primary, secondary, and catastrophic APS have been published. Current knowledge clearly suggests the need for further clinical trials to evaluate the effect of rituximab in the treatment of resistant APS [Erre *et al.* 2008]. In December 2008 the first report was published of a patient with APS without thrombocytopenia showing functional improvement after rituximab therapy and supports the growing body of evidence favoring the use of rituximab [Adamson *et al.* 2008].

The potential of both HSTC and rituximab-related B-cell depletion in APS appears promising but further investigation is required to evaluate the safety profile of these procedures and to identify the patients suitable for these aggressive therapeutic approaches. We consider that, at the moment, refractory APS and catastrophic APS could be the appropriate targets for these groundbreaking therapies.

Catastrophic antiphospholipid syndrome management

Catastrophic antiphospholipid syndrome (CAPS) is a severely acute form of APS characterized by rapid onset thromboses mainly affecting the small vessels and leading to a multiorgan failure in the presence of aPL antibodies. Fortunately, CAPS represents less than 1% of all patients with APS [Cervera *et al.* 2002], but it represents a critical life-threatening situation and the mortality rate is approximately 50% despite treatment [Asherson, 1998, 2001].

In the absence of RCTs, the optimal therapeutic option for patients with CAPS is unknown and often empiric. Since it is now known that the pathogenesis of CAPS is related to complex

interactions between coagulation and inflammation with the essential involvement of aPL antibodies [Belmont, 2000], the rationale for treatment is to prevent thrombosis by anticoagulation, to suppress the uncontrolled effects of cytokines and pro-inflammatory mediators, and obviously to halt the production of autoantibodies. In other words, therapy consists of a combination of anticoagulant and immunosuppressive agents such as corticosteroids and cyclophosphamide, or plasmapheresis.

Analysis of 130 reported cases of CAPS showed that older age and a higher number of involved organs are associated with death. In this series, patients treated with a combination of anticoagulants and steroids together with plasmapheresis or intravenous gammaglobulin had the highest survival rate (70%) [Asherson *et al.* 1998]. Unfortunately, a second analysis did not achieve the same results [Asherson *et al.* 2001].

The dramatic course of CAPS requires close attention and, in addition to the medical therapies, intensive care measures are pivotal in the survival of these patients.

Conclusions

The management of APS focuses on antithrombotic therapies and anticoagulation, however, there are many unanswered questions regarding the best practice for aPL-positive patients owing to difficulties in describing the wide clinical and serological spectrum of the syndrome. In accordance with recent reviews [Tuthill and Khamashta, 2009], patients with definite APS with first venous thrombosis should be treated with warfarin at a target INR of 2.0–3.0 and those at higher risk (recurrent events and/or arterial thrombosis) should be treated with warfarin to an INR of >3.0. The approach for women with obstetric manifestations of APS is based on the use of LMWH and aspirin. Patients with asymptomatic aPL-elevated titers, those with obstetric APS, and those with coexistent SLE should receive aspirin in monotherapy. It is possible that future studies, based on randomized controlled studies that recruit larger numbers of patients, could result in changes in these recommendations.

Conflict of interest statement

None declared.

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