



Revision

Therapeutic strategies in antiphospholipid syndrome

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ABSTRACT

The classical clinical picture of the antiphospholipid syndrome (APS) is characterized by venous or arterial thromboses, fetal losses and thrombocytopenia, in the presence of antiphospholipid antibodies (aPL), namely lupus anticoagulant, anticardiolipin antibodies or antibodies directed to various proteins, mainly $\beta 2$ glycoprotein I, or all three. Apart from being “primary” (without any discernable underlying systemic autoimmune disease), or associated to another disease (usually to systemic lupus erythematosus), it may also occur rapidly over days or weeks when it has been termed “catastrophic” APS. Therapy should not primarily be directed at effectively reducing the aPL levels and the use of immunotherapy (including high dose steroid administration, immunosuppression or plasma exchange) is generally not indicated, unless in the catastrophic APS. Treatment of APS patients should be based on the use of antiaggregant and anticoagulant therapy.

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Estrategias terapéuticas en el síndrome antifosfolipídico

RESUMEN

El síndrome antifosfolipídico (SAF) se caracteriza por la asociación de los anticuerpos antifosfolipídicos (AAF) con trombosis de repetición, abortos o pérdidas fetales recurrentes y trombocitopenia. Los AAF más estudiados son los anticuerpos anticardiolipina, el anticoagulante lúpico y los anticuerpos anti- $\beta 2$ -glucoproteína I. El SAF puede presentarse de forma aislada, denominándose SAF primario, o bien asociado a otras enfermedades autoinmunes sistémicas, fundamentalmente a lupus eritematoso sistémico. Más recientemente, se ha descrito un subgrupo de SAF en el que los pacientes desarrollan múltiples trombosis durante un corto espacio de tiempo, que se ha denominado SAF catastrófico. Aunque parece clara la asociación entre la presencia de AAF y trombosis, la actitud terapéutica no debe ir dirigida primariamente a la eliminación o a la reducción de los niveles de estos anticuerpos mediante recambios plasmáticos, gammaglobulinas intravenosas o inmunodepresores (excepto en el SAF catastrófico), y a que no existe una clara correlación entre los niveles de los AAF y los episodios trombóticos. El tratamiento de estos pacientes debe basarse en el uso de antiagregantes plaquetarios o anticoagulantes.

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Introduction

The term “antiphospholipid syndrome” (APS) is used to describe the association of antiphospholipid antibodies (APLA) to a clinical state of hypercoagulation characterized by recurrent thrombosis and abortions or recurrent fetal loss, which is often accompanied by discreet or moderate thrombocytopenia. APLA are a family of autoantibodies that recognize several combinations of phospholipids,

proteins bound to phospholipids or both. Of all of them, the most studied are anticardiolipin antibodies (aCl), Lupus anticoagulant (LA) and antibodies to $\beta 2$ -glucoprotein I.¹

APS can present in an isolated manner, called primary APS, or associated to other autoimmune diseases, fundamentally to systemic lupus erythematosus (SLE). APL can also be detected in other situations, such as infection, neoplasia or related to the use of certain medication. More recently, a subgroup of APS has been described in which the patients develop multiple thrombus, especially in small caliber vessels, in several organs and in a short period of time, which has been called catastrophic APS and which is responsible for a mortality of up to 30%.²

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Optimal treatment of patients with APS is controversial and is continually under review due to the small number of patients which in turns makes it difficult to carry out adequate prospective studies that allow for definite conclusions. Although the association between the presence of APLA and thrombosis seems clear, the therapeutic attitude is not primarily directed to the elimination or reduction in the levels of these antibodies through plasma exchanges, intravenous gammaglobulin or immunosuppressants (except in catastrophic APS), because of the absence of a clear correlation between APLA titers and thrombotic episodes. Treatment of these patients must be based on the use of platelet anti aggregating agents or anticoagulants. In addition, in patients with APLA, additional vascular risk factors, such as hypertension, elevated cholesterol levels, tobacco use or oral contraception containing estrogen must be reduced or eliminated.

Primary thromboprophylaxis

The first consideration in patients with elevated titers of APLA, but who still have not developed thrombosis (primary thromboprophylaxis), must be to avoid or control other thrombotic risk factors, such as the use of tobacco, a sedentary lifestyle, the use of oral contraceptives, hypertension, diabetes, nephritic syndrome, etc.³

With respect to pharmacologic treatment, the most common practice is platelet anti-aggregation therapy with low dose aspirin (75 to 150 mg).³ However, one of the few epidemiological studies that include this aspect observed that low dose aspirin does not prevent venous thrombosis or pulmonary embolism in males with APS.⁴ In addition, the only randomized, placebo-controlled clinical trial, performed by Erkan et al⁵ did not find the beneficial effect of aspirin to be superior to placebo, although the number of patients who developed thrombotic episodes was reduced in both groups.

However, in other studies, aspirin was effective in the prevention of thrombosis in patients with SLE⁶ and in women with APLA and a history of abortions.⁷ There is no data on the efficacy of other anti-aggregant drugs in patients with APLA.

In patients with SLE, an alternative to aspirin can be the use of antimalarial drugs such as hydroxycloquine or cloroquine. In addition to improving inflammatory manifestations of SLE, such as joint or skin affection, these drugs have been recognized as having anti-aggregant properties.⁸ The inconvenience of their long-term use is the possibility of developing ocular toxicity.

The use of oral anticoagulants, maintaining a low anticoagulation intensity (international normalization rate or INR=1.5) has shown to be effective to prevent thrombosis in other prothrombotic states, such as stage IV breast cancer, central venous catheter placement or male patients with a risk for coronary artery disease. It could therefore be a therapeutic alternative in these patients.

In the absence of data from larger prospective studies that suggest otherwise, the common clinical practice is to treat with low dose aspirin all patients with persistently positive LA or aCL, especially if they are of the IgG isotype and have medium or high titers, as well as to strictly control the existence of other associated risk factors.⁹

Secondary thromboprophylaxis

Patients with APS who have presented thrombosis have an elevated risk of suffering new thrombotic phenomena. Optimal treatment to prevent these recurrences is still the object of debate. While most studies coincide that treatment with oral anticoagulants is superior to treatment with anti-aggregating agents alone, there is not the same degree of agreement on the intensity and duration

of anticoagulation. The risk of hemorrhage, the major complication of anticoagulant treatment, and the need to frequently control the intensity of anticoagulation through INR determinations are factors that oblige us to look for therapeutic alternatives. A characteristic common to most patients with APS is that thrombosis tends to recur in the same vascular territory, in other words, venous thrombosis recurrence tends to be venous and arterial thrombosis recurs in arteries in almost 80% of cases.

Prevention of venous recurrent disease

With respect to the intensity of anticoagulation, several retrospective studies¹⁰⁻¹³ find few or no recurrences when INR is over 3. The main limitations of these studies are their retrospective nature and the fact that venous and arterial thrombosis was not separately analyzed, as well as the appearance of hemorrhagic episodes. The question of whether all patients with APS and a history of thrombosis need to have the same intensity of anticoagulation now becomes important. Two prospective studies conclude that an INR of between 2 and 3 is enough to prevent thrombosis recurrence.^{14,15} Anticoagulation with an INR over 3 should be reserved for those cases in which venous thrombosis recurrence has occurred while under an INR between 2 and 3 (fundamentally is there is a history of arterial thrombosis). The addition of aspirin has not been shown to reduce the risk of recurrence and does seem to increase the risk of hemorrhage.¹⁶

With respect to the duration of anticoagulation, studies by Rosove et al¹⁰ and Khamashta et al¹¹ describe a rate of recurrence of 53% and 69%, respectively. The study by Schulman et al¹⁴ finds that the presence of APLA is a risk factor for thrombotic recurrence. These authors measured IgG aCL after the first venous thrombosis and interrupted anticoagulation in all patients after 6 months. The results were that 29% of patients with aCL had a new thrombotic episode during the time of follow up (4 years) vs 14% of patients that had no aCL. This data suggests, therefore, that anticoagulation must not be suspended in patients with APS.

Several recent studies¹⁷⁻¹⁹ review evidence published regarding treatment of patients with APS after a venous thrombosis. The most common recommendation, therefore, is to use treatment with oral anticoagulants for an indefinite amount of time, in the absence of hemorrhage or risk factors for it (uncontrolled hypertension, advanced age, etc.) and maintain an INR between 2 and 3.⁹ In patients with a history of venous thrombosis clearly associated to a known risk factor, for example the use of oral contraception, interrupting anticoagulation might be considered.

Prevention of recurrent arterial disease

The most frequent arterial thrombosis in APS are stroke, transient ischemic attacks and myocardial infarctions.

Recommendations for the prevention of recurrent strokes in the general population depend on whether the patient has embolic heart disease. Patients with atrial fibrillation are generally anticoagulated for life, maintaining an INR between 2 and 3. Antiplatelet agents are used mainly in non-embolic strokes or transient ischemic attacks, in spite of the fact that some studies have described that these drugs only reduce the risk of arterial recurrence or death in 13%.²⁰ There is currently no conclusive data from prospective studies on stroke in patients with APS. Different options have proposed low dose aspirin or other antiplatelet agents, oral anticoagulation with an INR between 2 and 3 for a short period of time or a combination of both.²¹⁻²³ Antiplatelet therapy has also been suggested for those patients with evident risk factors for thrombosis and for those with low APLA antibody titers, reserving oral anticoagulation for those patients with recurrence of thrombosis in spite of antiplatelet therapy.²¹ Due to the high rate of thrombotic recurrence associated to the presence of

APLA and the high morbidity and mortality associated to stroke and myocardial infarction, oral anticoagulation for an indefinite amount of time is the most widely accepted option.^{9,24} Some retrospective studies^{11,25} and the results from the Euro-phospholipid observational cohort²⁶ propose high intensity anticoagulation (INR 3–4).

Treatment of catastrophic antiphospholipid syndrome

The treatment of catastrophic APS must take three objectives into account: treatment of any unleashing factor (the early use of antibiotics if infection is suspected, amputation of any necrotic limb, caution in APS patients undergoing surgery or an invasive procedure), treating the continuing thrombotic phenomena and suppressing the excessive “cascade” of cytokines.^{2,27–31} Large series of patients with this disease indicate that the combination of anticoagulation and steroids along with plasma exchange therapy or intravenous gammaglobulin lead to a higher rate of survival (70%).²⁹ Therefore, when catastrophic APS is suspected, the use of the following treatments is suggested (Figure).

First line therapy

Anticoagulation: the use of intravenous heparin in order to inhibit the production of clots and promote the lysis of existing ones is indicated. It is generally necessary to administer a larger dose of heparin than usual, with a follow up using serial measurements of activated partial thromboplastin time (APTT) in order to achieve correct anticoagulation. An initial dose of 5,000 units of heparin followed by a continuous infusion at a rate of 1,500 units/h with APTT control is suggested. If progression is satisfactory, heparin must be maintained for 7 to 10 days, and then replaced by oral anticoagulant therapy. INR is recommended to be maintained over 3,¹¹ although a lesser value (between 2.5 and 3) may be equally effective with minor hemorrhagic problems. Heparin must not be suspended before reaching a correct INR with oral anticoagulants.

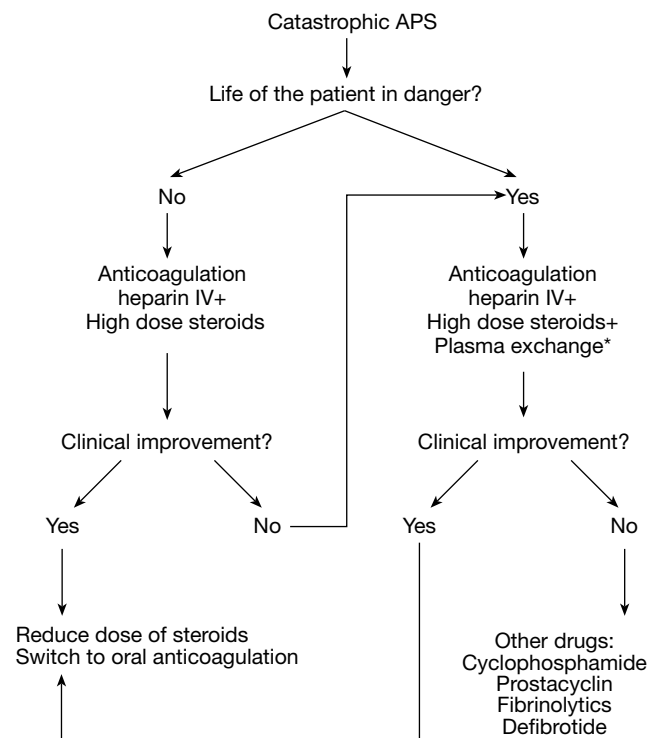
Steroids: early onset of therapy with intravenous steroids is necessary in order to suppress the excessive cytokine response in these patients.²⁸ They are also necessary for the treatment of coexisting vasculitis. In a life-threatening case, pulse methylprednisolone therapy (1,000 mg/day for 3 to 5 days) is recommended, followed by high dose intravenous methylprednisolone (1 to 2 mg/kg/day). The dose must be maintained in accordance to therapeutic response.

Second line therapy

In cases of disease progression or faced with a life threatening situation, the following measures are indicated.

Gammaglobulin: intravenous gammaglobulin has been effective in achieving a fast reduction in APLA titers in some patients. They are also useful for patients with intense thrombocytopenia (which does not respond to high dose steroid therapy). The recommended dose is 400 mg/kg/day (approximately 25 g/day) for 5 days.

Plasma exchange: the fundamental reasoning behind plasma exchange is based on the fact that it is the treatment of choice for patients with thrombotic thrombocytopenic purpura (TTP), who also develop thrombotic microangiopathy. Plasma exchange also eliminates APLA and, therefore, benefits the patient. In addition, fresh frozen plasma administered contains natural anticoagulants and may be beneficial when the process of coagulation has consumed these components. Plasma exchanges should therefore be indicated in patients with catastrophic APS that show serologic characteristics of microangiopathy (such as the presence of schistocytes due to microangiopathic hemolytic anemia) and must be continued for at



*Especially indicated when schistocytes present

Figure. Algorithm for the treatment of catastrophic antiphospholipid syndrome (APS). IV indicates intravenous.

least 3 to 5 days, although no treatment guidelines exist. Neuwelt et al³⁰ employed plasma exchanges for more than 3 years in a patient with catastrophic APS. It must be remembered that plasma exchanges may interfere with anticoagulant treatment. A combination of anticoagulants, steroids, and intravenous gammaglobulin or plasma exchanges used in more than 50 patients with APS led to improvement in more than 70% of them.^{29,31}

Other therapies

The following therapies must be considered in patients presenting multiorgan thrombosis resistant to the abovementioned treatments.

Fibrinolytics: fibrinolytics are justified in patients who do not respond to heparin.³² The main fibrinolytics are streptokinase, urokinase and tissue plasma activator, which can be followed by heparin, as previously described. Hemorrhage induced by fibrinolytic agents may be treated with blood transfusions.

Cyclophosphamide: large series^{29,31} have not shown benefit after the addition of cyclophosphamide. On the contrary, cyclophosphamide was associated to a lower degree of survival, although these patients could have presented a more severe form of disease. However, this drug could be used in cases of severe catastrophic APS associated to SLE reactivation or in those patients with high titers of APLA in order to avoid a rebound of the latter after plasma exchange or intravenous gammaglobulin use.²⁸ The usual dose of a pulse is 0.5 to 1 g/m².

Infrequent therapies

The following treatments have been employed occasionally in patients with catastrophic APS.

Prostacyclin: prostacyclin is a natural substance produced by vascular endothelium. It leads to vasodilation in all vascular territories and is a potent inhibitor of platelet adhesion. Prostacyclin has only been evaluated in patients with systemic sclerosis and catastrophic APS.³³ Continuous infusion of intravenous prostacyclin (5 ng/kg/min) was administered for 7 days but the patient died upon interruption of therapy.

Ancred: this is a purified fraction of the venom of a malaysian python serpent, which has been observed to correct deficiencies in prostacyclin stimulating factor and vascular activation factor. However, its use has been described in a patient who showed a good response to this drug.³⁴

Defibrotide: this compound is a single chain metallic salt that has been shown to act as a potent inhibitor of endothelin i, of platelet aggregation induced by thrombin and thromboxane synthesis, as well as a potent inhibitor of clot formation. As in the case on ancred, it has occasionally been employed successfully in patients with catastrophic APS.

Intensive care unit

Intensive treatment must be installed in cases that compromise the patient's life. Rapidly progressive renal failure requires dialysis; acute respiratory distress requires assisted ventilation and vasoactive drugs can also act in the case of cardiogenic shock. All of these measures play an essential role in the survival rate of patients with catastrophic APS.

In conclusion, catastrophic APS is a disease with a high probability of compromising the patient's life and an elevated mortality rate that requires intensive therapy. Therefore, early diagnosis and energetic treatment are essential. Treatment of choice in patients with this disease is a combination of high dose heparin and steroids as well as gammaglobulins or plasma exchange. Preventive measures can be effective in patients with APS in order to prevent the development of catastrophic APS.³⁵

Prevention of gestational loss

Current treatment for patients with APS without fetal loss includes low dose aspirin, heparin or both (Table). Steroids, used in the first years after the description of APS, are not currently employed after prospective studies demonstrated their lack of efficacy and association to morbidity.

Initially the recommendation was to treat with aspirin those patients who did not have a history of thrombosis or fetal loss and reserve treatment with heparin for those with a history of thrombosis or prior obstetric complications, associated to APLA.³⁶ This is still common practice in many centers. Two prospective studies have been recently published indicating that treatment with aspirin plus heparin is superior to aspirin alone to prevent pregnancy loss in women with APLA and a history of fetal loss.^{37,38} In contrast, another two prospective studies indicate that aspirin alone had a similar effect to the combination of aspirin and heparin³⁹ or aspirin combined with steroids.⁴⁰ Finally, another prospective study⁴¹ which includes patients with APLA and repeat abortions, without a history of thrombosis, describes the same ratio of live-born products (80%) between the group that received aspirin and another group who received placebo. For those patients who have presented fetal loss during the second or third trimester, treatment with aspirin plus heparin seems to be superior to aspirin alone.²⁴ Our group has shown that the use of aspirin alone, but administered since before conception, prevents fetal loss in more than 90% of cases,⁴²⁻⁴⁴ making this our common practice in patients with a history of fetal loss but no thrombosis.⁹

Treatment with intravenous immunoglobulin has been used in isolated cases, especially in patients with fetal loss in spite of treatment with aspirin plus heparin. There are cases described with good results but a prospective, randomized trial has found no difference between treatment with aspirin plus heparin and the group treated with aspirin, heparin and intravenous immunoglobulin.⁴⁵

Those patients with a history of thrombosis undergoing treatment with oral anticoagulants will need to continue anticoagulation during all of pregnancy. Oral anticoagulants have teratogenic effects, especially between weeks 6 and 11 of pregnancy and must be changed to subcutaneous heparin. Ideally, this substitution should take place before conception but, if this is not possible, at least at the moment the first pregnancy test results positive. They can instead be employed if a very intense prothrombotic state exists between weeks 14 and 34. Neither conventional heparin nor low molecular weight heparin cross the placenta and, therefore, do not affect fetal development. Prolonged use of fractionated heparin has been associated to the development of maternal osteoporosis. Low molecular weight heparin is being used to treat these patients and seem to have the least effects on bone mass.⁴⁶ Heparin must be maintained during all of pregnancy and postpartum until the patient reinitiates oral anticoagulation.

A cautious follow-up of these patients on the part of a multi-disciplinary team is important for the success of pregnancy such as drug treatment.

Treatment of hematological affection

Thrombocytopenia associated to the presence of APLA is usually moderate (normally above 50.000/ml) and does not require treatment. When intense, treatment with prednisone is usually effective. Other alternatives, in refractory cases, are intravenous

Table

Prophylaxis of pregnancy loss in patients with antiphospholipid antibodies and antiphospholipid syndrome

1) Pregnant with APLA and normal prior pregnancies: Optional: aspirin (100 mg/day) from the moment the patient finds out she's pregnant and throughout pregnancy
2) First with APLA: a) No associated disease: Optional: aspirin (100 mg/day) from the moment the patient finds out she's pregnant and throughout pregnancy b) Associated SLE: Recommended: aspirin (100 mg/day) from the moment the patient finds out she's pregnant and throughout pregnancy
3) Pregnant with APLA and associated obstetric disease but no history of thrombosis: Recommended: aspirin (100 mg/day) from the moment the patient finds out she's pregnant and throughout pregnancy Prednisone: only for non obstetric reasons (SLE activity or intense thrombocytopenia), preferably under 30 mg/day
4) Pregnant with APLA and history of thrombosis: Interrupt coumarin before 6 th week of pregnancy (maximum risk for teratogenesis is between 6 th and 11 th weeks) Administer aspirin (100 mg/day) associated to low molecular weight heparin Special considerations: a) If coumarin is reintroduced, this must occur from the 2 nd trimester of pregnancy onward b) If breast-feeding is desired, treatment with low molecular weight heparin must be maintained because coumarin passes into breast milk
5) Therapeutic failure with abovementioned guidelines: a) If the patient only received aspirin during the previous pregnancy: Add low molecular weight heparin to aspirin at the moment the pregnancy is confirmed b) If this fails: Evaluate adding intravenous gammaglobulin (400 mg/kg/day for 5 days, repeating monthly until pregnancy ends)

APLA indicates antiphospholipid antibodies; SLE, systemic lupus erythematosus.

gammaglobulins, danazole, dapsone or even splenectomy.⁴⁷ Chloroquine and low dose aspirin have achieved, occasionally, an increase in platelet numbers. Positive results have recently been described with the use of anti-CD20 (rituximab) monoclonal antibodies.⁴⁸ APLA associated Hemolytic anemia is infrequent and requires the same treatment as thrombocytopenia, to which it is frequently associated (Evans syndrome).⁹

Treatment of cardiac alterations

Heart valve lesions are frequent in patients with APS. Because valve thickening and vegetations can lead to embolism, anticoagulation is recommended for those patients with valvular disease who have presented an embolic phenomenon. Prophylaxis with antiplatelet agents could be appropriate in patients with asymptomatic valvular disease. Some authors consider the use of steroids for acute stages of valve inflammation, but their real effectiveness is unknown.

The presence of intracardiac thrombi obliges the use of anticoagulants and surgical options must be considered on a per patient basis.

Pulmonary hypertension requires treatment with anticoagulants, as well as treatment with vasodilators (bosentan, epoprostenol).⁴⁹

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