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Update on Antiphospholipid Antibody Syndrome Management

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1. Introduction

The antiphospholipid syndrome (APS) is characterized by a high risk of venous and arterial thrombosis and by complications during pregnancy, especially recurrent miscarriages. The thrombotic event is caused by a complex interaction between antiphospholipid antibodies (aPLs) and endothelium and platelets. Inflammation may play a role in the pathology of APS even though the consensus of Sydney (Miyakis et al., 2006) requires the absence of vascular inflammation signs for the diagnosis of APS. However, the complement system has recently been involved in the pathogenesis of fetal losses in animal models and, interestingly, the protective role of heparin in such cases could be due to the complement inhibition rather than to anticoagulation. The treatment of APS is based on antiplatelet drugs (aspirin) and anticoagulants (both heparins and vitamin K antagonists). In the acute phase the treatment is in general very similar to that of non-APS thrombosis, that is with unfractionated heparin (UFH) therapy followed by oral anticoagulation. However, APS treatment remains problematic due to lack of standardized laboratory tests and of randomized controlled trials (RCTs).

2. Prophylaxis of thromboembolism

2.1 Secondary prophylaxis of vascular thrombosis

The risk of thrombotic recurrences is lower if the venous district, rather than the arterial one, is involved. The key issue in the antithrombotic management of APS patients concerns whether arterial and venous events should receive the same intensity of therapy. According to Ruiz-Irastorza review we can treat lower-risk patients with conventional anticoagulation in order to reach Target International Ratio (INR) values between 2.0 and 3.0, reserving high-intensity anticoagulation (INR > 3.0) to patients with arterial thrombosis or venous thrombotic recurrences (Ruiz-Irastorza et al., 2007). On the contrary Lim argues in his systematic review that high-intensity anticoagulation (INR: 3.0-4.0) is not better than conventional anticoagulation in protecting patients with first thrombotic venous event and non-cerebral arterial thrombosis (Lim et al., 2006). The conclusions are based on two RCTs (Crowther et al., 2003; Finazzi et al., 2005) that are susceptible to criticism as: 1. recruitment mainly concerns venous thromboses, with the exception of strokes and recurrent

thrombosis, the sample is not representative of the APS population. 2. In the high-intensity anticoagulation arms, the warfarin dose is often subtherapeutic with frequent thrombotic recurrences with INR < 3.0. Cerebral thromboses are the most frequent arterial events of APS. The risk of new cerebral thromboses is addressed by the prospective Antiphospholipid Antibodies and Stroke Study (APASS) (Levine et al., 2006), that showed no difference in the comparison between a single antiplatelet (aspirin 325 mg/day) and a single anticoagulant (warfarin: INR 1.4 - 2.8). In this study the extension of the results to the APS population is questionable, as the analysis of aPLs is made on a single sample at the time of enrolment, while for the diagnosis of APS it is essential to have at least two measurements taken at a distance of some time. A recent small Japanese RCT (Okuma et al., 2009), that instead only enrolled patients with definite diagnosis of APS according to the consensus of Sydney, shows that the combination of conventional anticoagulation plus low-dose aspirin (LDA) (100 mg/day) is more effective than aspirin used on its own. In conclusion, we believe that the prevention of arterial thromboses requires either anticoagulation at INR 3.0-4.0 or a combined treatment. Apart from the debate regarding the intensity of anticoagulation, there is a general agreement upon it being maintained indefinitely, even if some authors argue that a finite treatment can be performed if the first episode of venous thromboembolism occurs in the context of a transient and reversible risk factor (surgery, prolonged immobilization, pregnancy, estrogen therapy) (Giannakopoulos & Krillis, 2009).

2.1.1 Prophylaxis of APS obstetric complications

The pregnancy morbidity of APS includes maternal thromboses, spontaneous abortions before the 10th week and late obstetric complications (fetal deaths, premature births caused by preeclampsia or placental insufficiency). Pregnant women with aPLs positivity should be stratified in order to perform the optimal treatment: A. Women with ascertained APS and previous thrombosis, B. Pregnant women with a history of recurrent miscarriages, C. Pregnant women with a history of fetal deaths > 10 weeks and premature births <34 weeks. A. Women with ascertained APS and previous thrombotic event, possibly already on warfarin therapy, should undergo combination therapy with LDA (75-100mg/day) plus therapeutic doses of unfractionated heparin (UFH) (subcutaneously every 8-12 h) or low molecular weight heparin (LMWH) (e.g. enoxaparin 1 mg/kg subcutaneously every 12 h). During pregnancy, warfarin must be stopped between the 6th and the 12th week due to its teratogenicity, and also afterwards it can cause fetal hemorrhage. B. Women with a history of recurrent miscarriages should be treated with a combination therapy of LDA plus prophylactic doses of UFH (5000-7500 IU subcutaneously every 12 h) or LMWH in prophylactic doses (e.g., enoxaparin 1 mg/kg/day). C. Women with a history of fetal deaths >10 weeks and premature births <34 weeks should be treated with a combination therapy of LDA plus prophylactic/intermediate doses of UFH (e.g., 7500-10000 IU subcutaneously every 12 h) or LDA plus LMWH usually in prophylactic doses (e.g., enoxaparin 1 mg/kg every 24 hours). These treatment patterns derive from meta-analysis and expert guidelines (Empson et al., 2005; Bates et al., 2008). There is not indisputable evidence that anticoagulation with heparins works better than aspirin alone and it has not even been established which is more effective between UFH or LMWH. In fact, if on the one hand RCTs have shown a reduction in the number of pregnancy losses with a combination of UFH-LDA, on the other hand other RCTs, that used LMWH-LDA, do not show a clear superiority. There are many observational studies in favor of the effectiveness of LDA alone.

Moreover, the PARIS Collaborative Group meta-analysis (Askie et al., 2007) shows that the pregnancy outcome in women at high risk of preeclampsia treated with LDA, is similar to that of the general population, after 20 weeks of gestation. Two pilot studies show no differences when comparing the LDA-UFH to the LDA-LMWH combination therapy (Noble et al., 2005; Stephenson et al., 2004). In order to clarify controversies, a trial with three arms is strongly needed: 1. UFH versus LDA, 2. LMWH versus LDA, 3. LDA alone (Mehdi et al., 2010)

2.1.2 Primary prophylaxis of vascular thrombosis

The group of subjects with aPLs positivity in absence of clinical APS manifestations (aPLs carriers), includes asymptomatic carriers, patients with SLE, and pregnant women aPL-positive without a history of obstetric complications and/or thrombosis. Only some of the aPLs carriers will progress towards overt APS and we still do not know why some will develop the thrombotic event and others will not. The role played by additional risk factors, both congenital and acquired, is also under investigation. It is clear, however, that the elimination of reversible risk factors and the prophylaxis during high risk periods, such as prolonged immobilization and surgery, are paramount in the primary prophylaxis of thrombosis. In asymptomatic carriers, for whom the risk of thrombosis is very low (<1%), a prophylactic use of aspirin is not justified. In the APLASA RCT (Erkan et al., 2007), aspirin at 81 mg/day did not prove superior to placebo in preventing the first thrombotic event in asymptomatic individuals persistently aPL-positive. Thus, the approach based on thrombotic risk stratification is reasonable in healthy carriers, reserving the LDA prophylaxis to individuals with additional risk factors (hypertension, diabetes, hypercholesterolemia, smoking, estrogen therapy) and/or immunological high risk profile (high aPLs titre, especially lupus anticoagulant (LA) and 'multiple' positivity: aCL, LA, β 2GPI). The risk of thrombosis in both SLE patients and pregnant women carriers, is on the other hand higher (3-4% and 3-7% respectively). These categories will benefit from LDA prophylaxis as demonstrated by several observational studies (Hereng et al., 2008 ; Erkan et al., 2001) . No randomized studies show that hydroxychloroquine, a drug that reduces platelet activation aPL-induced, has also an added prophylactic value in SLE patients (Kaiser et al., 2009).

3. Management of cardiac diseases in APS

3.1 Introduction

APL antibodies are associated with a wide spectrum of cardiac manifestations that include accelerated atherosclerosis, ischemic coronary artery disease (CAD), valve abnormalities, intracardiac thrombosis, pulmonary hypertension (PH).

3.1.1 Atherosclerosis and APS

Ischemic coronary artery disease in APS is largely due to atherosclerosis. The fact that the population of APS patients does not show an increased prevalence of Framingham 'traditional' risk factors when compared to the general population suggests that other 'non-traditional' risk factors, such as aPLs, might facilitate the development of atherosclerosis. Carotid intimal-medial thickness (IMT) detected by B-mode ultrasounds, is a known

predictor of coronary artery disease and stroke in adults. An increased frequency of higher IMT in patients with APS indicates that they are more likely to incur in atherosclerotic events. Ames (Ames et al., 2002) found that anticardiolipin antibodies (aCLs) independently predict the extension of IMT in the carotid arteries, while other authors (Vlachoyiannopoulos et al., 2003) failed to demonstrate such predictive role of aCLs. Ankle-brachial pressure index (ABPI), another marker of atherosclerotic risk, is abnormally high in APS, but no correlation with aPLs has been found (Baron et al., 2005). In conclusion, it is commonly acknowledged that a correlation between aPLs and atherosclerosis exists. APLs may play a role in atherogenesis due to procoagulant and proinflammatory effects on endothelial cells and/or their interference on LDL and HDL metabolism.

3.2 Management of coronary artery disease

The correlation between APS and coronary artery disease (CAD) is not well established. Vaarala's prospective study on a cohort of 4081 healthy middle-aged men found that a high level of aCLs constituted an independent risk factor with relation to myocardial infarction (MI) or cardiac death, with high prevalence in patients younger than 45 (22%) (Vaarala et al., 1995). It is therefore useful to recommend aPLs screening to infarcted patients under 45 in the absence of obvious risk factors. In previous studies the association between aPLs and MI has not been demonstrated. Anticoagulation with warfarin is usually prescribed to patients who have experienced coronary thrombotic occlusion. Petri in the Hopkins Lupus cohort highlighted the protective role of hydroxychloroquine due to the reduction of the lupus disease activity, the antiplatelet effect, the reduction of aPLs, and the lipid-lowering effect (Petri, 2000). Moreover, high homocysteine levels may be involved in APS-related thrombosis, suggesting a potential role of folic acid. Obviously, we need to identify and treat traditional cardiovascular risk factors in APS patients, including hypercholesterolemia with use of HMG-CoA inhibitors, cholesterol-lowering agents with anti-inflammatory properties. In conclusion, the Consensus Committee for treatment of cardiac diseases in APS (Lockshin et al., 2003), recommends an extensive use of statins, folic acid, B vitamins and hydroxychloroquine.

3.3 Management of valve abnormalities

Valve abnormalities in the form of vegetation and/or thickening similar to Libman-Sacks endocarditis, are the most common cardiac manifestation in APS (~ 35%). They are defined by the "coexistence of aPLs along with echocardiographic detection of lesions and/or regurgitation and/or stenosis of mitral and/or aortic valve or any combination of the above" (Miyakis et al., 2006). Although anticoagulation do not cure valve vegetations, treatment is recommended in order to prevent valve thrombosis and arterial thromboembolism. Valve vegetations are in fact associated with cerebral involvement, especially stroke but also epilepsy, migraine and cognitive dysfunction. Use of aspirin is appropriate in asymptomatic patients. Administration of corticosteroids is controversial, and some authors advise against their use, considering them ineffective or even capable of further compromising valve functionality. It has been suggested that aPLs cross-react with antigens on the surface of valves, roughly as in the case of rheumatic fever, leading to inflammation and thrombosis of valve leaflets. On the hypothesis that inflammation is the initial event of valve damage, Petri recommends a short course of corticosteroids with

follow-up 2D cardiac echocardiograms to determine the rate of corticosteroid taper (Petri, 2004). A small minority of APS patients (~ 5%) develop a valve disease that is severe enough to require surgical therapy including commisurotomy, annuloplasty and biological or mechanical valve replacement. Mechanical valve replacement may be a better option compared to bioprosthesis due to the fact that patients are already anticoagulated and that mechanical valves last longer.

3.4 Management of intracardiac thrombosis

Intracardiac thrombi are a rare complication of APS. They may occur in all cardiac chambers but mainly in the right heart and are a dangerous source of systemic embolization. Erdogan's series showed mural thrombi in 13% of cases in the absence of local conditions favoring blood stasis, and thrombi were treated with aggressive anticoagulation and surgical excision (Erdogan et al., 2005). There are no studies comparing medical, surgical or mixed treatments. The Committee Consensus recommends to start warfarin therapy as soon as a thrombus is detected, and to consult the cardiac surgeon when appropriate (Miyakis et al., 2006).

3.5 Management of anticoagulation in cardiopulmonary bypass surgery

APS patients undergoing cardiac surgery show very high perioperative morbidity and mortality rates due to thromboembolic events, especially cerebrovascular ones, to bleeding, acute biventricular failure and multiple organ failure caused by catastrophic APS triggered by surgery. Colli showed a 50% morbidity rate and a 22% mortality rate in nine patients who underwent heart valve surgery (Colli et al., 2010). Safe and effective anticoagulation during cardiopulmonary bypass (CPB) surgery depends largely on adequate monitoring of coagulation parameters, but that is a challenging task because of the aPLs interference with *in vitro* hemostasis tests. Furthermore, the contact of blood with extracorporeal surfaces during CPB stimulates the coagulation cascade. APLs prevent the binding of coagulation proteins to the phospholipid surfaces, resulting in prolonged activated partial thromboplastin time (aPTT) and/or activated clotting time (ACT). In these circumstances anti-Xa factor monitoring is the gold standard laboratory test to be used. When treating venous thromboembolism, the target range of anti-Xa activity is 0.6 ± 1.0 u/ml ± 1 . Anti-Xa levels of 1.5 ± 2.0 u/ml ± 1 are considered therapeutic for CPB. However, it is difficult to tune the implementation of anti-Xa assays to CPB, due to the time constraints of the latter (Koniari et al., 2010). Some authors have therefore suggested to double the ACT baseline value, on an empirical basis, to more than 999 seconds, while others (East et al., 2000) proposed a preoperative set-up of heparin-celite/ACT titration curves in order to assess the effect of aPL antibodies on ACT monitoring. There is no consensus in literature on the best way to ensure adequate intraoperative anticoagulation but heparin is routinely administered for its safety profile and the broader clinical experience. In the six case report Weiss refers to, unfractionated heparin was administered at doses ranging from 357U/Kg to 775U/Kg, without any intraoperative complications due to ineffective anticoagulation (Weiss et al., 2008). One patient suffered from postoperative bleeding, and in all cases target ACT was higher than 550 seconds. Other therapeutic strategies, such as the one based on the use of bivalirudin, have been performed on APS patients with heparin-induced thrombocytopenia.

Bivalirudin is a direct thrombin inhibitor that produces an effective attenuation of thrombus formation due to its particular action. In fact bivalirudin not only inhibits the active site of the thrombin, but it also recognizes its fibrinogen-binding site, preventing the activation of both the fluid-phase thrombin and the fibrin-bound thrombin. In the case of bleeding due to excessive anticoagulation, protamine sulfate should be continuously administered in small intravenous doses, e.g. 50 mg/h (Gorki et al., 2008), until the bleeding is reduced. Antifibrinolytic drugs, aprotinin or plasmin inhibitors, which are commonly used to stop the bleeding, are not usually given because of the potential risk of postoperative thrombosis. In two cases, however, epsilon-aminocaproic acid was administered without incurring in any subsequent complication. In conclusion, antithrombotic perioperative strategies, which must be agreed upon with the hematologist, should be identified in all APS patients undergoing cardiac surgery.

3.6 Management of myocardial dysfunctions

It is debated whether APS patients may experience a systolic or diastolic dysfunction unrelated to hypertension, valve heart disease or CAD. Isolated autopsic studies in subjects who died of heart failure, showed diffuse cardiomyopathy with microthrombosis of small intramyocardial arterioles with surrounding microinfarctions without vasculitis, suggesting a direct thrombotic effect of aPLs. Myocardial thrombotic microangiopathy has been found in catastrophic APS patients who suffered from MI with a normal angiographic profile of coronary arteries. Echocardiographic studies have shown the presence of primitive diastolic dysfunction despite the absence of systolic dysfunction or other cardiac disease. In a cross-sectional study (Tektonidou et al., 2001) the echocardiographic parameters reflecting right ventricular dysfunction (prolonged deceleration time, isovolumetric relaxation time, E/A ratio-parameters) were associated with high titers of aCLs. As in other cardiac diseases, the diastolic dysfunction may in some cases anticipate overt left ventricular failure. We do not know what treatment is effective in preventing myocardial dysfunctions and therefore the treatment administered should be the one recommended by the systolic and diastolic heart failure guidelines.

3.7 Management of Pulmonary Hypertension

See 4.3 Pulmonary Hypertension

4. Management of lung diseases

4.1 Introduction

A wide variety of pulmonary manifestations are found in APS patients. The most frequent ones are Pulmonary embolism (PE) and Pulmonary hypertension (PH), while the less common ones include Acute respiratory distress syndrome (ARDS) and Diffuse alveolar hemorrhage (DAH).

4.2 Acute pulmonary embolism. Treatment

Acute pulmonary embolism is the most frequent pulmonary complication (40%) and in about half the cases is preceded by deep venous thrombosis (DVT). Its treatment does not differ from the one adopted on non-APS patients: acute anticoagulation with unfractionated

or low molecular weight heparins, followed by long-term oral warfarin. In the event of adverse reactions or other contraindications to heparin, the use of direct thrombin inhibitors in the acute phase (e.g. intravenous hirudin and its derivative bivalirudin) or Xa factor inhibitors (fondaparinux) is recommended (Tapson & Humbert, 2007). In patients with recurrent PE due to persistent DVT of the legs, the placement of inferior vena cava filters may be performed. Thrombolytic therapy, as in all patients with acute PE, is indicated in the case of hemodynamic instability associated with acute right ventricular failure. As previously discussed when debating the intensity of anticoagulation, it seems reasonable to recommend an international normalized ratio (INR) between 2.5 and 3.5.

4.3 Pulmonary Hypertension

4.3.1 Preliminary remarks

Pulmonary Hypertension (PH) is a serious condition with significant morbidity and mortality rates, which has a frequency of 3.5% in primary APS and of 1.8% in APS with SLE. PH in APS develops as a result of: A - acute pulmonary embolism, B - mitral/aortic valvulopathy in Libman-Sacks endocarditis, and C - in the absence of identifiable lung or cardiac disease (Idiopathic pulmonary hypertension). A - Chronic thromboembolic pulmonary hypertension (CTEPH) develops in about 3% of subjects who experienced an episode of acute PE with relation to incomplete resolution of acute clotting, leading to an endothelial damage triggering a series of remodeling events with in situ development of microthrombi (Hoepfer et al., 2006). B - In the Libman-Sacks endocarditis, non-bacterial vegetations cause valvular regurgitation, high left heart filling pressures that lead over time to passive pulmonary venous hypertension. C - The association of aPLs with Idiopathic pulmonary hypertension (IPAH) is mentioned in studies regarding small series of patients: in 24 patients, mainly SLE ones, aPLs were found in 68% of cases (Asherson et al., 1990). The role of aPLs in the IPAH pathogenesis is unknown but they may induce the production of endothelin-1 (ET-1), a powerful vasoconstrictor, in some patients.

4.3.2 Pulmonary Hypertension. Treatment

Chronic anticoagulation, necessary to prevent the formation of new thromboemboli, is paramount in PH, but the treatment of choice remains the pulmonary thromboendarterectomy (PTE) introduced by Jamieson (Jamieson et al., 2003). The surgical procedure requires a very complex technique performed in cardiopulmonary bypass with intermittent circulatory arrest that allows the surgeon the full view of the thromboembolic material and its dissection. PTE should be performed early in the course of the illness when pulmonary vascular resistance, measured via right heart catheterization, is still not irreversibly high, as mortality is related to the degree of preoperative vascular resistance. If a high resistance persists after surgery, that is a sign of strongly negative outcome. For this reason some authors suggest to perform PTE only if a significant improvement in pulmonary vascular resistance (> 50%) is expected after surgery (Dartevelle et al., 2004). In patients who are ineligible for surgery, the literature produced between 1990 and 2000 reported variable success rates with relation to vasodilator therapy with calcium channel blockers or with long-term infusion of epoprostenol (prostacyclin). From a general point of view, we have drugs for the treatment of pulmonary arterial hypertension (PAH), approved by the United States Food

and Drug Administration (FDA), that antagonize the three pathogenic mechanisms of PAH: 1. endothelin receptor antagonists (relative excess of ET-1), 2. phosphodiesterase-5 inhibitors and 3. prostacyclin analogues (relative deficit of nitric oxide and prostaglandins). Bosentan, a non selective oral endothelin receptor antagonist, is used to improve exercising capacity in IPAP and in PH depending on either scleroderma or congenital systemic-to-pulmonary shunts of the Eisenmenger's syndrome, but its application in other forms of secondary pulmonary hypertension is uncertain. Pulmonary venous hypertension caused by valve abnormalities in Libman-Sacks endocarditis, requires the implementation of the usual measures aimed at reducing pulmonary congestion, first of all the administration of diuretics. Valve replacement may be necessary if left ventricular dysfunction becomes severe. Anticoagulation is recommended to prevent valve thrombosis and subsequent systemic embolic phenomena, but the treatment does not fix valvular lesions (See 3.3 - Management of valve abnormalities).

4.4 Acute respiratory distress syndrome (ARDS). Treatment

ARDS is a form of non-cardiogenic pulmonary edema that occurs in the setting of normal atrial and ventricular filling pressures. It is defined by the presence of bilateral pulmonary infiltrates with a partial pressure arterial oxygen (PaO₂) to fraction of inspired oxygen (FiO₂) ratio below 200, and it is most frequently reported in catastrophic APS. In the early stages of ARDS, the alveolar capillary membrane permeability is increased, causing the passage of red cells and neutrophils into the alveoli. The migration of immunoglobulins and aPLs into the alveoli has also been demonstrated, suggesting the key role of aPLs in driving the ARDS process. On the other hand, it is possible to assume that the 'cytokine storm' found in CAPS is the main event increasing capillary permeability with neutrophils migration. The management of ARDS patients consists, apart from anticoagulation, of high doses of steroids and, occasionally, of pulses of cyclophosphamide and plasmapheresis (Stojanovic, 2006).

4.5 Diffuse alveolar hemorrhage. Treatment

Diffuse alveolar hemorrhage (DAH) shows widespread alveolar infiltrates determining dyspnea, cough, fever, hypoxemic respiratory failure with hemoptysis found in 70 % of cases. The histological lesion at the basis of DAH is pulmonary capillaritis, in which the migration of neutrophils into the interstitium causes necrosis and damage to capillary integrity, with intra-alveolar red cell extravasation. Such migration may be caused either by aPLs, through the up-regulation of endothelial cell adhesion molecules, or by the C5a complement fraction that activates neutrophils. Treatment is the same as in ARDS, with corticosteroid and cyclophosphamide immunosuppression representing an important therapeutic tool. It starts with the administration of high doses of corticosteroids (IV methylprednisolon 1g/d for 3-5 days) and cyclophosphamide pulse therapy is used if recurrence occurs after the cessation of steroids. Almost all DAH patients already treated with corticosteroids improve after the addition of cyclophosphamide (Deane & West, 2005). In refractory cases, IV immunoglobulins and plasma exchange may be used. In the case of hemoptysis, it may be necessary to suspend anticoagulation and resume treatment as soon as lung conditions improve.

5. Management of kidney diseases in APS

5.1 Introduction

Renal manifestations in APS depend on the involvement of intrarenal small vessels, causing APS nephropathy (APSN), and of large extrarenal vessels.

5.1.1 APS nephropathy

APS nephropathy is a well defined clinicopathological entity characterized by a vasoocclusive disorder of the kidney microcirculation. It includes acute lesions in form of Thrombotic Microangiopathy (TMA) with mesangiolysis and/or double contours of the glomerular wall, variously associated with chronic lesions (fibrous intimal hyperplasia, focal cortical atrophy, arteriolosclerosis, tubular thyroidization) (Nochy et al., 1999). The prevalence of microangiopathic thrombotic lesions causes acute kidney failure often associated with malignant hypertension and nephrotic or sub-nephrotic proteinuria. Chronic lesions are associated with moderate hypertension, chronic kidney failure and mild proteinuria. Fibrous Intimal Hyperplasia (FIH) shows intimal thickening by myofibroblastic cells leading over time to arteriolar occlusion due to fibrous projections and organized thrombi. Focal Cortical Atrophy (FCA) is characterized by focal areas of fibrosis and retraction of the subcapsular cortex on ischemic basis. The described lesions are found in primary APS, in secondary APS with SLE nephritis, with TMA being especially observed in catastrophic APS. In SLE patients with aPLs, APSN occurs in a very high percentage (39.5%) (Tektonidou et al., 2004) while it is present in just 4.3% of SLE patients without aPLs. APSN in addition to SLE represents an additional risk factor for renal morbidity, hypertension and interstitial fibrosis, the last two being well known prognostic indicators of kidney function. During catastrophic APS, kidneys are the organs most frequently involved (71%) (Cervera et al., 2009), resulting in acute renal failure, severe hypertension, proteinuria and hematuria.

5.1.2 Involvement of extrarenal vessels

Hypertension is commonly observed in both primary and secondary APS, and is frequently associated with livedo reticularis. Uncontrolled hypertension can be caused by renal artery stenosis (RAS) or, less commonly, by renal infarctions (Alchi et al., 2010). RAS shows two angiographic patterns: generally smooth, non-critical stenosis in the mid-portion of the renal artery and, rarely, more proximal atherosclerotic-like lesions. The nature of RAS in APS remains unclear, but the good response to anticoagulation with recovery of renal function and normalization of blood pressure, suggests the existence of a thrombotic basis (Godfrey et al., 2000). Finally, both primary APS and aPL-positive patients with SLE nephritis, especially those who are LA positive, are prone to develop thrombosis of the renal veins and inferior vena cava, associated with nephrotic range proteinuria.

5.2 Treatment

The management of renal manifestations of APS depends mainly on the identification of specific complications, either intra- or extrarenal, and it is similar to the general treatment of APS. The basic principles of the treatment are as follows: A - general measures to reduce renal damage progression, B - treatment of APS nephropathy, C - treatment of extrarenal vascular occlusions/stenosis, D - treatment of kidney failure in CAPS. A - In an attempt to

slow down the decrease of the glomerular filtration rate, we should identify and address the factors that contribute to kidney damage, with particular relation to hypertension. Symptomatic treatment is based on the inhibition of the renin-angiotensin system, whose role in the genesis of renal injury is largely acknowledged. ACE inhibitors and AT1 receptor antagonists are the elective therapeutic remedies. The blocking effect of the renin-angiotensin system results in a specific renoprotective action (Fogo, 2001), in a containment of proteinuria and in a better control of hypertension. The mean arterial pressure should be kept within the 90 mm/Hg value. Other forms of renal protection include general measures of containment of the vascular risk and, where indicated, a low dietary protein intake, usually with serum creatinine > 2- 2,5 mg/dl. B - Treatment of APS nephropathy is based on anticoagulation with heparins and warfarin. Although there are no evaluation studies on anticoagulant therapy in aPL-associated nephropathy, anticoagulation with warfarin should be lifelong, because the risk of recurrent thrombotic events exceeds the risk of bleeding. Immunosuppressive agents are not used in primary APSN because they do not prevent thrombosis, even though a few reports showed beneficial effects, perhaps on the basis of a decrease in the aPL-induced inflammatory response. For instance, cyclophosphamide (500 mg/m² IV monthly for twelve months) or azathioprine (2.0 mg/kg/day) and steroids were administered by Korkmaz with some effectiveness in patients with moderate renal insufficiency (creatinine: 1.0-2.7 mg/dl) and variable proteinuria (0.6-10.1 g/24 h), in combination with warfarin (to ensure an INR > 2.5) (Korkmaz et al., 2003). The immunosuppressive treatment is mandatory in patients with APS nephropathy associated with SLE nephritis, where warfarin is administered with corticosteroids and cytotoxics, usually cyclophosphamide and azathioprine. Mycophenolate mofetil has recently proved more effective than cyclophosphamide in inducing remission of severe lupus nephritis with fewer side effects, and it might represent a viable alternative to azathioprine in maintenance therapy (Zhu et al., 2007). C - Occlusive and/or stenotic complications regarding extrarenal vessels are treated with unfractionated or low molecular weight heparins followed by oral anticoagulation with warfarin. With relation to RAS, anticoagulant therapy may play a role in stabilizing or improving stenosis and in preventing restenosis after angioplasty. Some reports showed that anticoagulation with INR >3 may reverse arterial stenosis and achieve subsequent clinical improvement (Sangle et al., 2005; Ben-Ami et al., 2006). D - First-line APSN therapy associated with catastrophic APS is based on a combination of corticosteroids plus IV immunoglobulins and/or plasma exchange (see 8.- Management of Catastrophic APS). We think that IV immunoglobulin or plasma exchange may also play a role in acute forms of APSN supported by TMA unresponsive to anticoagulation, and that extracorporeal immune-absorption procedures, that selectively remove IgG molecules, may represent a viable alternative to traditional apheretic techniques.

6. Management of thrombocytopenia in APS

6.1 Introduction

Thrombocytopenia, defined by a platelet (PLT) count of less than 100-150 x 10⁹/L, is one of the main features of APS, found in ~ 25% of PAPS patients and in ~ 40% of cases of APS with SLE. Furthermore, primary immune thrombocytopenia (PIT) and APS have in common aPL autoantibodies, suggesting a similar pathophysiology. Liebman's review reported six studies - published between 1994 and 2006 - that showed a very frequent (~ 50%) detection

of aPLs in PIT (Liebman, 2007). Those papers showed no correlation between aPLs titre and severity of thrombocytopenia (PLT count $<50 \times 10^9/L$). Two of them established a relation between aPLs and rates of thrombotic events, albeit with discordant results. In Stasi's study no thrombotic event was revealed at median follow-up of 31 months (Stasi et al., 1994), while Diz-Kucukkaya found that aPLs positivity, specifically LA positivity, is an important thrombotic risk factor (Diz-Kucukkaya et al., 2001). In fact 60% of aPL-positive patients, but none of the aPL-negative, developed thrombotic events at the five-year follow-up. The mechanism of thrombocytopenia in APS is unknown and most authors state it is immune-mediated and not due to a consumptive process.

6.2 Treatment

Thrombocytopenia associated with APS is usually moderate ($> 50 \times 10^9/L$), it shows no clinical manifestations and rarely requires interventions. Treatment is indicated when thrombocytopenia is marked ($<30 \times 10^9/L$) and symptomatic with bleeding. Therapeutic options include steroids, intravenous immunoglobulins (IVIG), immunosuppressive agents (azathioprine, cyclophosphamide) (Lim, 2009). The employment of newer agents such as rituximab, and exceptionally the practice of splenectomy, should be considered in case of failure of conventional therapies. In the absence of clinical trials or guidelines, Galli suggested that treatment regimes of APS thrombocytopenia should be similar to those of PIT, due to their shared features and pathophysiology (Galli et al., 1996). We extrapolated the following therapeutic patterns, with the relevant drug dosages, from the recent International Consensus Report on the Investigation and Management of Primary Immune Thrombocytopenia (Provan et al., 2010). *First-line therapy:* 1 - Glucocorticoids are the standard initial treatment. Prednisone is usually administered in doses of 0.5-2mg/kg/d. Administration of dexamethasone 40 mg/day (equivalent to 400 mg of prednisone a day) for 4 days every 2-4 wk for 1-4 cycles, produces sustained response on the PLT count. Parenteral administration of high-dose methylprednisolone (30 mg /kg/d for 7 d) followed by oral steroids, is also effective. 2 - IV immunoglobulins: IVIG treatment shows a quicker response in PIT compared to corticosteroids. The standard regimen includes the infusion of 0.4 g/kg/d for 4-5 days, but we are more likely to obtain a PLT increase using high doses of 1g/Kg/d for 1 or 2 days. Rare but dangerous toxicities include kidney failure and thrombosis. *Second-line treatment options:* 1 - immunosuppressive agents are used in order to achieve an increase of the PLT count considered hemostatic for the individual patient. Azathioprine is administered at doses of 1-2 mg/kg/d (maximum 150 mg/d), and it shows fewer side effects compared to other immunosuppressants: weakness, sweating, increased transaminases, neutropenia with infection, pancreatitis. Cyclophosphamide may be administered either orally (1-2 mg/kg/d) or IV (0.3-1g/Kg for 1-3 doses every 2-4 weeks). Toxicity is mild to moderate and it includes neutropenia, nausea and vomiting, deep leg venous thrombosis. 2 - Rituximab is usually given at doses of 375 mg/m² every week for 4 weeks. In PIT, Rituximab causes a PLT count response in approximately 64% of patients, with a response duration ranging from five to 48 months. The efficacy of rituximab in the treatment of APS patients with thrombocytopenia is still to be determined and only a few studies can be found in literature (Ames et al., 2007; Trappe et al., 2006; Ahn et al., 2005). The most common side effects are infusion-related, such as fever, chills, headache, rash, bronchospasm and hypotension, mostly occurring during the first infusion. After the administration of rituximab, peripheral B cell levels show a dramatic decrease, returning to

near baseline from 6 to 12 months after completion of therapy. Despite such B-cell depletion, a decrease in serum immunoglobulin levels is only found in a minority of patients. Rituximab should not be used in patients with active B hepatitis, because of the risk of hepatitis activation. 3 - Splenectomy is a viable treatment option in thrombocytopenic patients, as approximately 20% of them show a very low PLT count, despite medical treatment and pheresis. Eleven out of fifty-five APS patients with thrombocytopenia required a splenectomy in a retrospective study (Galindo et al., 1999), that reported a high rate of successful long term response. In view of the potential risk of post-splenectomy arterial thrombosis, intervention should be reserved to severe and symptomatic forms of thrombocytopenia, unresponsive to more conventional treatment. Finally, literature cites isolated cases of thrombocytopenia in APS with good therapeutic response to danazol, aspirin, dapsone, chloroquine.

6.3 Treatment of bleeding complications

Bleeding is considerably less frequent than thrombosis, as shown by the Italian Registry of Antiphospholipid Antibodies, which takes into account 319 patients: only 4 out of 80 of thrombocytopenic subjects suffered major bleeding events. Finazzi, revising the same Registry, found 32% of thrombotic events, but no bleeding, in 44 patients with a PLT count between 100-150 $\times 10^9/L$. (Finazzi, 1997). In the 32 patients with a PLT count $< 50 \times 10^9/L$, bleeding was observed in 6%, and thrombosis in 9% of cases, indicating the possibility of thrombosis in spite of severe thrombocytopenia. In accordance with Lim's review, we report the following practical recommendations regarding the treatment of active hemorrhages (Lim, 2009). Bleeding occurring in the central nervous, gastrointestinal or genitourinary system often requires a rapid increase of the PLT count. In some cases, it is sufficient to switch from the steroid to the immunoglobulin therapy, but it seems more appropriate to adopt a combination treatment with corticosteroids and IVIG. Platelet transfusions, leading to a post-transfusional PLT increase of about 20 $\times 10^9/L$, may be associated. Antifibrinolytic agents, such as oral or IV tranexamic acid (1 g, three times a day) and epsilon-aminocaproic acid (1-4 g every 4-6 hours) may be useful in preventing recurrent bleeding. On the other hand, if bleeding is due to the anticoagulant treatment, therapy should be temporarily discontinued administering the relevant antidotes (protamine sulfate for heparin, vitamin K for warfarin), and practising the transfusional support (fresh plasma for heparin and warfarin, prothrombin concentrated complexes for warfarin). In patients with severe thrombocytopenia and high thrombotic risk, the PLT count should be brought to at least 30-50 $\times 10^9/L$, for anticoagulation to be adequately performed. It does not seem useful to reduce the intensity of anticoagulation in those cases, as we infer from data regarding secondary prevention of deep vein thrombosis that low doses of warfarin are not protective.

7. Management of dermatological diseases in APS

7.1 Introduction

The skin appears to be an important target organ for aPLs and 40% of the patients may present cutaneous features as a major complaint. Skin lesions may be sorted according to their seriousness in 'major' (widespread cutaneous necrosis and/or digital gangrene) and 'minor' (e.g. livedo reticularis, superficial thrombophlebitis, pseudo-vasculitis lesions, circumscribed ulcerations, subungual splinter hemorrhages). Major ones are caused by non inflammatory

thrombosis of small arteries of the dermis and subcutaneous fat. The most frequent (17.5% to 40%) and typical skin manifestation is livedo in both its reticularis and racemosa versions, characterized by a purplish reticular or mottled skin pattern consisting of regular unbroken circles (livedo reticularis) or irregular circles (livedo racemosa), that is irreversible even after rewarming. Livedo racemosa has a more generalized location, being widespread all over the trunk, limbs and buttocks. The distinctive skin color of livedo is related to the reduced blood flow and the oxygen tension caused by vasoconstriction. Some authors state that livedo racemosa is a predictor of systemic thrombotic events, as there is evidence of a strong association between the former and cerebrovascular/ocular ischemic events, arterial thrombosis, migraine, epilepsy and renal artery stenosis (Toubi et al., 2005). The association of livedo with Sneddon's syndrome, typically affecting women before or during their middle age, is debated. This syndrome shows widespread livedo that precedes the onset of stroke by several years, and many authors found that 40%-50% of the patients affected are aPL-positive (Frances et al., 1999). The relationship between livedo and arterial thrombosis suggests a possible common role played by endothelial cells. In fact, many aPLs interact with the phospholipid-protein complexes on the surface of endothelial cells, therefore leading to the production of procoagulant substances such as tissue factor (TF), plasminogen activator inhibitor-1 and endothelin-1. This interaction between aPLs and endothelial cells may cause the vasoconstriction typical of livedo racemosa (Amengual et al., 1999).

7.2 Treatment

The treatment of patients with cutaneous manifestations should take into account the kind of skin lesion and the overall clinical situation. In the absence of RCTs regarding prophylaxis and therapy of dermatological lesions, treatment remains empirical. Digital gangrene and skin necrosis are the major thrombotic events requiring full anticoagulation with heparin (Rossini et al., 2002). Should lesions persist despite anticoagulation, some reports suggest alternative treatments (iloprost, tissue plasminogen activator, gammaglobulins, corticosteroids, plasma exchange and immunosuppressive therapy) (Frances et al., 1989; Srinivasan et al., 2001; Zahavi et al., 1993). Major cutaneous lesions may appear particularly serious in the context of multiorgan thrombotic occlusion during catastrophic APS in which combined treatments are required (see 8.- Management of Catastrophic APS). Frances recommends long-term anticoagulation with INR targeted to 2.5 for the prophylaxis of severe skin lesions (Frances, 2010). In patients who have 'minor' cutaneous manifestations with no other systemic features, e.g. circumscribed ulcers or pseudovasculitis lesions, the administration of low doses (75 mg/d) of aspirin may be useful, although anticoagulant therapy must be adopted if lesions persist or worsen (Asherson et al., 2006). In any case, removal of the necrotic tissue and local antiseptic therapy are paramount for the reduction of the infective risk. Livedo racemosa resists to anticoagulant or antiplatelet therapies, as it appears and extends in spite of them. In the European APS cohort (Cervera et al., 2002), where most patients were anticoagulated, livedo appeared in 26 cases during the five-year follow-up. Livedo is less evident in tanned areas, but it is known that exposure to sunlight is not recommended for SLE patients with APS. In view of the thrombotic risk in aPL-positive patients with livedo, it is important to reduce or remove other provoking factors, therefore men are advised to stop smoking and women not to use contraceptive pills containing estrogens. For the same reason, those patients should

be properly screened in order to detect silent cerebral ischemia and/or kidney illnesses, and warfarin therapy should be adopted if needed. Even though low doses of aspirin are commonly prescribed to patients with livedo and no systemic features, its effectiveness in the prevention of strokes remains doubtful.

8. Management of catastrophic APS

8.1 Introduction

In 1992 Asherson described a potentially life-threatening variant of APS called catastrophic APS (CAPS), and subsequently named Asherson's syndrome (Asherson, 1992). It is characterized by multiple organ failure due to thrombotic microangiopathy (TMA) involving several organs, either simultaneously or in rapid sequence: brain, heart, kidneys, lungs, gastrointestinal tract. In 35% of cases it is possible to identify a triggering factor, which is mainly an infection or sepsis originating from the respiratory, urinary, gastrointestinal tracts. A pathogenic link between infections and CAPS has been acknowledged and its rationale is based on the theory of molecular mimicry, according to which β 2GPI peptides share the amino acid sequence and conformational structure with common bacteria and viruses. As common microbial structures represent the natural ligand for toll-like receptors (TLRs), it has been argued that β 2GPI might interact with TLRs and that anti- β 2GPI antibodies recognizing the molecule might cross-link it together with TLRs (Espinosa et al., 2007). Ultimately, TLRs intracellular signaling pathway leads to a proinflammatory and prothrombotic phenotype of endothelial cells, respectively through the production of proinflammatory cytokines and adhesions molecules, and the up regulation of the tissue factor. Other triggering factors of CAPS are the withdrawal or the administration of low doses of anticoagulants, invasive or surgical procedures, cancer, lupus flares, obstetric complications.

8.2 Treatment

CAPS appears in less than 1% of APS patients and carries a high mortality rate. Although there are no RCTs for this rare syndrome, the CAPS International Registry, accessible via the Web, provides us with important clinical, prognostic and therapeutic data. We can see that the CAPS mortality rate went to 33% between 2001 and 2005, down from 50% in the years before 2000 (Bucciarelli et al., 2006), and that may be due to the early treatment of triggering factors and even more to the improvement of first-line therapy, which should always include anticoagulation, corticosteroids and plasma exchange. This is in accordance with the International Consensus on CAPS management guidelines (Asherson et al., 2003) that recommends: effective anticoagulation with IV heparin, plus high doses of steroids, plus IV Immunoglobulins (IVIg) and/or plasma exchange (PE). The following are some considerations on the use of A. corticosteroids, B. immunoglobulins and C. plasma exchange with relation to this syndrome: A. Corticosteroids interact with the cytoplasmic receptor, and the resulting steroid receptor complex neutralizes Nuclear Factor- κ B (NF- κ B), which in turn activates transcription genes for the synthesis of pro-inflammatory molecules (TNF- α , interleukins-1 and 2, cyclooxygenase-2 and intercellular adhesion molecules (ICAM). Moreover, corticosteroids partly neutralize activator protein-1, triggering the transcription of several genes involved in the synthesis of pro-inflammatory proteins. There is evidence of NF- κ B playing an important role in states, such as sepsis and ARDS, frequently associated with

CAPS. Consequently, the inhibition of NF- κ B and the down regulation of the cytokines, both corticosteroid-induced, are beneficial in reducing host-derived tissue injury and organ dysfunctions when treating CAPS. B. IV immunoglobulins, that are immunomodulating agents, perform several activities. These include block of pathological autoantibodies, modulation of complement activation, clearance of pathological IgG and suppression of pathogenic cytokines. IVIG contain anti-idiotypic antibodies capable of recognizing and specifically suppressing different autoantibodies. That might explain both the short term neutralization of the aPLs pathogenic role and the long term decrease in the aPLs titre. (Vora and al., 2006). C. The effectiveness of plasma exchange therapy is widely acknowledged, although both the replacement fluid to be used (whether albumin solutions or fresh frozen plasma) and the timing and frequency of treatments, are still debated (Uthman et al., 2005). The guidelines recommend the use of fresh frozen plasma (FFP), especially in the presence of thrombotic microangiopathic hemolytic anemia (e.g. schistocytes). In fact thrombotic microangiopathies (TTP, HUS, HELLP syndrome) have in common with CAPS similar hematological manifestations (aPL positivity, thrombocytopenia, microangiopathic hemolytic anemia) and triggering factors (e.g. infections, drugs) (Asherson, 2007). Moreover such conditions, including HELLP syndrome at post-partum period, may require similar treatment with plasma exchange, using fresh frozen plasma instead of albumin reinfusion. (Szczepiorkowski et al., 2007). Although the exact mechanism of plasma exchange is still unknown, it has been demonstrated that PE is effective in removing IgG-CL, anti- β 2GPI, cytokines, complement and TNF- α . We propose the use of IV methylprednisolon at doses of 1g/d for 3-5 consecutive days, followed by oral steroid at a dose equivalent to 1mg/Kg/d of prednisone; IV Immunoglobulins at 1g/Kg/d for two days ; plasma exchange with reinfusion of FFP not inferior to the volume of plasma, for at least 3-5 days. In the absence of clinical improvement, other therapies should be provided: cyclophosphamide in SLE flares, prostacyclin or fibrinolytics or defibrotide. In CAPS patients with severe thrombocytopenia resistant to other forms of treatment, the administration of rituximab may be useful, as the direct inhibition of B-lymphocytes contributes to the decrease of the aPLs titre and the subsequent platelet activation (Erre et al., 2008). Finally, the objectives to be aggressively pursued in the management of CAPS are essentially four: 1 - addressing the triggering factors (adoption of antibiotic therapy in the event of infection and surgical toilet of the infection sources), 2 - maintenance of effective anticoagulation, also when CAPS is associated with thrombocytopenia, 3 - suppression and/or removal of cytokine excess, 4 - adoption of intensive care measures when necessary. Such strategy plays an essential role in the survival of CAPS patients whose mortality, as shown by the CAPS registry data analysis regarding 112 patients, is due to: neurologic involvement (mainly stroke) (27.2%); cardiac involvement (mainly cardiac failure) (19.8%); infections (mainly bacterial sepsis) (19.8%); multi organ failure (17.3%); pulmonary involvement (mainly ARDS) (9.8%); abdominal involvement, including liver failure and acute abdomen, in four patients (Espinosa et al., 2008). The presence of SLE is the only prognostic factor predicting a higher mortality (59% vs 37.9%) regardless of clinical manifestations, number of organs involved, laboratory parameters and treatment adopted (Bayraktar et al., 2007).

9. Conclusions

In APS patients, the current therapeutic standard is oral anticoagulation aimed at preventing thrombotic events. Warfarin or coumarin inhibit the synthesis of vitamin K-

dependent clotting factors (FII, FVII, FIX, FX) and of anticoagulant plasma proteins C and S. The INR target should be kept between 2 and 3 in case of first venous thrombotic event, while it should be higher than 3 in case of arterial thrombosis and/or recurrent venous thrombosis. In women with obstetric complications treatment is based on the use of aspirin and heparin. The treatment of choice for patients suffering from acute thromboembolic event is the administration of unfractionated heparin which, through the activation of ATIII, indirectly inhibits thrombin formation and inactivates Xa factor. Alternatively, we can use LMWH, whose binding to ATIII causes above all of all the inactivation of Xa factor, and then of thrombin to a lesser extent. LMWHs have a more predictable pharmacological effect and they induce thrombocytopenia less frequently, due respectively to their weaker binding with plasma proteins and with platelets. Anticoagulation may be ineffective or even contraindicated under certain clinical circumstances. In fact, some manifestations of APS, such as cardiac valvular disease, livedo reticularis and thrombocytopenia, are unresponsive to anticoagulation. Moreover, some patients experience thromboembolic events despite anticoagulation, while others do not tolerate full doses of warfarin because of its hemorrhagic side effects. Additional drugs have been introduced over the years in order to overcome such problems. Their therapeutic use has been found following experimental evidence, tested *in vitro* and/or on animal models, that revealed the pathogenic effects of aPL/ β 2GPI complexes both on hemostatic reactions and on the activation of cellular elements (endothelial cells, monocytes, platelets), also clarifying the role of B cells in the aPLs synthesis. We think that clinical experiences based on thrombin-inhibitors, on hydroxychloroquine, statins and B-cell depletion therapy (e.g. rituximab) have been so far the most interesting ones and we can assume they will be consistently adopted in the management of APS. In particular dabigatran, a new direct thrombin-inhibitor, usually prescribed at a dose of 150 mg twice a day for the prophylaxis of post-operative venous thromboembolism, could represent a viable alternative to warfarin. Dabigatran is administered orally and does not require anticoagulation monitoring, although we need clinical studies validating its use in APS patients. Hydroxychloroquine, which directly inhibits the binding of aPL/ β 2GPI complexes to phospholipid surfaces, has the advantage of not causing bleeding, and therefore it is useful in patients showing hemorrhagic side effects caused by warfarin. Hydroxychloroquine can also be used, in view of its antiplatelet effect, in those patients who have experienced thrombotic recurrences despite anticoagulation. It is usually administered at doses of 400-800 mg/d and, because of its potential retinal toxicity, ophthalmic examination is essential prior to therapy. Controlled studies regarding the effectiveness and safety of its use have not been produced yet. Statins are an additional tool in the APS treatment due to their anti-atherosclerotic and anti-inflammatory effect, only partially depending on the relevant cholesterol decrease. Experimental studies indicate that they may act by reducing the aPL-induced endothelial activation, by blocking NF-kB pathway and the subsequent synthesis of adhesion molecules and IL-6, and by reversing the up-regulation of the tissue factor (Espinosa & Cervera; 2010). In addition, it has been shown that rosuvastatin is effective in reducing venous thromboembolic events in non-APS patients but also in this case we do not have clinical data indicating that statins prevent the formation of thrombi in APS patients. The experience with rituximab is still limited although encouraging reports, mainly dealing with the recovery of thrombocytopenia, have recently been published. We are currently waiting for the results of the ongoing Pilot Study of Rituximab for the anticoagulation-resistant manifestations of APS (RITAPS). This open-label trial will assess safety and efficacy of rituximab in those manifestations of APS which

prove unresponsive to anticoagulation. In conclusion, despite promising results provided by the aforementioned treatments, we feel that well-designed randomized trials are still needed.

10. References

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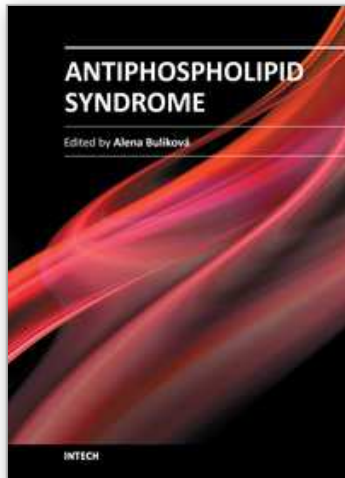
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The antiphospholipid syndrome has been described for the first time by Graham Hughes in 1983 as a condition connected with thromboses or foetal losses and antiphospholipid antibodies presence. From that time there has been a great progress in knowledge, including antiphospholipid antibodies characterisation, their probable and also possible action, clinical manifestations, laboratory detection and treatment possibilities. This book provides a wide spectrum of clinical manifestations through Chapters written by well known researchers and clinicians with a great practical experience in management of diagnostics or treatment of antiphospholipid antibodies' presence.

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