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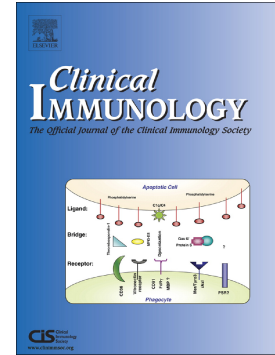
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Treatment of Antiphospholipid Syndrome

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Abstract

Antiphospholipid syndrome (APS) is the most common acquired thrombophilia. The clinical manifestations of APS are mainly vascular thrombosis (venous and/or arterial) and/or pregnancy morbidity with the concomitant persistent presence of antiphospholipid antibodies (aPL). Therefore, the goals of the treatment of patients with APS are reducing the pregnancy morbidity

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and/or the prevention of thrombotic events during the follow-up. Optimal treatment of APS has long been discussed, due to the heterogeneity of the clinical manifestations and the consequent plurality in the medical specialties involved in managing this condition. This review summarizes the available evidence on primary thromboprophylaxis in aPL-positive individuals with no prior thrombotic events, secondary prophylaxis in patients with positive history for thrombotic events, the management of refractory or difficult cases and the current strategies for the management of APS during pregnancy.

Keywords

Antiphospholipid syndrome, APS, Antiphospholipid antibodies, aPL, anticoagulation, thrombosis, pregnancy, immunotherapy

Introduction

Antiphospholipid syndrome (APS) is characterized by the presence of persistent positivity for antiphospholipid antibodies (aPL) in patients who experience recurrent pregnancy morbidity and/or vascular thrombosis, which can potentially affect the vascular bed at any level[1]. Therefore, the main goals in patients with aPL are counterbalancing the pro-thrombotic status aiming to prevent thrombotic events (venous and/or arterial) and the optimal care and management of women with aPL during pregnancy and the puerperium. Treatment of APS has

long been debated. The APS Treatment Trends Task Forces, created a consensus document for treatment of APS as part of the International Congress on aPL[2–6]. The task forces systematically reviewed the available evidences on APS treatment and potential future treatment strategies for aPL-positive patients. More recently, the European League Against Rheumatism (EULAR) recommendations for the management of APS in adults have been released[7].

In this review, we will discuss the current evidence for primary thromboprophylaxis in aPL-positive individuals with no history of thrombosis, secondary prophylaxis in patients with previous thrombotic events, with a special focus on the treatment of refractory or difficult cases of thrombotic APS. Current strategies for the management of APS during pregnancy and lactation will be also discussed. A summary of our therapeutic algorithm is summarized in Figure 1.

Primary Thromboprophylaxis

Despite the huge progresses that have been made in understanding APS mechanisms, it is still a matter of discussion whether prophylactic treatment is needed in all subjects with persistent aPL positivity without a previous history of thrombosis. To date, a demonstrated value of undergoing active therapy against placebo has never been proven. However, we advise a cautious thrombotic risk assessment as part of any good clinical practice, considering traditional cardiovascular (CV) risk factors for all aPL positive patients. Based on APS pathophysiology, the main management target in aPL positive patients consists in controlling CV risk factors, to include high blood pressure, hypercholesterolemia, body weight and avoidance of smoking. These concepts are an essential part of the updated EULAR recommendations for the management of the syndrome in

adults[7]. In addition, due to their prothrombotic effects, estrogen-containing oral contraceptive pills or estrogen replacement therapy should be avoided in women with aPL.

It is now accepted that autoimmune diseases, as systemic lupus erythematosus (SLE), have an increased risk of thrombotic events. Consequently, in all patients with an underlying systemic autoimmune disease and aPL at medium–high titers [immunoglobulin (Ig)G or IgM >40 IgG aPL units (GPL) or IgM aPL units (MPL) or >99th percentile] primary thromboprophylaxis should be considered with low-dose aspirin (LDA, 75–100 mg/day). In patients with SLE and with persistently positive aPL, primary thromboprophylaxis including LDA and/or hydroxychloroquine (HCQ, 200–400 mg/day) is strongly recommended. This recommendation is made based on studies that have shown a protective role of HCQ against thrombotic events in patients with SLE, including those aPL-positive[8].

While there is no study that has specifically assessed whether the combined use of different antiplatelet agents offers an additional protection, LDA is usually considered to be an effective first option in the setting of primary thromboprophylaxis[9]. Due to the general therapeutic recommendation of HCQ in patients with SLE, the addition of LDA should be considered on individual basis. Specifically, the addition of LDA may be considerate in patients at higher thrombotic risk, such as in patients with a high risk aPL profile [e.g., triple positivity for lupus anticoagulant (LA), anticardiolipin (aCL), and anti- β 2-glycoprotein I (a β 2GPI)] and/or other concomitant traditional CV risk factors, and for SLE patients with a history of obstetric APS.

Although LDA seems a logical prophylactic approach, supportive evidences are still anecdotal. The Physician Health Study demonstrated no protection against deep venous thrombosis in men with aCL receiving LDA[10]. However, more recent evidence suggested a protective role for LDA for venous thrombosis, at least in the general population[11].

In asymptomatic aPL carriers without an underlying connective tissue disease, the decision regarding thromboprophylaxis should be best based on the individual aPL profile. In this setting, LDA is recommended for those with a high-risk aPL profile, such as patients with LA, and particularly triple-positive individuals, especially with medium–high titers[10,12–14].

The ALIWAPAS was a prospective, multicenter, randomized, open, controlled trial in aPL positive patients, in which it has been investigated the efficacy and safety of LDA versus LDA plus low-intensity warfarin in primary thrombosis prevention of aPL-positive patients with SLE and/or obstetric morbidity[15]. The study did not find a statistically significant difference between the number of thrombotic events in patients treated with LDA versus those treated with LDA plus low-intensity warfarin. However, more episodes of bleeding were detected in the LDA plus warfarin group. The authors, therefore, concluded that the LDA plus warfarin regimen was significantly less safe and not as acceptable as LDA alone. Indeed, one should keep in mind that LDA treatment alone is also associated with an increased risk of major bleeding events. Among others, for instance, the Framingham Heart Study estimated that the risk for upper gastrointestinal bleeding of LDA is of 1 event per 1000 person-years with adjustment for documented risks associated with individual factors[16].

In order to improve the thrombotic risk assessment in patients with positive aPL, at least two score systems have been created. Otomo et al. developed the aPL-score (aPL-s), in order to determine whether aPL titres influence the risk of thrombosis, comparing high to medium/low titres of aCL and anti- β 2GPI IgG and IgM, respectively. The group showed that high levels of IgG aCL, anti- β 2GPI (and also aPS/PT) were closely related to the clinical manifestations of APS[17].

The Global Anti-Phospholipid Syndrome Score (GAPSS) was developed by our group, combining the aPL profile and traditional CV risk factors. The GAPSS score was also independently validated as an effective tool to help physicians in stratifying patients according to their thrombotic risk[18,19]. Patients with a GAPSS score ≥ 10 might be considered to be at a higher risk of thrombotic events and therefore require a closer follow-up, especially in high-risk prothrombotic situations (e.g., surgery, immobilization).

Recurrent Thrombotic Events

To date, giving the high rate of thrombotic recurrences (~29% per year without treatment), the main treatment of APS patients with previous thrombosis is based on long-term anticoagulant therapy [20]. Some unanswered questions still remain open: should patients with APS receive the same therapy as the general population with similar manifestations and should arterial and venous events be treated in a different way[20,21].

In two randomized, controlled trials, high target international normalized ratio (INR) (3.0-4.0) with standard intensity of anticoagulation (target INR 2.0–3.0) for secondary thromboprophylaxis in patients with APS were compared[22,23]. The two trials did not show significant differences in terms of efficacy or safety between the two anticoagulation regimens. However, both approaches suffered from a main bias due to the over-representation of patients with first venous thromboembolism. Thus, we recommend indefinite anticoagulant therapy with vitamin K antagonist (VKA) to a target INR of 2.0–3.0 for patients with APS and first venous event. In patients with clear provoking prothrombotic factors (e.g. surgery, prolonged

immobilization) at the time of the thrombosis and low risk aPL profile, a reduction in the duration of treatment with VKA could be considered.

The management of arterial events is more controversial, and many questions remain open for discussion. From the one hand, results from studies such as the APS and Stroke Study (APSSS) concluded that patients with previous stroke event and persistent aPL positivity not fulfilling classification criteria would be best treated as the general population, with LDA[24]. On the other hand, a more aggressive approach has been employed and proposed for those patients with definite APS with arterial disease and/or recurrent thrombotic events using VKA with a target INR of 3.0–4.0. In some cases at higher thrombotic risk, combined anticoagulant (e.g. VKA with INR 2-3) and anti-aggregant therapy has been also considered[25]. Recurrences among the patients receiving effective oral anticoagulation to an INR of 3.0–4.0 are, in fact, quite infrequent (0.016–0.031 events per patient per year) [26]. However, it should be reminded that a regimen of high-intensity oral anticoagulation therapy carries inevitably an increased risk of serious hemorrhage[25].

The management of venous thromboembolism (VTE) is also considered a rapidly changing scenario. The direct oral anticoagulants (DOACs) (dabigatran etexilate, rivaroxaban, apixaban, and edoxaban) have been shown to be effective in the management of VTE with the additional benefit of not requiring laboratory monitoring[27]. However, despite some pilot experiences have shown promising results for the use of DOACs in the management of VTE in the specific setting of APS[28] a recent randomized controlled trial on the use of rivaroxaban versus warfarin in patients with APS with triple aPL positivity was prematurely terminated due to an excess of thromboembolic events (mostly arterial) in the rivaroxaban arm[29]. With the current level of

evidence, rivaroxaban should not be used in patients with triple aPL positivity. The use of DOACs in selected clinical cases with lower aPL has to be carefully evaluated. Similarly, more data are highly needed to investigate the efficacy and safety of other agents other than rivaroxaban in this setting.

Recurrent Thrombosis: Alternative Approaches

Despite appropriate management and adequate treatment strategy, APS patients can still experience thrombotic recurrences. In this case, after proper evaluation of the intensity of anticoagulation and adherence to prescribed therapy, adding medications to traditional treatment regimens represents a useful option[7,30,31].

Hydroxychloroquine

HCQ showed its efficacy in primary and secondary thromboprophylaxis, both in aPL positive and aPL negative SLE patients[32–36]. Many *in vitro* and *in vivo* studies have suggested more than one mechanism through which HCQ could exert its anti-thrombotic ability [37–43] and it shows an excellent safety profile [44]. A prospective non-randomized controlled trial on primary APS (PAPS) patients, showed that adding HCQ 400mg/daily to standard anticoagulation therapy prevented recurrent thrombosis, in a three-year follow-up, compared to control group in which a high rate of relapses (30%) was observed[45]. Moreover, a retrospective study by Nuri and colleagues have reported a significant reduction of arterial events (0% Vs 1.14%), along with a lower, although not significant, risk of thrombotic recurrences (1.16% Vs 1.71%), and a decrease of aPL titers after HCQ administration when comparing exposed and non-exposed patients [46].

A recent randomized, openlabel, prospective trial on long-term efficacy of HCQ in reducing the risk of thrombotic recurrences, in addition to standard of care, corroborated previous results. In fact, patients receiving HCQ showed a lower thrombotic rate (1/25 vs. 6/25, log-rank $p=0.048$) and a down-trending aPL titer[47]. In conclusion, despite the promising results, further evidences are needed in order to confirm the effective role of HCQ in preventing thrombotic recurrences in APS setting. In this scenario, prospective studies, such as the HIBISCUS trial are ongoing, hopefully leading to solid conclusions on this controversial issue[48].

Intravenous Immunoglobulins

Administration of intravenous immunoglobulins (IVIg) exerts both immunomodulatory and anti-inflammatory effects [49,50]. In APS, IVIg have shown to inhibit aPL production due to the presence of anti-idiotypic antibodies, along with aPL activity interference and inactivation of B-cell clones, ultimately leading to a decreased aPL production[51]. Despite an overall good safety profile, severe side effects, such as thrombosis, have been reported and therefore their use in APS patients is still a matter of debate and particular caution should be taken in this setting[52,53]. However, Hsieh have described a case of refractory thrombotic PAPS patient, efficiently treated with IVIg and have observed a concomitant decrease in aPL titers[54]. A prospective five-year follow-up study on high-risk aPL profile refractory thrombotic APS patients showed absence of recurrence after IVIg treatment [55,56]. Furthermore, a prospective open-label study including both PAPS and secondary APS (SAPS) patients have confirmed previous findings showing absence of thrombotic recurrences (0 vs. 3) and significant lower aPL titers in the treated group[57]. In summary, IVIg therapy could represent an additional treatment approach in order to prevent recurrences in thrombotic APS patient.

However, available evidence is limited by the lack of solid and well-designed prospective trials on safety, timing and dosage [58].

Low Molecular Weight Heparins

LMWH could represent a proper alternative to VKA, considering its excellent bioavailability, predictable dose-response, dose-independent clearance and inhibition of APS hypercoagulable state [6,26,59]. Nevertheless, subcutaneous administration is compliance-challenging and side effects, such as induced thrombocytopenia and osteoporosis, have to be acknowledged. Dalteparin (5000U/day) administration resulted in absence of thrombotic recurrence, after a medium follow-up time of 309 days, in a cohort of 24 APS patients [60]. Two case reports have documented lack of thrombotic recurrences after two and six years of follow-up respectively, in patients with refractory thrombotic APS treated with enoxaparin 10.000U/day and dalteparin 10.000 U/day [61]. A retrospective study on 23 refractory APS patients (10 PAPS and 13 SAPS) confirmed previous results: LMWH use [enoxaparin (1mg/kg every 12 hours or 1.5 mg/kg/day) and subcutaneous dalteparin (100 U/kg every 12hours or 200 U/kg/day)] determined absence of thrombotic relapses on a medium follow-up time of 36 months [62]. To date, data on long-term efficacy of LMWH in preventing thrombotic recurrences lack of prospective randomized trial. In this context, international literature describes cases of LMWH therapeutic failure and consequent recurrent thrombosis despite treatment [63,64].

Rituximab

Rituximab (RTX) is a chimeric monoclonal antibody targeting CD20 on B-cells surface. The rationale of its administration in APS patients derived from the key role exerted by B-cells in

APS pathogenesis[65]. The BIOGEAS study group have described a 92% response rate to RTX administration in APS resistant cases [66]. A retrospective study on 63 refractory thrombotic SAPS patients, have reported the absence of relapsing thrombosis after RTX therapy, with a mean follow-up of 39.3 ± 20.9 months [67]. Four weekly doses of 375 mg/m^2 is considered the common regime, although some groups applied different schemes as result of previous experiences[68,69]. To note, data on RTX-induced thrombotic prevention and aPL titer decrease in APS setting are extremely heterogeneous and therefore inconclusive[65,68–72]. Moreover, episodes of severe acute thrombotic exacerbations have been reported after drug administration[66,73]. At present, recommendations sustain RTX treatment in refractory APS patients, particularly in those with hematologic and microthrombotic/microangiopathic manifestations [5]. However, well-structured prospective randomized trials will clarify the real efficacy of RTX in preventing APS thrombotic recurrences.

Recurrent Thrombosis: New Perspectives

Anticoagulation (with VKA or heparins) is currently considered the main therapeutic strategy for preventing thrombotic APS manifestations. Recently, based on the proinflammatory and procoagulant phenotype of APS patients, which have been attributed to immune dysregulation, this paradigm is progressively shifting from anticoagulant agents to also include immunomodulant drugs. Targeting the immune dysregulation has been mainly investigated in refractory cases or when targeting some so called “extra-criteria” manifestation of the syndrome (e.g., cytopenia, skin ulcers) [74]. In this paragraph we summarised the available evidence analysing the role of immunomodulatory agents (beyond HCQ) in the management of APS. A

list of ongoing and upcoming clinical trials focusing on immunomodulator agents for APS is shown in Table 1.

Belimumab

The main role of aPL in the pathogenesis of APS explains the interest in B-cells as autoantibodies' source. The B-cell activating factor (BAFF), by interacting with its receptors, supports B-cells survival and differentiation. Moreover the BAFF's inhibition in murine models led to B-cells depletion [65].

Belimumab is a monoclonal antibody that works by blocking the soluble circulating BAFF. It is approved for patients with active SLE, but little is known in the specific context of thrombotic APS. Nevertheless, belimumab has recently shown to be able to induce PL negativization in SAPS cases [75].

Moreover, two PAPS patients, treated with belimumab for a history of recurrent diffuse alveolar haemorrhage and cutaneous ulceration due to ischemic panniculitis respectively, have been reported [76]. In both cases, the use of belimumab resulted in clinical improvement that allowed to reduce steroid dosage. These evidences suggest that belimumab might have a role in the management of aPL-positive patients with "extra-criteria" manifestations.

Furthermore, it has been demonstrated that PAPS patients present elevated serum levels of BAFF, particularly in those subjects with higher adjusted GAPSS values[77], suggesting that patients with higher thrombotic risk profile might benefit from the use of belimumab.

Eculizumab

aPL induce thrombosis and placental injury through multiple mechanisms, including binding endothelial cells through anti- β 2GPI and inducing a procoagulant state by promoting the expression of adhesion molecules, tissue factor (TF) and the activation of complement pathways. Products of complement activation are potent mediators of platelets, neutrophils, monocytes and endothelial cells activation [78]. Moreover, the anaphylatoxin C5a triggers the release of proinflammatory mediators such as tumour necrosis factor, vascular endothelial growth factor receptor-1, as well as it may inhibit fibrinolysis through increased activation of thrombin activated fibrinolysis inhibitor [79]. Together, these changes lead to the overall increase in inflammatory markers and the enhancement of the pro-thrombotic state, thus, the complement system is likely to play a critical role in the pathogenesis of APS.

Eculizumab is a recombinant humanized monoclonal antibody that binds C5, blocking the formation of the terminal complex C5b-9. It may represent a valuable therapeutic alternative in APS patients, especially in case of concomitant hypocomplementemia. Currently available clinical data supporting the use of eculizumab consist of small number of case reports or case series in severe refractory cases of APS, such as catastrophic APS (CAPS) or thrombotic microangiopathy (TMA).

TMA is a rare disease characterized by endothelial injury that leads to thrombosis in capillaries and arterioles and results in haemolytic anaemia, thrombocytopenia, purpura and renal insufficiency. The complement mediated TMA includes atypical haemolytic uremic syndrome (HUS) and secondary HUS, such as autoimmune forms. The use of eculizumab showed improvement in platelet counts and hematologic value in refractory TMA complicating SLE/APS, proving to be a valid option in case of standard of care failure [80].

TMA in association with aPL antibodies can present as CAPS. This is a rare and the most severe form of APS characterised by a rapid onset of multiple organ thrombosis, that usually affect small vessels. The current treatment consists in administration of anticoagulant, pulse of corticosteroids and plasmapheresis or IVIG. Several case reports have suggested the efficacy of eculizumab in patients who are non-responder to triple therapy [81].

Pregnancy and childbirth represent a potential additional thrombotic trigger which can promote progression of a CAPS in triple positive female APS patients. Eculizumab has been used in pregnant patients with HUS or paroxysmal nocturnal hemoglobinuria and it has shown to cross the placenta only minimally and to not affect the foetus[82]. However, the use of eculizumab in pregnant APS patients is limited to few case reports about patients deemed to be at very high risk for developing CAPS [83]. In this case, administering a complement inhibitor before signs of multi-organ failure develop it could be effective as well as safe.

All patients must be immunized against *neisseria meningitidis*, *haemophilus influenzae* and *streptococcus pneumoniae* before treatment with eculizumab.

Even in the absence of catastrophic manifestation, APS can be associated with vasculopathy: vascular cellular infiltrates and fibrosis of the intima have been observed in patients affected by APS nephropathy, along with coronary, carotid and mesenteric arteries of patients with life-threatening complications [84].

Sirolimus

The mammalian target of rapamycin (mTOR) pathway is involved in different biological functions such as cell differentiation, proliferation and survival. *In vitro* studies have proven that this signalling pathway is upregulated by aPL- $\alpha\beta$ 2GPI linkage and its activation induces the

expression of TF and inflammatory cytokines, such as interleukin-8, contributing to APS vasculopathy and vascular occlusion [85].

Sirolimus has the ability to inhibit this specific pathway. In 2014 Canaud and Colleagues identified an increased activation of mTOR in vascular endothelium of APS nephropathy patients. A retrospective analysis of renal allograft survival involving ten aPL positive patients treated with sirolimus to prevent graft rejection revealed a significantly lower vascular proliferation and better graft survival[86].

Additional supporting clinical data includes a case report by Sartorelli et al. which describes a case of APS myocardial microangiopathy in a man presented with contractile dysfunction and arrhythmic outburst, successfully treated with sirolimus[87].

Finally, since aPL directed against β 2GPI can activate platelets, mTOR inhibitors can prevent platelet activation and aggregation[88], which is one of the mechanisms underlying thrombocytopenia in APS. While the management of thrombocytopenia in APS should require a separate discussion, with the current knowledge Sirolimus' usability in case of resistant thrombocytopenia can be speculated, albeit it requires clinical confirmation. Similarly, the use of other agents (e.g., Bortezomib) for the management of complex cases of APS is now confined to anecdotal experiences[89].

Recurrent Pregnancy Morbidity and Refractory Obstetric APS

Recurrent pregnancy morbidity (PM) represents one of the main clinical features of APS, a major reproductive health issue, and a delicate challenge even for expert rheumatologists. The prevalence of APS in women who experience recurrent pregnancy losses varies widely among different studies, ranging from 5% to 20% [4,90,91]. Over the last decades, pregnancy outcomes

in aPL positive subjects and APS patients have improved enormously due to the combination of a multidisciplinary management, pharmacological treatment and pre-conceptual counselling [92].

The management of women with aPL is summarised in Table 2.

Since VKA must be avoided especially during the first trimester of gestation due to its teratogenicity, the use of LDA in addition to heparin at prophylactic dose, both with unfractionated heparin (UFH) and LMWH, although the relative lack of strong evidences, is considered the standard therapy in patients with pure obstetric APS (three or more recurrent spontaneous abortions before 10 weeks of gestation, fetal loss at or beyond 10 weeks of gestation, and preterm delivery before 34 weeks of gestation due to eclampsia, severe pre-eclampsia or placental insufficiency) [1], regardless the presence or the absence of a concomitant autoimmune disease such as SLE [7]. Nevertheless, the use of LDA alone can be taken into consideration after a careful individual risk assessment, which includes aPL profile (single or multiple aPL positivity, low or medium-high aPL titers, and isotypes), previous PM events (early and/or late pregnancy complications), the presence of other CV risk factors, a concomitant diagnosis of SLE, and previous live births. LDA should be started before conception and stopped 4 weeks before the delivery, while LMWH (subcutaneous enoxaparin 40 mg/daily, subcutaneous dalteparin 5000 U/daily, or subcutaneous tinzaparin 4500 U/daily) or UFH should be started with a positive pregnancy test, and continued for 3-6 weeks during the post-partum period, although, to date, no study specifically addressed this issue. The duration of anticoagulation therapy has to be tailored according to the presence of additional risk factors[3]. In clinical practice, LMWH is generally preferred since osteopenia seems to be more associated with the use of UFH [93], but with comparable efficacy.

Patients with history of PM not fulfilling the classification criteria for obstetric APS [1], can be treated with LDA alone or in combination with LMWH, according to the individual risk profile. In this particular setting, treatment decision only relies on expert opinion, since the available amount of evidences only came from small studies not designed to directly address this matter [94–97].

Despite the strict monitoring and the use of LDA in combination with heparin, a proportion of women (around 30%) still experience recurrent pregnancy complications and miscarriages. Therefore, several drugs have been proposed in combination with the anticoagulant and anti-platelets agents in order to potentiate treatment efficacy. The use of heparin at therapeutic dose (subcutaneous enoxaparin 1 mg/kg every 12 hours or 1.5 mg/kg/daily or subcutaneous deltaeparin 100 U/kg every 12 hours or 200 U/kg/daily) in combination with LDA, is not currently supported by any data and is therefore limited to APS patients with history of previous thrombotic events. In this setting, the switch from VKA to heparin needs to be made before 6 weeks of gestation.

Despite the role of corticosteroids in reducing complement activation and inflammation [98], the use of high dose of steroids (prednisone 0.8-0.5 mg/kg/daily) in refractory obstetric APS should be avoided based on its association with an increased risk of preterm delivery (before 37 weeks of gestation), arterial hypertension, gestational diabetes mellitus, and cataracts [99]. Nevertheless, limited data suggest the use of prednisolone (10 mg/daily) in addition to standard therapy (LDA and heparin) during the first trimester of gestation in patients with refractory aPL-related fetal losses [100].

Alternative approaches include the addition of HCQ and statins to standard treatment. In fact, a growing amount of data support the safety profile and the role of HCQ (200-400 mg/daily) in

the prevention of fetal and maternal complications and in patients, with and without a concomitant autoimmune disease, with refractory obstetric APS due to its immunomodulatory effects [101–103]. HCQ should be started before conception, continued during gestation, and is compatible with breastfeeding. Current practice is based on few retrospective studies [104–106] but results are very promising and prospective trials are ongoing, including HYPATIA, HYDROSAPL, and HIBISCUS [48,107,108] which will hopefully put evidence-based practices in place.

Currently, statins are extensively employed in CV disease prevention and treatment, but their beneficial role seems to be more complex and not only limited to cholesterol levels reduction, including inflammation and oxidative stress modulation, along with the inhibition of coagulation cascade, endothelium homeostasis, and angiogenesis [109]. The addition of statins to standard treatment in patients with refractory obstetric APS has not been fully investigated yet, and therefore its use in clinical practice is based on physician judgment according to individual risk profile (e.g. concomitant presence of traditional CV risk factors). Based on preliminary data on animal models, a clinical trial on the use of rosuvastatin in the treatment of preeclampsia is currently ongoing [110].

In line with the 2019 EULAR recommendations for the treatment of adult APS patients [7], the use of IVIG in patients with recurrent PM events despite standard therapy, can be taken into consideration only in selected cases, including patients refractory to heparin or when additional indications are present such as autoimmune thrombocytopenia, due to the limited number of data supporting their efficacy and the high cost.

The challenge for the future will be to personalized anti-thrombotic treatment during pregnancy according to the patients clinical and laboratory profiles [102]. The restoration of

immunological abnormalities[103] or the use of the GAPSS have been proposed as tool to guide choices[111]. Both these approaches, albeit promising, require further clinical validation.

Conclusions

To date, the management of APS is still centered on anti-thrombotic therapies, to include vitamin K antagonists, aspirin, and heparins. Despite the initial hope posed in the use of direct oral anticoagulants, the most recent randomized studies have raised concerns about their inferiority to vitamin K antagonists, at least in some subgroups such as patients with the so called “triple positivity”. Other approaches to treating APS beyond anti-thrombotic strategies are under investigation and receiving increased attention in mechanistic and preclinical studies. Nevertheless, the use of biological or immunomodulatory treatments is still confined to patients with refractory and/or microvascular disease.

What are our hopes for the future in the management of APS? Continue progress should be made to improve not just mortality and morbidity rates but also the quality of life of individuals with APS. The challenge for the future will be to improve our ability to predict the individual risk of developing new events among all subjects tested positive for aPL, with upcoming molecular technologies potentially playing a promising role in improving sub-phenotyping of patients.

The ultimate goal is personalizing risk profiles and ideally define the optimal therapeutic strategy based on future risk, rather than only on previous clinical manifestations.

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References

1. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost.* 2006 Feb;4(2):295–306.
2. Cervera R, Tektonidou MG, Espinosa G, Cabral AR, Gonzalez EB, Erkan D, et al. Task Force on Catastrophic Antiphospholipid Syndrome (APS) and Non-criteria APS Manifestations (I): catastrophic APS, APS nephropathy and heart valve lesions. *Lupus.* 2011 Feb;20(2):165–73.
3. Branch W. Report of the Obstetric APS Task Force: 13th International Congress on Antiphospholipid Antibodies, 13th April 2010. *Lupus.* 2011 Feb;20(2):158–64.
4. De Jesus GR, Agmon-Levin N, Andrade CA, Andreoli L, Chighizola CB, Flint Porter T, et al. 14th International Congress on Antiphospholipid Antibodies Task Force Report on Obstetric Antiphospholipid Syndrome. Vol. 13, *Autoimmunity Reviews.* Elsevier; 2014. p. 795–813.
5. Erkan D, Aguiar CL, Andrade D, Cohen H, Cuadrado MJ, Danowski A, et al. 14th International Congress on Antiphospholipid Antibodies: task force report on antiphospholipid syndrome treatment trends. *Autoimmun Rev.* 2014 Jun;13(6):685–96.
6. Ruiz-Irastorza G, Cuadrado MJ, Ruiz-Arruza I, Brey R, Crowther M, Derksen R, et al. Evidence-based recommendations for the prevention and long-term management of thrombosis in antiphospholipid antibody-positive patients: Report of a Task Force at the 13th International Congress on Antiphospholipid Antibodies. In: *Lupus.* 2011. p. 206–18.
7. Tektonidou MG, Andreoli L, Limper M, Amoura Z, Cervera R, Costedoat-Chalumeau N,

- et al. EULAR recommendations for the management of antiphospholipid syndrome in adults. *Ann Rheum Dis*. 2019 May;annrheumdis-2019-215213.
8. Tektonidou MG, Laskari K, Panagiotakos DB, Moutsopoulos HM. Risk factors for thrombosis and primary thrombosis prevention in patients with systemic lupus erythematosus with or without antiphospholipid antibodies. *Arthritis Rheum*. 2009 Jan;61(1):29–36.
 9. Wahl DG, Bounameaux H, de Moerloose P, Sarasin FP. Prophylactic antithrombotic therapy for patients with systemic lupus erythematosus with or without antiphospholipid antibodies: do the benefits outweigh the risks? A decision analysis. *Arch Intern Med*. 2000 Jul;160(13):2042–8.
 10. Ginsburg KS, Liang MH, Newcomer L, Goldhaber SZ, Schur PH, Hennekens CH, et al. Anticardiolipin antibodies and the risk for ischemic stroke and venous thrombosis. *Ann Intern Med*. 1992 Dec;117(12):997–1002.
 11. Belcaro G, Dugall M, Hu S, Feragalli B, Cotellesse R, Ledda A, et al. Prevention of recurrent venous thrombosis and post-thrombotic syndrome. *Minerva Cardioangiol*. 2018 Jun;66(3):238–45.
 12. Becattini C, Agnelli G, Schenone A, Eichinger S, Bucherini E, Silingardi M, et al. Aspirin for preventing the recurrence of venous thromboembolism. *N Engl J Med*. 2012 May;366(21):1959–67.
 13. Pengo V, Ruffatti A, Lignani C, Testa S, Fierro T, Marongiu F, et al. Incidence of a first thromboembolic event in asymptomatic carriers of high-risk antiphospholipid antibody profile: A multicenter prospective study. *Blood*. 2011;118(17):4714–8.
 14. Erkan D, Harrison MJ, Levy R, Peterson M, Petri M, Sammaritano L, et al. Aspirin for primary thrombosis prevention in the antiphospholipid syndrome: A randomized, double-blind, placebo-controlled trial in asymptomatic antiphospholipid antibody-positive individuals. *Arthritis Rheum*. 2007 Jul;56(7):2382–91.
 15. Cuadrado MJ, Bertolaccini ML, Seed PT, Tektonidou MG, Aguirre A, Mico L, et al. Low-dose aspirin vs low-dose aspirin plus low-intensity warfarin in thromboprophylaxis: a prospective, multicentre, randomized, open, controlled trial in patients positive for

- antiphospholipid antibodies (ALIWAPAS). *Rheumatology (Oxford)*. 2014 Feb;53(2):275–84.
16. Lanas A, Polo-Tomás M, Casado-Arroyo R. The aspirin cardiovascular/gastrointestinal risk calculator - A tool to aid clinicians in practice. *Aliment Pharmacol Ther*. 2013;37(7):738–48.
 17. Otomo K, Atsumi T, Amengual O, Fujieda Y, Kato M, Oku K, et al. Efficacy of the antiphospholipid score for the diagnosis of antiphospholipid syndrome and its predictive value for thrombotic events. *Arthritis Rheum*. 2012;64(2):54–12.
 18. Sciascia S, Radin M, Sanna G, Cecchi I, Roccatello D, Bertolaccini ML. Clinical utility of the global anti-phospholipid syndrome score for risk stratification: a pooled analysis. *Rheumatology (Oxford)* [Internet]. 2018 [cited 2019 Oct 16];57(4):661–5. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/29342292>
 19. Sciascia S, Sanna G, Murru V, Roccatello D, Khamashta MA, Bertolaccini ML. GAPSS: the Global Anti-Phospholipid Syndrome Score. *Rheumatology*. 2013 Aug;52(8):1397–403.
 20. Khamashta MA, Cuadrado MJ, Mune F, Taub NA, Hunt BJ, Hughes GR. The management of thrombosis in the antiphospholipid-antibody syndrome. *N Engl J Med*. 1995 Apr;332(15):993–7.
 21. Brunner M, Greinix HT, Redlich K, Knöbl P, Smolen J, Leitner G, et al. Autologous blood stem cell transplantation in refractory systemic lupus erythematosus with severe pulmonary impairment: A case report. *Arthritis Rheum*. 2002 Jun;46(6):1580–4.
 22. Crowther MA, Ginsberg JS, Julian J, Denburg J, Hirsh J, Douketis J, et al. A Comparison of Two Intensities of Warfarin for the Prevention of Recurrent Thrombosis in Patients with the Antiphospholipid Antibody Syndrome. *N Engl J Med*. 2003 Sep;349(12):1133–8.
 23. Finazzi G, Brancaccio V, Schinco P, Wisloff F, Musial J, Baudo F, et al. A randomized clinical trial of high-intensity warfarin vs. conventional antithrombotic therapy for the prevention of recurrent thrombosis in patients with the antiphospholipid syndrome (WAPS). *J Thromb Haemost*. 2005 May;3(5):848–53.
 24. Levine SR, Brey RL, Tilley BC, Thompson JLP, Sacco RL, Sciacca RR, et al.

- Antiphospholipid Antibodies and Subsequent Thrombo-occlusive Events in Patients With Ischemic Stroke. *JAMA*. 2004 Feb;291(5):576.
25. Ruiz-Irastorza G, Khamashta MA, Hunt BJ, Escudero A, Cuadrado MJ, Hughes GRV. Bleeding and recurrent thrombosis in definite antiphospholipid syndrome: Analysis of a series of 66 patients treated with oral anticoagulation to a target international normalized ratio of 3.5. *Arch Intern Med*. 2002 May;162(10):1164–9.
 26. Ruiz-Irastorza G, Hunt BJ, Khamashta MA. A systematic review of secondary thromboprophylaxis in patients with antiphospholipid antibodies. Vol. 57, *Arthritis Care and Research*. 2007. p. 1487–95.
 27. Büller HR, Prins MH, Lensin AWA, Decousus H, Jacobson BF, Minar E, et al. Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism. *N Engl J Med*. 2012 Apr;366(14):1287–97.
 28. Cohen H, Hunt BJ, Efthymiou M, Arachchi J, George DRJ, Mackie IJ, Clawson S, et al. Rivaroxaban versus warfarin to treat patients with thrombotic antiphospholipid syndrome, with or without systemic lupus erythematosus (RAPS): a randomised, controlled, open-label, phase 2/3, non-inferiority trial. *Lancet Haematol* [Internet]. 2016;3(9):e426–36. Available from: [http://dx.doi.org/10.1016/S2352-3026\(16\)30079-5](http://dx.doi.org/10.1016/S2352-3026(16)30079-5)
 29. Pengo V, Denas G, Zoppellaro G, Jose SP, Hoxha A, Ruffatti A, et al. Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. *Blood*. 2018 Sep;132(13):1365–71.
 30. Dobrowolski C, Erlan D. Treatment of antiphospholipid syndrome beyond anticoagulation. *Clin Immunol* [Internet]. 2019;206:53–62. Available from: <https://doi.org/10.1016/j.clim.2018.03.001>
 31. Bettacchioli E, Nafai S, Renaudineau Y. News and meta-analysis regarding anti-Beta 2 glycoprotein I antibodies and their determination. *Clin Immunol* [Internet]. 2019;205(May):106–15. Available from: <https://doi.org/10.1016/j.clim.2019.06.002>
 32. Ramos-casals ASM, Bove A, Soria N, Muñoz S, Testi A, Plaza J, et al. Previous antimalarial therapy in patients diagnosed with lupus nephritis : Influence on outcomes and survival. *Lupus*. 2008;17(4):281–8.

33. Petri M. Use of hydroxychloroquine to prevent thrombosis in systemic lupus erythematosus and in antiphospholipid antibody-positive patients. *Curr Rheumatol Rep.* 2011;
34. Ruiz-Irastorza G, Egurbide M-V, Pijoan J-I, Garmendia M, Villar I, Martinez-Berriotxo A, et al. Effect of antimalarials on thrombosis and survival in patients with systemic lupus erythematosus. *Lupus.* 2006 Sep;15(9):577–83.
35. Mo YM, Chan EYT, Fong DYT, Leung KFS, Woon SW, Chak SL. Antiphospholipid antibody profiles and their clinical associations in Chinese patients with systemic lupus erythematosus. *J Rheumatol.* 2005 Apr;32(4):622–8.
36. R Kaiser, C M Cleveland and LAC. Risk and protective factors for thrombosis in systemic lupus erythematosus. *Ann Rheum Dis.* 2009, 58(2):238–41.
37. Rand JH, Wu X-X, Quinn AS, Ashton AW, Chen FP, Hathcock JJ, et al. Hydroxychloroquine protects the annexin A5 anticoagulant shield from disruption by antiphospholipid antibodies: evidence for a novel effect for an old antimalarial drug. *Blood.* 2010 Mar;115(11):2292–9.
38. Rand JH, Wu XX, Quinn AS, Chen FP, Hathcock JJ, Taatjes DJ. Hydroxychloroquine directly reduces the binding of antiphospholipid antibody- β 2-glycoprotein I complexes to phospholipid bilayers. *Blood.* 2008;
39. Espinola RG, Pierangeli SS, Ghara AE, Harris EN. Hydroxychloroquine reverses platelet activation induced by human IgG antiphospholipid antibodies. *Thromb Haemost.* 2002;
40. Schreiber K, Breck K, Parmar K, Rand JH, Wu X-X, Hunt BJ. The effect of hydroxychloroquine on haemostasis, complement, inflammation and angiogenesis in patients with antiphospholipid antibodies. *Rheumatology (Oxford).* 2018;57(1):120–4.
41. Xourgia E, Tektonidou MG. Type I interferon gene expression in antiphospholipid syndrome: Pathogenetic, clinical and therapeutic implications. Vol. 104, *Journal of Autoimmunity.* Academic Press; 2019. p. 102311.
42. Khamashta MA, Nigel Harris E, Gharavi AE, Derue G, Gil A, Vázquez JJ, et al. Immune mediated mechanism for thrombosis: Antiphospholipid antibody binding to platelet membranes. *Ann Rheum Dis.* 1988;

43. Edwards MH, Pierangeli S, Liu X, Barker JH, Anderson G, Nigel Harris E. Hydroxychloroquine reverses thrombogenic properties of antiphospholipid antibodies in mice. *Circulation*. 1997;
44. Ruiz-Irastorza G, Ramos-Casals M, Brito-Zeron P, Khamashta MA. Clinical efficacy and side effects of antimalarials in systemic lupus erythematosus: a systematic review. *Ann Rheum Dis*. 2010 Jan;69(01):20–8.
45. Schmidt-Tanguy A, Voswinkel J, Henrion D, Subra JF, Loufrani L, Rohmer V, et al. Antithrombotic effects of hydroxychloroquine in primary antiphospholipid syndrome patients. *J Thromb Haemost*. 2013 Oct;11(10):1927–9.
46. Nuri E, Taraborelli M, Andreoli L, Tonello M, Gerosa M, Calligaro A, et al. Long-term use of hydroxychloroquine reduces antiphospholipid antibodies levels in patients with primary antiphospholipid syndrome. *Immunol Res*. 2017 Feb;65(1):17–24.
47. Kravvariti E, Koutsogianni A, Samoli E, Sfakaki PP, Tektonidou MG. The effect of hydroxychloroquine on thrombosis prevention and antiphospholipid antibody levels in primary antiphospholipid syndrome: A pilot open label randomized prospective study. *Autoimmun Rev*. 2020 Feb;102491.
48. Belizna C, Pregnotato F, Abad S, Alijotas-Reig J, Amital H, Amoura Z, et al. HIBISCUS: Hydroxychloroquine for the secondary prevention of thrombotic and obstetrical events in primary antiphospholipid syndrome. Vol. 17, *Autoimmunity Reviews*. Elsevier B.V.; 2018. p. 1153–68.
49. Gelfand EW. Intravenous immune globulin in autoimmune and inflammatory diseases. Vol. 367, *New England Journal of Medicine*. Massachusetts Medical Society; 2012. p. 2015–25.
50. Pierangeli SS, Espinola R, Liu X, Harris EN, Salmon JE. Identification of an Fcγ receptor-independent mechanism by which intravenous immunoglobulin ameliorates antiphospholipid antibody-induced thrombogenic phenotype. *Arthritis Rheum*. 2001 Apr;44(4):876–83.
51. Sherer Y. Intravenous immunoglobulin therapy of antiphospholipid syndrome. *Rheumatology*. 2000;

52. Guo Y, Tian X, Wang X, Xiao Z. Adverse effects of immunoglobulin therapy. Vol. 9, *Frontiers in Immunology*. Frontiers Media S.A.; 2018.
53. Cherin P, Marie I, Michallet M, Pelus E, Dantal J, Crave JC, et al. Management of adverse events in the treatment of patients with immunoglobulin therapy: A review of evidence. *Autoimmunity Reviews*. 2016.
54. Hsiao GR, Wolf RE, Kimpel DL. Intravenous immunoglobulin to prevent recurrent thrombosis in the antiphospholipid syndrome. *J Clin Rheumatol*. 2001 Oct;7(5):336–9.
55. Sciascia S, Cosseddu D, Montaruli B, Kuzenko A, Bertero MT. Risk Scale for the diagnosis of antiphospholipid syndrome. *Ann Rheum Dis*. 2011 Aug;70(8):1517–8.
56. Sciascia S, Giachino O, Roccatello D. Prevention of thrombosis relapse in antiphospholipid syndrome patients refractory to conventional therapy using intravenous immunoglobulin. *Clin Exp Rheumatol*. 2012;30(3):109–13.
57. Tenti S, Guidelli GM, Bellisai F, Galeazzi M, Fioravanti A. Long-term treatment of antiphospholipid syndrome with intravenous immunoglobulin in addition to conventional therapy. *Clin Exp Rheumatol*. 31(6):877–82.
58. Tenti S, Chelieschi S, Guidelli GM, Galeazzi M, Fioravanti A. Intravenous immunoglobulins and antiphospholipid syndrome: How, when and why? A review of the literature. *Autoimmunity Reviews*. 2016.
59. Frank M, Sodin-Šemrl S, Rozman B, Potočnik M, Kralj-Iglič V. Effects of low-molecular-weight heparin on adhesion and vesiculation of phospholipid membranes: A possible mechanism for the treatment of hypercoagulability in antiphospholipid syndrome. In: *Annals of the New York Academy of Sciences*. Blackwell Publishing Inc.; 2009. p. 874–86.
60. Bick RL, Rice J. Long-term outpatient dalteparin (fragmin) therapy for arterial and venous thrombosis: Efficacy and safety - A preliminary report. In: *Clinical and Applied Thrombosis/Hemostasis*. 1999.
61. Dentali F, Manfredi E, Crowther M, Ageno W. Long-duration therapy with low molecular weight heparin in patients with antiphospholipid antibody syndrome resistant to warfarin therapy [11]. *Journal of Thrombosis and Haemostasis*. 2005.

62. Vargas-Hitos JA, Ateka-Barrutia O, Sangle S, Khamashta MA. Efficacy and safety of long-term low molecular weight heparin in patients with antiphospholipid syndrome. *Ann Rheum Dis*. 2011 Sep;70(9):1652–4.
63. S. A, A. K, D. P, R. S, J. M. Low-molecular weight heparin: Treatment failure in a patient with primary antiphospholipid antibody syndrome. *American Journal of the Medical Sciences*. 2002.
64. Biernacka-Zielinska M, Lipinska J, Szymanska-Kaluza J, Stanczyk J, Smolewska E. Recurrent arterial and venous thrombosis in a 16-year-old boy in the course of primary antiphospholipid syndrome despite treatment with low-molecular-weight heparin: A case report. *J Med Case Rep*. 2013 Aug;7:221.
65. Khattri S, Zandman-Goddard G, Peeva E. B-cell directed therapies in antiphospholipid antibody syndrome--new directions based on murine and human data. *Autoimmun Rev*. 2012 Aug;11(10):717–22.
66. Ramos-Casals M, García-Hernández E, de Ramón E, Callejas JL, Martínez-Berriotxo A, Pallares L, et al. Off-label use of rituximab in 196 patients with severe, refractory systemic autoimmune diseases. *Clin Exp Rheumatol*. 2010;
67. Wang CR, Liu MF. Rituximab usage in systemic lupus erythematosus-associated antiphospholipid syndrome: A single-center experience. *Semin Arthritis Rheum*. 2016 Aug;46(1):102–8.
68. Sciascia S, Narotto C, Bossi D, Bazzan M, Roccatello D. Treatment-induced downregulation of antiphospholipid antibodies: effect of rituximab alone on clinical and laboratory features of antiphospholipid syndrome. *Lupus*. 2011 Oct;20(10):1106–8.
69. Erre GL, Pardini S, Faedda R, Passiu G. Effect of rituximab on clinical and laboratory features of antiphospholipid syndrome: a case report and a review of literature. *Lupus*. 2008 Jan;17(1):50–5.
70. Ioannou Y, Lambrianides A, Cambridge G, Leandro MJ, Edwards JCW, Isenberg DA. B cell depletion therapy for patients with systemic lupus erythematosis results in a significant drop in anticardiolipin antibody titres. *Ann Rheum Dis*. 2008 Mar;67(3):425–6.
71. Bakshi J, Stevens R. Rituximab therapy for recurrent thromboembolic disease in

- antiphospholipid syndrome. *Lupus*. 2013.
72. Erkan D, Vega J, Ramón G, Kozora E, Lockshin MD. A pilot open-label phase II trial of rituximab for non-criteria manifestations of antiphospholipid syndrome. *Arthritis Rheum*. 2013 Feb;65(2):464–71.
 73. Suzuki K, Nagasawa H, Kameda H, Amano K, Kondo T, Itoyama S, et al. Severe acute thrombotic exacerbation in two cases with anti-phospholipid syndrome after retreatment with rituximab in phase I/II clinical trial for refractory systemic lupus erythematosus. *Rheumatology (Oxford)*. 2009 Feb;48(2):198–9.
 74. 1A.Targeted therapies in systemic sclerosis, myositis, antiphospholipid syndrome, and Sjögren's syndrome _ Elsevier Enhanced Reader.pdf.
 75. Sciascia S, Rubini E, Radin M, Cecchi I, Rossi D, Roccatello D. Anticardiolipin and anti-beta 2 glycoprotein-I antibodies disappearance in patients with systemic lupus erythematosus and antiphospholipid syndrome while on belimumab. *Ann Rheum Dis*. 2018 Nov;77(11):1694–5.
 76. Yazici A, Yazirli B, Erkan D. Belimumab in primary antiphospholipid syndrome. *Lupus*. 2017;26(10):1123–4.
 77. van den Hoogen LL, Palla G, Bekker CPJ, Fritsch-Stork RDE, Radstake TRDJ, van Roon JAG. Increased B-cell activating factor (BAFF)/B-lymphocyte stimulator (BLyS) in primary antiphospholipid syndrome is associated with higher adjusted global antiphospholipid syndrome scores. *RMD Open*. 2018;4(2):e000693.
 78. Erkan D, Salmon JE. Trombotik anjiyopati ve antifosfolipid sendromunda kompleman İnhibisyonunun rolü. *Turkish J Hematol*. 2016;33(1):1–7.
 79. Chaturvedi S, Brodsky RA, McCrae KR. Complement in the pathophysiology of the antiphospholipid syndrome. *Front Immunol*. 2019;10(MAR):1–9.
 80. Kello N, Khoury L El, Marder G, Furie R, Zapantis E, Horowitz DL. Secondary thrombotic microangiopathy in systemic lupus erythematosus and antiphospholipid syndrome, the role of complement and use of eculizumab: Case series and review of literature. *Semin Arthritis Rheum*. 2019;49(1):74–83.

81. Rodríguez-Pintó I, Espinosa G, Cervera R. Treatment of Catastrophic Antiphospholipid Syndrome. *Handb Syst Autoimmune Dis*. 2017;12(3):243–55.
82. Gerardi MC, Fernandes MA, Tincani A, Andreoli L. Obstetric Anti-phospholipid Syndrome: State of the Art. *Curr Rheumatol Rep*. 2018;20(10).
83. Rovere-Querini P, Canti V, Erra R, Bianchi E, Slaviero G, D'Angelo A, et al. Eculizumab in a pregnant patient with laboratory onset of catastrophic antiphospholipid syndrome A case report. *Med (United States)*. 2018;97(40):7–10.
84. Eikelboom JW, Weitz JI, Arnold S, Relman, 1923-2014. *N Engl J Med*. 2014;371(4):368–9.
85. Xia L, Zhou H, Wang T, Xie Y, Wang T, Wang X, et al. Activation of mTOR is involved in anti- β 2GPI/ β 2GPI-induced expression of tissue factor and IL-8 in monocytes. *Thromb Res*. 2017;157:103–10.
86. Canaud G, Bienaimé F, Tabarin F, Bataillon G, Seilhean D, Noël LH, et al. Inhibition of the mTORC pathway in the antiphospholipid syndrome. *N Engl J Med*. 2014;371(4):303–12.
87. Sartorelli S, De Luca G, Campochiaro C, Peretto G, Sala S, Esposito A, et al. Successful use of sirolimus in a patient with cardiac microangiopathy in primary antiphospholipid syndrome. *Scand J Rheumatol*. 2019;48(6):515–6.
88. Hollerbach A, Müller-Calleja N, Ritter S, Häuser F, Canisius A, Orning C, et al. Platelet Activation by Antiphospholipid Antibodies Depends on Epitope Specificity and is Prevented by mTOR Inhibitors. *Thromb Haemost*. 2019;119(7):1147–53.
89. Tkachenko O, Lapin S, Maslyansky A, Myachikova V, Mikhailova L, Gilburd B. Relapsing Evans syndrome and systemic lupus erythematosus with antiphospholipid syndrome treated with Bortezomib in combination with plasma exchange. *Clin Immunol [Internet]*. 2019;199:44–6. Available from: <https://doi.org/10.1016/j.clim.2018.12.010>
90. Andreoli L, Chighizola CB, Banzato A, Pons-Estel GJ, De Jesus GR, Erkan D. Estimated frequency of antiphospholipid antibodies in patients with pregnancy morbidity, stroke, myocardial infarction, and deep vein thrombosis: A critical review of the literature. Vol. 65, *Arthritis Care and Research*. Arthritis Care Res (Hoboken); 2013. p. 1869–73.

91. Opatrny L, David M, Kahn SR, Shrier I, Rey E. Association between antiphospholipid antibodies and recurrent fetal loss in women without autoimmune disease: A metaanalysis. *J Rheumatol*. 2006 Nov;33(11):2214–21.
92. Bramham K, Hunt BJ, Germain S, Calatayud I, Khamashta M, Bewley S, et al. Pregnancy outcome in different clinical phenotypes of antiphospholipid syndrome. *Lupus*. 2010 Jan;19(1):58–64.
93. Pettilä V, Leinonen P, Markkola A, Hiilesmaa V, Kaaja R. Postpartum bone mineral density in women treated for thromboprophylaxis with unfractionated heparin or LMW heparin. *Thromb Haemost*. 2002 Feb;87(2):182–6.
94. Alijotas-Reig J, Esteve-Valverde E, Ferrer-Oliveras R, LLarba E, Ruffatti A, Tincani A, et al. Comparative study between obstetric antiphospholipid syndrome and obstetric morbidity related with antiphospholipid antibodies. *Med Clin (Barc)*. 2018 Sep;151(6):215–22.
95. Sugiura-Ogasawara M, Ozaki Y, Nakamishi T, Sato T, Suzumori N, Kumagai K. Occasional antiphospholipid antibody positive patients with recurrent pregnancy loss also merit aspirin therapy: A retrospective cohort-control study. *Am J Reprod Immunol*. 2008 Mar;59(3):235–41.
96. LASKIN CA, SPITZER VA, CLARK CA, CROWTHER MR, GINSBERG JS, HAWKER GA, et al. Low Molecular Weight Heparin and Aspirin for Recurrent Pregnancy Loss: Results from the Randomized, Controlled HepASA Trial. *J Rheumatol*. 2009 Feb;36(2):272–87.
97. Del Ross T, Ruffatti A, Visentin MS, Tonello M, Calligaro A, Favaro M, et al. Treatment of 139 pregnancies in antiphospholipidpositive women not fulfilling criteria for antiphospholipid syndrome: A retrospective study. *J Rheumatol*. 2013 Apr;40(4):425–9.
98. Sneiderman CA, Wilson JW. Effects of corticosteroids on complement and the neutrophilic polymorphonuclear leukocyte. *Transplant Proc*. 1975 Mar;7(1):41–8.
99. Laskin CA, Bombardier C, Hannah ME, Mandel FP, Ritchie JWK, Farewell V, et al. Prednisone and aspirin in women with autoantibodies and unexplained recurrent fetal loss. *N Engl J Med*. 1997 Jul;337(3):148–53.

100. Bramham K, Thomas M, Nelson-Piercy C, Khamashta M, Hunt BJ. First-trimester low-dose prednisolone in refractory antiphospholipid antibody - related pregnancy loss. *Blood*. 2011 Jun;117(25):6948–51.
101. Sciascia S, Branch DW, Levy RA, Middeldorp S, Pavord S, Roccatello D, et al. The efficacy of hydroxychloroquine in altering pregnancy outcome in women with antiphospholipid antibodies: Evidence and clinical judgment. *Thromb Haemost*. 2016;115(2):285–90.
102. Flessa CM, Vlachiotis S, Nezos A, Andreakos E, Mavragani CP, Tektonidou MG. Independent association of low IFN λ 1 gene expression and a type I IFN score/IFN λ 1 ratio with obstetric manifestations and triple antiphospholipid antibody positivity in primary antiphospholipid syndrome. *Clin Immunol* [Internet]. 2019;209:108265. Available from: <https://doi.org/10.1016/j.clim.2019.108265>
103. Wang M, Zhang P, Yu S, Zhou G, Lv J, Nalapatthula D, et al. Heparin and aspirin combination therapy restores T-cell phenotype in pregnant patients with antiphospholipid syndrome-related recurrent pregnancy loss. *Clin Immunol* [Internet]. 2019;208(May):108259. Available from: <https://doi.org/10.1016/j.clim.2019.108259>
104. Mekinian A, Lazzaroni MG, Kuterko A, Alijotas-Reig J, Ruffatti A, Levy P, et al. The efficacy of hydroxychloroquine for obstetrical outcome in anti-phospholipid syndrome: Data from a European multicenter retrospective study. Vol. 14, *Autoimmunity Reviews*. Elsevier B.V.; 2015. p. 498–502.
105. Sciascia S, Hunt BJ, Talavera-Garcia E, Lliso G, Khamashta MA, Cuadrado MJ. The impact of hydroxychloroquine treatment on pregnancy outcome in women with antiphospholipid antibodies. *Am J Obstet Gynecol*. 2016 Feb;214(2):273.e1-273.e8.
106. Ruffatti A, Tonello M, Hoxha A, Sciascia S, Cuadrado MJ, Latino JO, et al. Effect of Additional Treatments Combined with Conventional Therapies in Pregnant Patients with High-Risk Antiphospholipid Syndrome: A Multicentre Study. *Thromb Haemost*. 2018 Apr;118(4):639–46.
107. Schreiber K, Breen K, Cohen H, Jacobsen S, Middeldorp S, Pavord S, et al. HYdroxychloroquine to Improve Pregnancy Outcome in Women with AnTIphospholipid

- Antibodies (HYPATIA) Protocol: A Multinational Randomized Controlled Trial of Hydroxychloroquine versus Placebo in Addition to Standard Treatment in Pregnant Women with Antipho. *Semin Thromb Hemost.* 2017;43(6):562–71.
108. Mekinian A, Vicaut E, Cohen J, Bornes M, Kayem G, Fain O. Hydroxychloroquine to obtain pregnancy without adverse obstetrical events in primary antiphospholipid syndrome: French phase II multicenter randomized trial, HYDROSAPL. *Gynecol Obstet Fertil Senol.* 2018 Jul;46(7–8):598–604.
109. Girardi G. Can statins prevent pregnancy complications? *J Reprod Immunol.* 2014;101–102(1):161–7.
110. Rosuvastatin in Order to Induce Preeclampsia Resolution in Severe PET up to 48 Hours Following Delivery - Full Text View - ClinicalTrials.gov.
111. Radin M, Cecchi I, Schreiber K, Rubini E, Roccatello D, Cuadrado MJ, et al. Pregnancy success rate and response to heparins and/or aspirin differ in women with antiphospholipid antibodies according to their Global Antiphospholipid Syndrome Score. *Semin Arthritis Rheum* [Internet]. 2020;50(3):553–6. Available from: <https://doi.org/10.1016/j.semarthru.2020.01.007>
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Legend of Figures and Tables

Figure 1. Treatment Flow-Chart of Thrombotic APS

Table 1. Ongoing and upcoming clinical trials focusing on immunomodulator agents for Antiphospholipid Syndrome

Table 2. Recommended treatment strategies for antiphospholipid syndrome patients during pregnancy

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Figure 1. Treatment Flow-Chart of Thrombotic APS

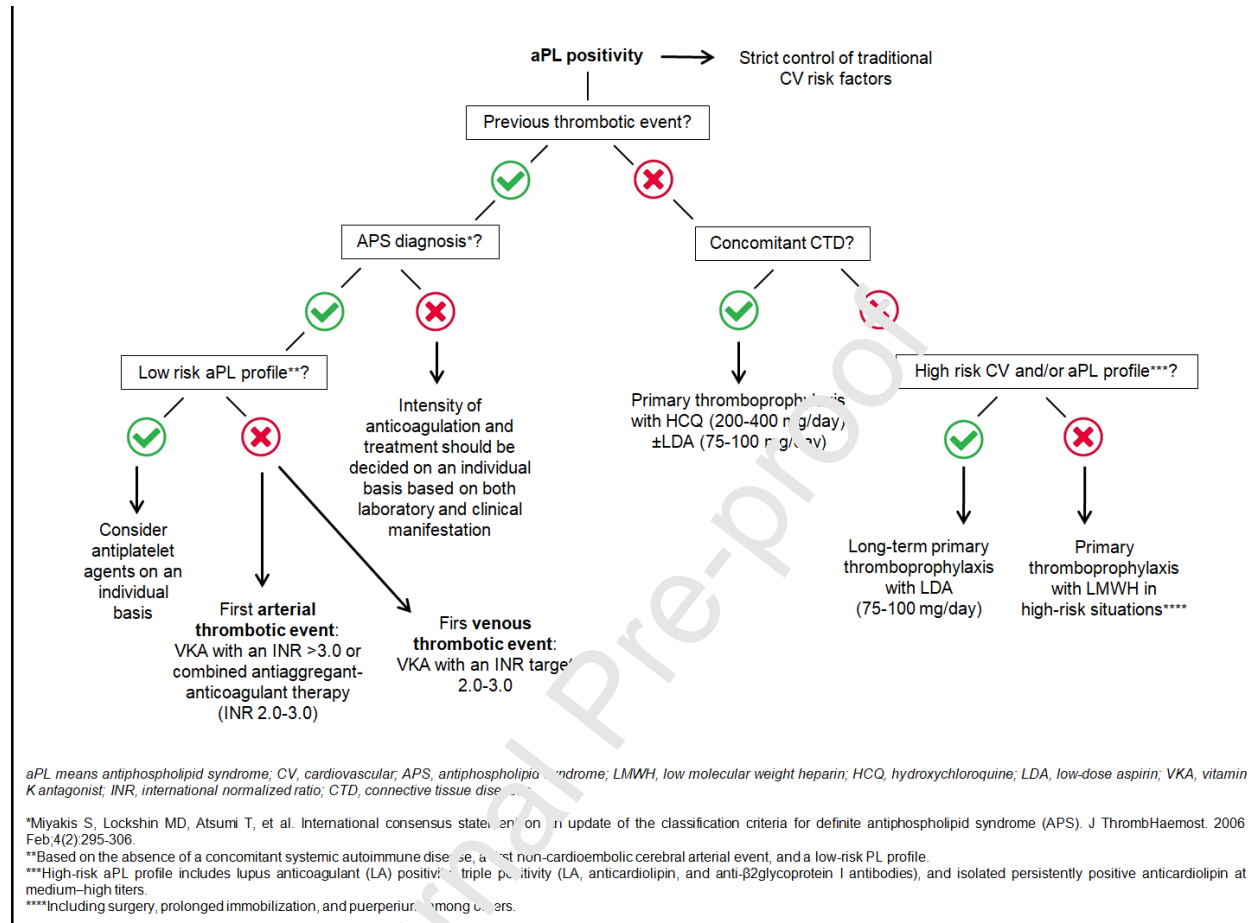


Table 1. Ongoing and upcoming clinical trials focusing on immunomodulator agents for Antiphospholipid Syndrome

Study:	Status/trial design	Interventions:
Dose Intralipid Infusion Reduces Pregnancy Complications Caused by Antiphospholipid Antibody Syndrome?	Not yet recruiting/ Randomized double blind	Intralipid, 20% Intravenous Emulsion
Eculizumab to Enable Renal Transplantation in Patients With History of Catastrophic Antiphospholipid Antibody Syndrome	Active, not recruiting/ Single Group Assignment	Eculizumab
Omega 3 in LES and APS	Unknown status/randomized double-blind	Omega-3 polyunsaturated fatty acid (n-3 PUFA)
IMPACT Study: IMProve Pregnancy in APS With Certolizumab Therapy	Recruiting/ Single Group Assignment	CertolizumabPegol

(interventional study as retrieved on clinicaltrial.gov on 19 April 2020, searching for Recruiting,

Not yet recruiting, Active, not recruiting, Enrolling by invitation, Unknown status Studies for

Antiphospholipid Syndrome, excluding study on DOAC and HCQ)

Table 2. Recommended treatment strategies for antiphospholipid syndrome patients during pregnancy

Recurrent Early (Pre-Embryonic or Embryonic) Miscarriages
<ul style="list-style-type: none"> LDA (75–100 mg/day) plus LMWH at prophylactic doses (e.g., subcutaneous enoxaparin 40 mg/day, subcutaneous dalteparin 5000 U/day, or subcutaneous tinzaparin 4500 U/day) or unfractionated heparin LDA (75–100 mg/day) alone in selected cases
Fetal Death (>10weeks' gestation) or prior early delivery (<34week' gestation) due to severe pre-eclampsia or placental insufficiency
<ul style="list-style-type: none"> LDA (75–100mg/day) plus LMWH at prophylactic doses (e.g., subcutaneous enoxaparin 40mg/day, subcutaneous dalteparin 5000 U/day, or subcutaneous tinzaparin 4500 U/day) or unfractionated heparin
APS patients with previous thrombosis
<ul style="list-style-type: none"> LDA (75–100 mg/day) plus LMWH at therapeutic doses (e.g., subcutaneous enoxaparin 1 mg/kg every 12 h or 1.5 mg/kg/day or subcutaneous dalteparin 100 U/kg every 12 h or 200 U/kg/day)

LDA means low-dose aspirin; LMWH, low molecular weight heparin; APS, antiphospholipid antibodies.

Highlights

1. The treatment aim of APS is reducing pregnancy morbidity and the prevention of thrombotic events
2. To date, the management of APS is still centered on anti-thrombotic therapies
3. High risk patients experience recurrent disease and may require additional therapies
4. Immunomodulatory treatments is still confined to refractory or microvascular disease

Journal Pre-proof

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* Low risk aPL profile (non LAC low titer single aPL positivity); absence of previous PM events and/or presence of previous live births; absence of other CV risk factors and/or absence of a concomitant diagnosis of SLE.

**LDA should be started before conception and stopped four weeks before the delivery.

***LMWH or unfractionated heparin should be started with a positive pregnancy test and continued for 3-6 weeks during the post-partum period. Nonetheless, the duration of anticoagulation therapy has to be tailored according to the presence of additional risk factors.