

# Management of Thrombotic Antiphospholipid Syndrome

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## Abstract

Persistent serum positivity for antiphospholipid antibodies (aPL) is required to diagnose antiphospholipid syndrome (APS), an autoimmune disease characterized by recurrent vascular thrombosis and/or pregnancy morbidity. The current therapeutic management of patients with thrombotic APS aims at preventing recurrences and long-term complications by attenuating the procoagulant state. There is overall consensus to reserve moderate-intensity anticoagulation to aPL-positive patients with a previous venous thrombosis; the therapeutic options for those with a history of arterial event comprise antiplatelet agents and high-intensity anticoagulation. Unfortunately, thrombotic occurrences might occur despite adequate anticoagulation, carrying a significant burden of morbidity and mortality. The management of refractory thrombotic APS and catastrophic APS is still not clear, warranting the issue of recommendations. Vitamin-K antagonists are limited by significant side effects, and a careful weighting of risks and benefits should be performed to reserve the optimal treatment to each patient. To overcome these limitations, novel oral anticoagulants have been introduced in the market, but their efficacy in thrombotic APS has still to be unraveled. The poor safety profile and the scarce efficacy of drugs acting on the coagulation cascade explain why novel therapeutic approaches are currently under investigation, to identify pharmacological tools specifically counteracting aPL-mediated prothrombotic effects.

## Keywords

- ▶ antiphospholipid antibodies
- ▶ antiphospholipid syndrome
- ▶ thrombosis
- ▶ treatment

Persistent serum positivity for antiphospholipid antibodies (aPL) is required to diagnose antiphospholipid syndrome (APS), an autoimmune disease characterized by recurrent vascular thrombosis and/or pregnancy morbidity. Thrombotic events might affect the arterial as well as the venous district; obstetric complications encompass early or late pregnancy losses and premature birth due to preeclampsia, eclampsia, or HELLP syndrome (hemolysis, elevated liver enzyme levels, and low platelet levels). According to the Updated Sapporo criteria, aPL are currently detected by three

laboratory tests: solid-phase assays for antibodies against  $\beta$ 2 glycoprotein I (anti- $\beta$ 2GPI antibodies) and cardiolipin (aCL) plus lupus anticoagulant (LA), a functional assay.<sup>1</sup> Noteworthy, aPL are not only APS biomarkers but also exert a direct pathogenic role in mediating clinical events. In particular, autoantibodies targeting  $\beta$ 2-glycoprotein I ( $\beta$ 2GPI), a single-chain serum 43-kDa glycoprotein consisting of five domains (D), have been extensively identified as the main pathogenic subset.<sup>2</sup> In vivo findings show that aPL are sufficient per se to induce pregnancy loss, but a second hit is required to trigger

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vascular events. The so-called two-hit hypothesis fits well with clinical evidence: aPL carriers develop thrombosis only occasionally, usually when an additional prothrombotic risk factor, such as arterial hypertension, supervenes. The association with concomitant risk factors, mainly infections, is particularly striking for the catastrophic variant of APS (CAPS), a rare and serious aPL-related manifestation characterized by multiple small-vessel thrombotic events occurring concomitantly at different anatomic sites.<sup>3</sup> Consequently, aPL positivity is regarded as a prothrombotic risk factor, carrying an increase—to a highly variable extent—of the hazard of thrombosis. All the parameters contributing to the risk of vascular events should be weighted to tentatively assess the real clinical impact of aPL positivity: an associated autoimmune disease, genetic and acquired cardiovascular risk factors, and the aPL profile. In this regard, it should be remembered that the thrombotic risk increases with the number of positive aPL tests: triple positive patients display the highest vascular hazard. In addition, each aPL test confers a characteristic thrombotic risk, with LA being appointed as the strongest predictor of clinical events.<sup>4</sup> The stratification of the risk of thrombosis is a key feature in the management of individuals with aPL positivity. The treatment of asymptomatic aPL carriers is highly controversial because of the poor protection against thrombosis conferred by available therapeutic options, while the need of a secondary thromboprophylaxis in aPL-positive patients is universally acknowledged. The current therapeutic management of patients with thrombotic APS aims at preventing recurrences and long-term complications by attenuating the procoagulant state. There is overall consensus to reserve anticoagulation at a target international normalized ratio (INR) of 2.0 to 3.0 (moderate-intensity anticoagulation) to aPL-positive patients with a previous venous thrombosis; the therapeutic management of those with a history of arterial event is more debated. The poor agreement among clinicians is mirrored in the different therapeutic options enlisted in available recommendations to manage APS patients with a history of arterial thrombosis: antiplatelet agents, low- or high-intensity anticoagulation.<sup>5</sup> Unfortunately, thrombotic occurrences might occur despite adequate anticoagulation, carrying a significant burden of morbidity and mortality. In addition, anticoagulant agents are limited by significant side effects, thus warranting a careful weighting of risks and benefits. The poor safety profile and the scarce efficacy of drugs acting on the coagulation cascade explain why novel therapeutic approaches are currently under investigation, to identify pharmacological tools specifically counteracting aPL-mediated prothrombotic effects.

### Treatment of aPL-Positive Subjects with a First Venous Thrombosis

Deep venous thrombosis provides the most common APS presenting event, being recorded in 31.7% of cases; pulmonary embolism occurs in 9% of patients.<sup>6</sup> As in the general population, the initial treatment of aPL-related venous thrombosis envisages unfractionated heparin

(UFH) or low-molecular-weight heparin (LMWH) for at least 5 days, embraced with vitamin K antagonists (VKAs). Anticoagulation is almost always prescribed at moderate-intensity, but some authors support anticoagulation at a target INR of 3.0 to 4.0 as a therapeutic option.<sup>5</sup>

### Moderate-Intensity Anticoagulation

**PROs:** Standard anticoagulation at a target INR below 3.0 has been shown to confer effective protection against venous recurrences. In particular, the two randomized clinical studies comparing moderate- and high-intensity anticoagulation in patients with a definite APS diagnosis failed to report any difference between the two regimens.<sup>7,8</sup> Consequently, a meta-analysis considering these two trials could not report any difference in the rate of thrombosis recurrence between the two regimens, although an almost significant excess thrombotic risk was observed with high-intensity anticoagulation.<sup>8</sup> This observation might reflect the strong difficulties that patients experience in keeping INR in the high-intensity range: patients in the high-intensity group presented an INR below the target range for over 40% of the follow-up time, thus limiting the interpretation of the efficacy of high-intensity regimen.

**CONs:** Some retrospective studies suggested that the high-intensity regimen was more effective in preventing thrombotic recurrence compared with low-intensity anticoagulation among unselected APS patients and those with a history of venous thrombosis.<sup>9</sup> It should also be considered that many of the studies in support of the equality of moderate- and high-intensity regimens recruited patients presenting laboratory tests not fulfilling criteria for full-blown APS. Even the two randomized studies presented a few limitations, such as the small sample size, the limited statistical power, and few patients with a high-risk aPL profile. The third is a strong bias: patients on standard anticoagulant therapy with a previous venous event and a high-risk aPL profile, namely, those carrying triple aPL positivity, presented a 45% recurrence rate over a 6-year period.<sup>10</sup> This body of evidence might thus suggest that standard-intensity anticoagulant therapy confers poor protection against thrombotic recurrences in the high-risk group.

### Debated Issue: Duration of Anticoagulation

Even though it is current practice to prescribe indefinite anticoagulation to APS patients with a history of venous thrombosis, an increasing debate about the potential withdrawal of anticoagulation in subjects with previous venous thrombosis who turn aPL-negative has emerged. This is based on two case series, where anticoagulation was safely terminated among APS patients eventually becoming aPL negative.<sup>11,12</sup> Accordingly, it has been recently suggested that APS patients with a first venous event and a low-risk aPL profile plus a known transient precipitating risk factor (second hit) could be candidate for 3 to 6 months of anticoagulation, provided that there is a normal D-dimer and no ultrasonographical evidence of residual thrombosis. This approach is supported by a randomized trial comparing 1- to 3-month anticoagulation in patients with venous thrombosis and a transient reversible risk factor: subgroup analysis showed that aPL positivity tested at the time of randomization is

not predictive of venous recurrence.<sup>13</sup> Caution should be considered when stopping anticoagulation: the risk of vascular recurrence is highest in the 6 months following drug discontinuation.<sup>14</sup>

### Treatment of aPL-Positive Subjects with a First Arterial Thrombosis

Arterial thrombosis provides the presenting manifestation in 27% of patients; most commonly, the cerebral district is involved. Among noncerebral thrombosis, the most common presentation is myocardial infarction.<sup>6</sup> There are two different therapeutic approaches to aPL-positive subjects who experience an arterial event in noncerebral districts. Some experts commonly prescribe moderate-intensity anticoagulation, while other clinicians opt for VKA anticoagulation at a target INR of 3.0 to 4.0.<sup>5</sup>

#### Moderate-Intensity Anticoagulation

**PROs:** The efficacy of moderate-intensity anticoagulation is supported by the two randomized controlled trials that also recruited patients with a history of arterial events, even though less represented than those with venous thrombosis. As previously discussed, these two studies are not in support of the advantages offered by high-intensity compared with moderate-intensity anticoagulation.<sup>7,8</sup>

**CONs:** The main critical issue in the management of patients with arterial thrombosis concerns the risk of a new thrombotic event despite adequate treatment. The risk of recurrence is particularly relevant in case of a first arterial thrombosis, as these patients have always been considered at higher risk of recurrent event, almost invariably involving the same circulatory district. This belief is mainly supported by the only survey analyzing arterial and venous events separately and two cohort studies, all concordantly concluding that the risk of recurrence is higher for arterial than venous events.<sup>9</sup> This evidence is, however, in clash with the results emerging from a study considering high-risk triple-positive APS patients, where the presenting event did not predict the site of the recurrence.<sup>10</sup>

#### High-Intensity Anticoagulation

**PROs:** Some clinicians prescribe a high-intensity regimen to APS patients with arterial thrombosis, advocating that in many studies oral anticoagulation to a standard target INR of 2.0 to 3.0 did not offer a sufficient protection against recurrences.<sup>9</sup> The choice of a high-intensity regimen is further supported by the higher recurrence risk experienced by APS patients with previous arterial events, as suggested in some—but not all—studies.<sup>9</sup> In a cohort of triple positive APS subjects with a history of arterial thrombosis on standard anticoagulation, a 47% recurrence rate was registered, suggesting its poor efficacy.<sup>10</sup>

**CONs:** The main limitation affecting the use of anticoagulants at high intensity is the risk of bleeding. A 2007 systematic review reported a yearly bleeding rate between 0.57 and 10%.<sup>15</sup> When only recent studies exploiting a target INR of 2.0 to 3.0 are taken into account, the annual bleeding rate drops

down to 0.8 to 1.6%.<sup>9</sup> Undoubtedly, the risk of bleeding increases progressively with the rising of anticoagulation intensity. To note, at higher intensity of anticoagulation, there are wider INR fluctuations contributing to the instauration of a thrombogenic status. It should be stressed that the mortality rate due to aPL-related thrombosis is higher than the mortality rate due to bleeding: the single study specifically addressing the risk of bleeding in APS reported no fatal bleeding episodes, with precipitating factors identified in all cases.<sup>16</sup>

### Treatment of aPL-Positive Subjects with Stroke

aPL-mediated events present a particular tropism for the cerebral circulation: the most frequent site of arterial thrombosis in APS is the cerebral vasculature. Indeed, stroke is the presenting clinical manifestation in 13% of cases, while 7% of APS patients develop a transient ischemic attack at disease presentation. Stroke accounts for significant morbidity and mortality: in a large European cohort, 13% of deaths were due to cerebral ischemia, at a mean age of 42 years.<sup>17</sup> Besides anticoagulants, the therapeutic armamentarium in case of cerebral arterial thrombosis also comprises antiplatelet agents.

#### Low-Dose Aspirin

**PROs:** The use of low-dose aspirin (LDASA) in aPL-mediated stroke is supported by the Antiphospholipid Antibodies and Stroke Study (APASS). In this randomized controlled trial, when only aPL-positive patients were considered, aspirin given at a daily dose of 325 mg was as effective as low-intensity anticoagulation in stroke secondary prevention.<sup>18</sup>

**CONs:** In the APASS study, many patients had aCL positivity at low titers, and positivity in aPL tests was not confirmed 12 weeks apart. Subjects with baseline positivity for both LA and aCL tended to have a higher event rate (31.7%) than those negative for both antibodies (24%). These flaws prevent the extrapolation of results to patients with definite APS.<sup>18</sup>

#### Low-Dose Aspirin plus Anticoagulation

**PROs:** The combo approach of LDASA plus moderate-intensity anticoagulation was proposed as a therapeutic option in stroke patients diagnosed with APS in a 2009 randomized controlled trial. This study reported a lower rate of stroke recurrences in the arm receiving LDASA plus warfarin compared with LDASA alone; the cumulative stroke-free survival was 74 and 25%, respectively.

**CONs:** This study is limited by a small sample size and few details about aPL profiles and limited data on stroke recurrences.<sup>19</sup>

### New Therapeutic Approaches to Thrombotic APS

#### Novel Anticoagulants

A novel class of anticoagulants, the direct oral anticoagulants (DOACs), has been synthesized. These oral pharmacological agents are highly selective, each inhibiting a single

coagulation enzyme. Dabigatran acts as a thrombin inhibitor: it potentially directly binds to thrombin and reversibly blocks its interaction with substrates. Rivaroxaban, apixaban, and edoxaban are direct FXa inhibitors.<sup>20</sup> Dabigatran and rivaroxaban were used in some cohorts of APS patients: in a cohort of 26 French APS patients, a single recurrent event and two bleeding episodes were registered; a UK cohort of 35 APS subjects proved rivaroxaban to be safe.<sup>20</sup> Several randomized controlled clinical trials are currently assessing rivaroxaban versus low-intensity anticoagulation in APS management. The RAPS (Rivaroxaban in APS) trial has been promoted by a UK group; it is a phase II/III study that has recruited 156 APS patients with a history of venous thromboembolism<sup>21</sup>; a Spanish phase III trial has recruited 218 patients with venous or arterial events; the TRAPS (trial on rivaroxaban in high-risk patients with APS) trial, an Italian noninferiority study considering exclusively triple positive APS patients, is still recruiting<sup>22</sup>; the ASTRO-APS (Apixaban for the secondary prevention of thromboembolism among patients with APS), a randomized open-label trial, will randomize APS patients to adjusted-dose warfarin or apixaban twice daily.<sup>23</sup>

**PROs:** Thanks to the dose-dependent predictable anticoagulant effect, DOACs can be administered at a fixed dose. In addition, as they are metabolized by a system different from cytochrome P450, dietary constituents, alcohol, and drugs do not interact with DOACs. Therefore, DOACs do not require routine monitoring of anticoagulant intensity, with a significant improvement in quality of life for patients.<sup>24</sup>

**CONs:** DOACs are burdened by a significant bleeding risk.<sup>25</sup> Several case reports of thrombotic recurrence in concomitance of switching from warfarin to rivaroxaban have been published, although possibly reflecting a publication bias.<sup>26–28</sup>

## Adjuvant Therapies in the Treatment of Thrombotic APS

### Hydroxychloroquine

Hydroxychloroquine (HCQ) is an antimalarial drug with immunomodulatory, anti-inflammatory, and antithrombotic action. In vitro, HCQ has been demonstrated to (1) prevent activation of Toll-like receptor (TLR) 3, TLR7, and TLR9; (2) inhibit the processing and the presentation of antigens; (3) reduce serum immune complexes; (4) impair platelet aggregation induced by collagen or ADP; (5) downregulate membrane glycoprotein (GP) IIb/IIIa expression on platelets activated by aPL; (6) reverse the formation of aPL- $\beta$ 2GPI-phospholipid bilayer complexes; and (7) prevent the aPL-induced disruption of the Annexin A5 shield. Its antithrombotic properties have been confirmed in vivo: HCQ injection to mice induced a dose-dependent decrease in thrombus size. In patients, HCQ exerts antilipidemic effects with lower levels of triglycerides and low-density lipoprotein cholesterol.<sup>29</sup> In primary thrombotic APS, patients receiving a dual regimen including HCQ and oral anticoagulation had a lower recurrence rate compared with those on anticoagulants only. However, data extrapolation is affected by the small sample size (40 patients) and the limited follow-up (36 months).<sup>30</sup>

### Statins

The observation that low high-density lipoprotein cholesterol and high triglyceride levels are the most frequent cardiovascular risk factors among APS patients suggests that statins might be beneficial in the prevention of aPL-mediated thrombosis. In APS setting, these pharmacological compounds exert additional pleiotropic anti-inflammatory and antithrombotic effects. In vitro, statins have been demonstrated to (1) inhibit the synthesis of tissue factor (TF) in endothelial cells (ECs); (2) suppress endothelial adhesiveness induced by anti- $\beta$ 2GPI antibodies; (3) reduce the adhesion of monocytes to the vascular endothelium; and (4) prevent VCAM upregulation by aPL. In vivo, fluvastatin reduced the size of the thrombus induced by aPL infusion and the leukocyte adhesion to EC. Ex vivo studies provide consistent findings. In a trial considering 42 APS patients, a 30-day fluvastatin course decreased several thrombogenic and inflammatory mediators in monocytes; a significant reduction in some proinflammatory and procoagulant parameters was reported after a 3-month treatment with fluvastatin in 41 aPL asymptomatic carriers.<sup>31</sup>

### Vitamin D

Among APS patients, the frequency of the deficiency of vitamin D ranges between 10 and 50%; insufficiency may occur in up to 70% of patients.<sup>2</sup> Low levels of vitamin D are more frequently detected among subjects with arterial and venous thrombosis as well as with noncriteria APS manifestations. In vitro, vitamin D acts as an immunomodulator and antithrombotic agent, mainly preventing anti- $\beta$ 2GPI antibody-mediated TF expression. Thus, vitamin D supplementation might be beneficial in the secondary prevention of thrombotic events.<sup>32</sup>

### Intravenous Immunoglobulins

The therapeutic potential of intravenous immunoglobulins (IVIg) in APS is suggested by in vivo and in vitro models. IVIg were shown to (1) partially neutralize LA phenomenon and prevent aCL binding to the antigen; (2) inactivate idiotype-bearing B cell clones; (3) increase IgG catabolism; (4) block complement activation; (5) inhibit Fc $\gamma$  receptor on macrophages; and (6) downregulate proinflammatory cytokine. Treatment with IVIg inhibited aPL thrombogenic effects, reducing aCL levels. There are some published reports of successful treatment with IVIg of aPL-related clinical manifestations, mainly hematological. A response to treatment was reported in all patients but one.<sup>33</sup>

### Anti-B Cell Agents

B lymphocytes exert a key role in APS etiopathogenesis: they synthesize autoantibodies, promote germinal center formation, and induce cytokines. In lupus-prone mice, treatment with IgG against B cell activating factor (BAFF) receptor did not affect aCL development but prolonged survival, preventing aPL-related thrombosis. Therefore, anti-B cell agents, such as belimumab (an anti-BAFF monoclonal antibody) and rituximab (an anti-CD20 monoclonal antibody), might be beneficial in APS. Interestingly, in belimumab-treated lupus

patients, seroconversion toward aCL negativity was reported. In the clinical setting of APS, experience of B cell inhibition is still restricted to rituximab. In the multicenter registry by the Spanish Study Group of Biological Agents in Autoimmune Diseases (BIOGEAS), a beneficial effect was observed in 92% of 12 cases.<sup>34</sup> In the Rituximab in Antiphospholipid Syndrome study (RITAPS), an open-label phase IIa descriptive pilot study, 20 patients with noncriteria APS manifestations refractory to conventional therapies were treated with rituximab, resulting in a satisfactory control of some noncriteria manifestations, without affecting aPL profile.<sup>35</sup> Given this body of evidence, the task force on APS treatment trends claimed a therapeutic role for anti-B cell agents in APS cases with unresponsive hematologic and microangiopathic manifestations.<sup>34</sup> Severe acute thrombotic exacerbations have been reported in two APS lupus subjects on rituximab, thus suggesting caution.<sup>34</sup>

## Treatment of APS Patients with Thrombotic Recurrences

Approximately 3 to 24% of APS patients develop recurrent events even during adequate treatment.<sup>9</sup> Despite the important morbidity and mortality effects that recurrences yield, clear recommendations to manage these situations are still lacking. Indeed, no randomized clinical study has ever assessed the management of patients who had a thrombosis on anticoagulation. The current clinical approach envisages first the assessment of INR at the time of the recurrence. If the thrombotic event occurred at a subtherapeutic INR range, a moderate-intensity regimen can be continued, keeping the INR in the therapeutic range. In case of an INR within the therapeutic range, the intensity of anticoagulation should be increased to a target INR of 3.0 to 4.0.

### Low-Molecular-Weight Heparin

Switching to long-term LMWH may also be considered as a safe and effective alternative to warfarin. This approach was even considered in the evidence-based consensus guidelines formulated at the 13th International Congress on Antiphospholipid Antibodies.<sup>5</sup> The efficacy of LMWH in thrombotic recurrences emerged outside APS field: the 2003 CLOT (Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer) study stated that dalteparin was even more effective than warfarin in reducing the risk of recurrent embolic events among cancer patients.<sup>36</sup> The rationale of prescribing LMWH is even stronger for APS patients. Indeed, heparin exerts pleiotropic effects, beyond its anticoagulant action. Heparin (1) interacts directly with  $\beta$ 2GPI (the primary heparin-binding site is located on the second positively charged site within DV of  $\beta$ 2GPI); (2) enhances the plasmin-mediated cleavage of Lys317-Thr318 site in  $\beta$ 2GPI, resulting in a diminished ability of  $\beta$ 2GPI to recognize phospholipids and the consequent impairment of the prothrombotic activity of anti- $\beta$ 2GPI antibodies; and (3) inhibits, at variance of other anticoagulants, complement

activation in animal models of obstetric APS, thus preventing aPL-mediated fetal loss. LMWH use is limited because of the subcutaneous administration and side effects (heparin-induced thrombocytopenia, osteoporosis).<sup>9</sup>

### Dual Antiplatelet Treatment

Another possible approach envisages a dual antiplatelet treatment (different combination of LDASA, ticlopidine, clopidogrel, and cilostazol), based on the results of a Japanese study where, among 82 APS patients with relapsing arterial events, no recurrence was documented.<sup>37</sup>

### Low-Dose Aspirin

In patients with recurrent arterial events, LDASA could be added to anticoagulant treatment, even though this option is burdened by a higher bleeding risk. To date, only a small, low-quality randomized controlled trial has shown that combination therapy was more effective than aspirin alone in the secondary prevention of aPL-related stroke.<sup>18</sup>

### Rituximab and Eculizumab

Novel biologic agents have also been proposed as therapeutic option for refractory thrombotic APS. In a 2012 review paper, 27 APS patients who received rituximab were identified, with decrease of aPL titers and clinical improvement in all cases.<sup>38</sup> Eculizumab is a humanized monoclonal antibody which binds with high affinity to C5. It inhibits the cleavage of C5 to C5a and C5b, thus preventing the generation of membrane attack complex. The potent anaphylatoxic, proinflammatory, and chemotactic C5a plays a central role in APS: it induces the expression of TF on ECs and neutrophils; in vivo, C5 mediates fibrin deposition in aPL-induced thrombi.<sup>9</sup> There is a single report of eculizumab use in the secondary thromboprophylaxis of APS. This is the case of a 59-year-old APS woman who received eculizumab while undergoing bypass surgery to treat a critical vascular occlusion of the femoral artery.<sup>39</sup> Eculizumab has also been proposed in the management of APS patients who required renal transplantation. In three kidney transplant recipients, eculizumab improved posttransplant aPL-mediated thrombotic microangiopathy resistant to plasmapheresis. In an additional series of three patients receiving anticoagulation and eculizumab, no systemic thrombotic events or early graft losses occurred after a follow-up between 4 months and 4 years.<sup>9</sup>

### Intravenous Immunoglobulins

Another option that could be exploited is the addition to standard treatment of IVIg, as suggested by two open studies. IVIg were effective in five APS patients with relapsing thrombosis: no new thrombotic event occurred at 5-year follow-up.<sup>40</sup> In the other study, IVIg prevented thrombosis when added to conventional therapy in seven patients with refractory APS at 2 years.<sup>33</sup>

## Treatment of Catastrophic APS

Most of the available evidence for CAPS management comes from an international registry by the European Forum on

Anti-phospholipid Antibodies. In this registry, two therapeutic approaches were identified as the most effective in CAPS. The first one comprised anticoagulation, corticosteroids, and plasma exchange, with a 77.8% recovery rate. Anticoagulation, corticosteroids, plasma exchange, and/or IVIg allowed controlling the disease in 69% of cases. Plasma exchange is specially indicated when schistocytes are present, and should be initiated within 12 hours from the onset.<sup>41</sup> When these therapeutic approaches do not lead to disease control, second-line agents such as rituximab and eculizumab can be used, even though experience is only anecdotal. In literature, there are 20 reports of rituximab prescription to CAPS patients, differently combined with anticoagulation, high doses of steroids, plasma exchange, and IVIg, with a lower mortality rate. Eculizumab has been administered to a few CAPS patients refractory to all the other therapeutic strategies; a positive effect was reported in two cases.<sup>42</sup>

### Treatment of Thrombotic APS in the Near Future

The currently available strategies in APS management are limited to agents counteracting coagulation; however, as already discussed, these drugs display several limitations and are not effective in all patients. An alternative approach aims at preventing the prothrombotic effects via the inhibition of the cellular mechanisms engaged by aPL. The first strategy could envisage the prevention of aPL binding to target cells; this could be pursued thanks to TIFI, which is a 20-amino acid synthetic peptide spanning Thr101 to Thr120 of ULB0-HCMVA from human cytomegalovirus. TIFI is similar to  $\beta$ 2GPI-DV, where the phospholipid-binding site is located. TIFI thus competes with  $\beta$ 2GPI for binding to phospholipids in the cell membrane and is not targeted by aPL. In vitro and in vivo findings suggest its efficacy: TIFI inhibited the binding of labeled  $\beta$ 2GPI to human ECs and mouse monocytes, and its infusion to animals decreased the size of aPL-mediated thrombi and reduced the binding of fluoresceinated  $\beta$ 2GPI to the endothelium.<sup>9</sup> Similarly, a peptide homologous to  $\beta$ 2GPI-DI, the most relevant epitope involved in  $\beta$ 2GPI/anti- $\beta$ 2GPI antibody binding, has been synthesized. This peptide inhibits the prothrombotic effects mediated by aPL both in vivo and in vitro.<sup>43</sup> Another approach exploits a nonpathogenic monoclonal anti-DI antibody, MBB2ACH2. This is a CH2-deleted variant of the novel monoclonal antibody targeting DI- $\beta$ 2GPI, MBB2, which exerts prothrombotic effects. MBB2ACH2 does not activate the complement cascade, thus not inducing clotting, but competes with circulating aPL for binding to  $\beta$ 2GPI. When infused to rats together with MBB2, MBB2ACH2 prevented the MBB2-procoagulant effects.<sup>44</sup> The immunodominant epitope DI is a cryptic and conformation-dependent structure; the surface exposition of the critical B cell structure might be induced by several factors, including oxidative stress. Indeed, oxidative conditions favor the formation of disulfide bonds within the molecule, which lead to the unmasking of the relevant epitope.<sup>2</sup> This process is catalyzed by the enzyme protein disulphide isomerase (PDI); therefore, quercetin-3-rutinoside, an inhibitor of this enzyme, might be effective in

APS. In animal models, PDI inhibitors treated thrombosis. In monocytes, inhibiting the intracellular reactive oxygen species results in the prevention of the upregulation of aPL-induced TF.<sup>31</sup> Consequently, antioxidant compounds as N-acetylcysteine, vitamin C, and coenzyme Q10 might play a beneficial role in the management of APS patients.

The pharmacological interference with the mediators engaged by aPL could provide another option: aPL induce a proinflammatory and procoagulant endothelial phenotype upregulating cellular adhesion molecules, TF, TNF- $\alpha$ , and IL-6. Several drugs available over the counter inhibit the expression of TF, the major initiator of the clotting cascade. This is the case of ACE inhibitors, dilazep and dipyridamole. In particular, both dilazep and dipyridamole prevent TF upregulation in monocytes induced by polyclonal IgG purified from APS patients.<sup>9</sup> To date, the role of these compounds in APS management has been scarcely documented. Similarly, it can be envisaged that blocking of TNF- $\alpha$  and IL-6 with biologic agents might be beneficial.<sup>34</sup>

aPL-induced effects on the endothelium are mainly mediated by autoantibody reactivity with  $\beta$ 2GPI on the EC membrane. Therefore, antagonists or neutralizing monoclonal antibodies acting on the potential receptors involved in  $\beta$ 2GPI interaction with ECs (Annexin A2, TLR2, TLR4, heparan-sulfate, and ApoER2<sup>3</sup>) might be effective in APS.  $\beta$ 2GPI-DV binds the A1 ligand-binding type A module of ApoER2'; in vitro, a dimer constituted of two A1 molecules has been reported to block the binding of anti- $\beta$ 2GPI antibody/dimerized  $\beta$ 2GPI immune complexes to negatively charged phospholipids and ApoER2', to a more potent extent than monomeric A1. Such a dimeric molecule was shown to be effective in two animal models of APS.<sup>45</sup> In platelets, the interaction of aPL with cell surface is mediated by GPIIb/IIIa. Abciximab, a specific GPIIb/IIIa inhibitor, commonly prescribed to patients with stroke and acute coronary syndromes, can thus be proposed for APS management. Downstream of cell receptors, nuclear factor  $\kappa$ B (NF $\kappa$ B) and p38 mitogen-activated protein kinase (p38MAPK), are involved in aPL-induced EC and monocyte activation. Therefore, blockers of the downstream mediators engaged by aPL may reverse the prothrombotic phenotype: NF $\kappa$ B and p38MAPK inhibitors can prevent prothrombotic and proinflammatory effects induced by aPL treatment in vitro. DHMEQ, an inhibitor of NF $\kappa$ B, ameliorated the prothrombotic state induced in mice by the treatment with the monoclonal antibody WB-6.<sup>31</sup> aPL have been recently demonstrated to recruit the mammalian target of rapamycin (mTOR) via the phosphatidylinositol 3-kinase-AKT pathway. mTOR is a kinase modulating cellular growth, proliferation, and apoptosis. The mTOR inhibitor sirolimus has been used in patients with APS nephropathy requiring kidney transplantation, leading to a higher rate of functioning allograft at 144 months and a decreased vascular proliferation on biopsy compared with the standard regimen arm.<sup>46</sup>

### Conclusion

The treatment of thrombotic APS is a rather relevant issue from a socioeconomic point of view. Although there are no sound epidemiological studies on the prevalence of aPL or APS in the

**Table 1** Current recommendations for treatment of patients with thrombotic APS<sup>5</sup>

	Recommendations	Grade of recommendations
Venous thrombosis	Moderate-intensity anticoagulation	1B
Noncerebral arterial thrombosis	Moderate-intensity anticoagulation High-intensity anticoagulation	No consensus
Stroke	High-intensity anticoagulation Moderate-intensity anticoagulation + LDASA Moderate-intensity anticoagulation LDASA	No consensus

Abbreviation: APS, antiphospholipid syndrome; LDASA, low-dose aspirin.

general population, the disease has been estimated to affect 40 to 50 individuals per 100,000 persons, usually presenting in early adulthood.<sup>47,48</sup> These epidemiological data imply that APS carries high socioeconomic morbidity and mortality, making pivotal the optimal management of APS patients. Antiplatelet and anticoagulant agents still provide the cornerstone of APS treatment, as suggested in available recommendations<sup>5</sup> (► **Table 1**). However, it should be borne in mind that most evidence in support of these treatments comes from studies including patients not fulfilling APS laboratory criteria. Indeed, several limitations flaw these studies, mainly concerning aPL testing. Most studies do not fulfill international requirements in terms of number of aPL tests performed, the confirmation of aPL positivity, and the choice of aPL cutoff. In this scenario, it is not surprising that in multicenter cohort of patients with longstanding APS, anticoagulation appears not to protect against recurrences at long term. The poor benefit exerted by anticoagulants is further suggested by the fact that 55% of APS patients presented with organ damage.<sup>49</sup> The scarce protection conferred by anticoagulants might underline the necessity of a “tailored treatment strategy.” In other words, a more aggressive treatment should be reserved to aPL-positive patients with a high-risk aPL profile and additional prothrombotic risk factors. Consequently, a better stratification of aPL-positive patients upon the aPL profile (triple/double positivity vs. single positivity) and associated cardiovascular risk factors is mandatory to accurately evaluate the magnitude of the risk. Novel diagnostic and prognostic tools, such as antidomain antibodies, may allow an even more accurate risk stratification. It would be advisable to soon assess the potential effects of a strict control of cardiovascular status and the benefit of pleiotropic agents such as statins and HCQ on outcome, hopefully leading to a better disease control. Given the many limitations of available treatments, it is to be hoped that the novel pharmacological agents that have been identified in these recent years will optimize APS management in the near future.

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