Emerging Therapies in Antiphospholipid Syndrome

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Abstract

The antiphospholipid syndrome (APS) is the most common cause of acquired immune-mediated thrombophilia. This syndrome is broadly defined by the presence of arterial or venous thrombosis, or pregnancy morbidity, in the presence of high levels of antiphospholipid antibodies. Despite recognition of this disorder more than 50 years ago, a fundamental unifying pathogenesis has not been determined. Due to this, mechanism-based therapies for APS are not available, and current management following thrombotic events suggests anticoagulation of indeterminate duration, or for obstetric complications, heparin/low molecular weight heparin and aspirin. However, APS is an autoimmune disorder, and several approaches focused on modulating the immune response or its effectors have been employed. Those which have been most extensively studied include hydroxychloroquine, rituximab and eculizumab, an inhibitor of complement C5. In this report, we review in depth, and critique, key clinical studies of these agents. Since all of these studies are small, our conclusions are qualified. However, it appears that hydroxychloroquine may enhance the anticoagulant efficacy of vitamin K antagonists in APS patients, and that rituximab may ameliorate some of the "non-criteria" manifestations of APS. The catastrophic antiphospholipid syndrome (CAPS) is associated with diffuse thrombosis, multi-organ dysfunction, and ~30% mortality. A high incidence of complement regulatory gene mutations, and compelling data concerning the efficacy of eculizumab in CAPS, suggests an important role for complement in this disorder. However, additional work is needed to clarify the role of complement in non-catastrophic APS, though emerging data suggests that complement inhibition may be effective in preventing thrombosis in these patients as well.

Keywords

Antiphospholipid; Lupus; Complement; Eculizumab; Plasma exchange; Thrombophilia

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Conflicts of Interest

The authors have no conflict of interest to disclose in relation to the submitted review.

Introduction

The antiphospholipid syndrome (APS) is an autoimmune disorder characterized by arterial or venous thrombosis and/or recurrent obstetrical morbidity accompanied by persistently high levels of antiphospholipid antibodies (aPL) [1]. aPL are autoantibodies with specificity primarily toward phospholipid binding proteins [2] and include the lupus anticoagulant (LAC), anti-beta2-glycoprotein-I (B2GPI), anti-cardiolipin (aCL), and anti-prothrombin antibodies (IgG or IgM), [1] among others. Cofactor-independent aPL have also been described [3,4]. APS is the most common acquired thrombophilia [5] and results in both venous and arterial thrombosis, most commonly deep vein thromboses (DVT) and stroke, respectively [6]. APS is also associated with significant obstetric morbidity [6]. A comprehensive pathogenic model that can inform effective therapies remains to be established. The cornerstone of management following a thrombotic event is indefinite anticoagulation with a vitamin K antagonist (VKA), or aspirin and heparin for obstetric manifestations [7]. Several novel treatment approaches that target immune components of the syndrome have been described [8,9]. Agents that have been most extensively studied include hydroxychloroquine, the B-cell depleting monoclonal antibody rituximab, and eculizumab, a monoclonal antibody to complement C5. In the discussion that follows, we review the relevant pathophysiology, and the strength of the evidence supporting a role for these therapies in APS management.

Diagnosis of APS

The revised Sapporo criteria [10], originally developed to standardize enrollment of APS patients into clinical studies rather than to diagnose APS, are nevertheless widely used in clinical practice for APS diagnosis. These criteria include both clinical and laboratory parameters. Clinical criteria include objectively confirmed venous, arterial, or small vessel thrombosis, or obstetrical morbidity (unexplained death of a morphologically normal fetus at or beyond the 10th week of gestation, the premature birth of a neonate before the 34th week of gestation, and/or 3 or more unexplained, consecutive pregnancy losses before the 10th week of gestation) [1]. Laboratory criteria include a lupus anticoagulant, defined by International Society of Thrombosis and Hemostasis (ISTH) guidelines [11], and/or the presence of IgG or IgM anticardiolipin or anti-β2GPI antibodies at levels exceeding the 99th percentile of normal controls (ELISA) [11]. As aPL can be transient, the laboratory criteria must be met on 2 separate occasions at least 12 weeks apart. A subset of APS patients (approximately 1%) [6] present with the highly thrombotic phenotype referred to as catastrophic APS (CAPS). CAPS presents with simultaneous or rapidly successive thromboses in 3 or more organ systems occurring in less than 1 week in the presence of aPL [12]. Thrombosis in CAPS may pre-dominately affect microvascular beds, although large vessel venous or arterial events occur [12]. CAPS is highly morbid [13], may be refractory to standard treatment with anticoagulation, glucocorticoids and plasma exchange, and is associated mortality of approximately 30% [6]. Additional clinical features not formally included in the revised Sapporo criteria, but nonetheless recognized to occur in APS have been termed "non-criteria" manifestations, and include superficial venous thrombosis, thrombocytopenia, cardiac valvular disease, skin ulcers and livedo reticularis,

aPL-associated nephropathy, migraine headaches, and cognitive dysfunction, among others [14].

In practice, the Sapporo criteria have several shortcomings. For example, there is limited guidance as to whether patients who develop thrombosis or pregnancy morbidity in the presence of low or intermediate aPL levels should be considered to have APS [11]. Similarly, patients presenting with a convincing clinical picture but with transient, or persistently negative aPL titers, are sometimes diagnosed with "seronegative APS" though there is a lack of consensus around this entity [15,16]. In contrast, some patients may have persistently high levels of aPL without experiencing thrombotic or obstetrical events. Laboratory analytical issues such as interassay and interlaboratory variability present additional challenges in APS diagnosis [7,11,17]. Hence, despite recent advances, the ability to risk stratify aPL patients remains limited, reflecting incomplete information concerning disease mechanisms in individual patients.

Pathophysiology

aPL are primarily directed against phospholipid-binding proteins such as prothrombin and B2GPI [2,18], although prothrombotic, cofactor-independent aPL have also been described [3,4]. The majority of published work in APS has focused on anti-β2GPI antibodies [2,19,20], and these studies generally demonstrate a significant association of anti-β2GPI antibodies with clinical events [2]. A "two hit" hypothesis proposes that aPL prime the intravascular space and a "second hit" (eg, infection, vessel injury, surgery) triggers a thrombotic event [2,7]. This hypothesis is supported by the observation that aPL positivity alone may be insufficient to drive the disease manifestations. For example, in a murine model, affinity purified IgG antibodies against B2GP1 from APS patients caused thrombosis in mice treated with a proinflammatory factor (LPS) in a complement-dependent manner, but did not cause thrombosis alone [20]. Passive infusion of human aPL IgG or affinity-purified anti-β2GPI antibodies into mice has been shown to potentiate thrombosis induced by a triggering event, such as vessel injury [20–22]. aPL generate the prothrombotic milieu through multiple mechanisms, including platelet, endothelial cell, and monocyte activation, in concert with inhibition of natural anticoagulant and fibrinolytic systems [2,7,22]. Activated endothelial cells increase the expression of adhesion molecules and tissue factor, and the release of von Willebrand factor, proinflammatory cytokines and extracellular vesicles, while decreasing endothelial cell-derived nitric oxide, in response to anti-β2GPI antibodies [7,23]. Anti-β2GP1 antibodies also stimulate monocyte tissue factor expression and release of inflammatory cytokines [24], as well as the release of neutrophil extracellular traps (NETs). [25] aPL associated with pregnancy loss may have additional mechanisms, including impairment of trophoblast migration leading to defective placentation [2].

There is compelling evidence for a role of complement in the pathogenesis of APS [2,22,26,27]. The complement system consists of numerous membrane-bound and soluble proteins that play a central role in innate immunity [28]. Activation of complement results in opsonization of pathogens but requires precise regulation to avoid damage to normal tissues; dysregulation of complement plays a critical role in disorders such as paroxysmal

nocturnal hemoglobinuria (PNH) and complement-mediated hemolytic uremic syndrome (CM-HUS) [28]. There is significant interplay between the complement and coagulation systems [29,30] and some evidence suggests that activated complement contributes to aPL-associated thrombotic events (Figure 1) [26,31–33]. In preclinical models, enhancement of thrombosis and/or fetal loss that follows passive infusion of aPL into mice is ameliorated in mice deficient in C3, C5 or C6 [32,33], as well as in mice pretreated with the C5 inhibitor, coversine [34]. Moreover, in a murine model of fetal loss, complement activation led to local generation of C5a, which stimulated migration of tissue factor-expressing neutrophils into the placental bed [35]. Studies in humans, however, are not as clear cut and further study is needed. Patients with APS have elevated levels of circulating complement activation products C3a and C4a, demonstrating ongoing complement activation in many [36] (Figure 2); however, these do not appear to clearly distinguish patients with thrombosis from those without (Figure 3) [37]. This may reflect the fact that relevant complement effects occur on cell surfaces rather than in plasma.

Despite some uncertainty in "standard" APS, evidence of unregulated complement activation is present in patients who develop CAPS and is likely to play a role in pathogenesis. A high incidence of complement regulatory gene mutations, similar to that observed in CM-HUS, has been reported in these individuals, and supports the premise of complement activation as a driver of the disease process [31]. As the low incidence of CAPS precludes randomized trials of complement inhibitors, complement inhibition therefore has become an emerging target in management of CAPS and refractory APS. In the discussion that follows we review several reports of use of the complement C5 inhibitor eculizumab in these settings.

Complement Inhibitors in CAPS and Refractory Antiphospholipid Syndrome

Current management of CAPs is empiric. Guidelines from an expert panel that attempted to develop an evidence-based approach to APS concluded that all recommendations were based on very low certainty of evidence, with the majority being conditional [38]. CAPS is initially treated using a combination of anticoagulation and high dose steroids, with most experts also recommending plasma exchange; of these approaches, however, only anticoagulation was considered to be a strong recommendation. Intravenous immunoglobulin (IVIg) has been used in some cases, particularly in patients who cannot tolerate plasma exchange [5,12]. Rituximab may be added in cases refractory to first line therapy [39], and cyclophosphamide or other immunosuppression has been used in patients with systemic lupus erythematosus or secondary APS/CAPS, though neither has shown convincing benefit [5,12].

Eculizumab is a humanized monoclonal antibody with specificity for complement C5. Binding inhibits cleavage of C5, preventing the generation of the terminal complement C5b9 complex [40]. Several case reports, case series, and systematic reviews [41–43] have described responses to eculizumab in CAPS (Table 1). The majority of reported cases describe favorable responses, though whether these reports truly reflect efficacy or publication bias to highlight positive outcomes is unknown. Two small retrospective cohort studies provide insight. Yelnik et al [44] conducted a retrospective cohort study of 11 patients presenting with severe CAPS. Despite standard management with anticoagulation,

glucocorticoids, and plasma exchange, these patients experienced a deteriorating course, and received eculizumab a median (range) of 25 days (3–100) after episode onset. Five of 11 patients responded (45%), but 6 had no response; 4 of the non-responders died of CAPS complications. This was the first study to report inconsistent responses of patients with CAPS to eculizumab. The authors suggested likely publication bias in prior case reports, but also questioned whether earlier initiation of eculizumab might have salvaged additional patients. In response to the question of time to treatment, Faguer and Ribes [45] published results from a retrospective study of 5 patients (6 total episodes of CAPS) refractory to corticosteroids, anticoagulation and plasma exchange, as well as rituximab (given in 5/6 episodes), who were ultimately treated with eculizumab. Eculizumab was given relatively soon, a median (range) of 7 (2–15) days after episode onset. Four patients (5 episodes) demonstrated rapid and sustained responses to eculizumab. One patient died of refractory CAPS and associated hemophagocytic lymphohistiocytosis. No increase in infectious complications was observed with early administration of eculizumab.

The most comprehensive data on eculizumab use in CAPS to date comes from Lopez-Benjume [46] who published a descriptive analysis from the "CAPS Registry." Of the 584 patients in this registry, 39 (6.7%) were treated with eculizumab. Seventy-seven percent of the treated patients had primary APS. Twenty-nine (74%) patients recovered from the episode of CAPS, 4 showed a partial response, 9 (23%) had progressive symptoms and 5 patients ultimately died. Responses were sustained with only 1 relapse during a median follow up of 10.7 months. Most patients were treated with 900 mg of eculizumab weekly for 4 weeks, followed by 1200 mg every 2 weeks for variable durations.

Taken together, these data suggest a potentially important role for eculizumab in treatment of CAPS. However, these reports are retrospective, and reporting bias may exist, thus additional studies are needed to answer multiple outstanding questions and guide the most efficient and effective use of this expensive agent. The presence of mutations in complement regulatory genes in these patients, that in some cases resemble those seen in CM-HUS, suggest an important role for the alternative pathway of complement. However, whether APS patients with specific complement regulatory gene mutations will respond better to complement inhibition has not been assessed. The optimal timing of administration, and duration of eculizumab in CAPS is unknown, and how to incorporate eculizumab into a multiagent regimen that includes plasma exchange has also not been determined. In most reports, treatment with eculizumab was continued for weeks to more than a year, but whether prolonged treatment is needed likely varies among patients and at this point there are no biomarkers to suggest the safety of treatment discontinuation. Given the rarity of CAPS, prospective randomized trials of eculizumab will be difficult, and answers to these questions may need to be derived from databases of real-world experience with this agent.

Occasional patients with APS, while not meeting criteria for CAPS, follow an aggressive course and develop recurrent thrombotic events despite optimal anticoagulation. Others may experience small thrombi, resembling vasculitis. While there is no clear treatment path for such patients, a recent case report suggests potential benefit of eculizumab in refractory APS [47]. This report describes an 18-year old female with persistently triple-positive APS, who developed spontaneous thrombosis in multiple areas, including the inferior

vena cava, brachiocephalic and axillary veins. She was treated with multiple anticoagulant regimens over the course of several years, including enoxaparin, fondaparinux, apixaban, rivaroxaban, and warfarin, both alone and in combination with antiplatelet agents (aspirin, clopidogrel). Despite these measures, as well as the use of hydroxychloroquine (HCQ), corticosteroids, rituximab, and even extensive plasma exchange (that was ineffective in lowering her aPL levels), she continued to develop recurrent thrombi. Ultimately, after developing hepatic infarction and another episode of pulmonary embolism, the patient was initiated on eculizumab at a dose of 600 mg/wk for 4 weeks, followed by 900 mg every 2 weeks thereafter. Fondaparinux, clopidogrel, HCQ and clopidogrel were continued. On this regimen, she remained thrombosis free for more than 27 months, with follow up ongoing (Figure 4). Though only a single case, much can be learned from such experiences, and this remarkable outcome suggests that complement activation may have been substantially contributing to this patient's refractory thrombosis. Though the cost of eculizumab precludes its use in all but the most severely affected APS patients, several orally available complement inhibitors are in development and may offer a promising new approach to APS. We are unaware of any reports concerning the long acting C5 inhibitor raviluzumab, or the newly-approved C3 inhibitor, pegcetoplan, in APS. Further work is needed to better define APS patients likely to benefit from these and other emerging agents.

Antithrombotic Effects of Hydroxychloroquine in Primary Antiphospholipid Syndrome

Hydroxychloroquine (HCQ) has been shown to reverse aPL-mediated disruption of annexin A5 crystal structures that shield phospholipid, with inhibition of coagulation reactions and implications for thrombosis and pregnancy complication [48]. Other studies have suggested an immunomodulatory action of HCQ mediated by decreasing antigen presentation and reducing production of proinflammatory cytokines. Anti-thrombotic effects may also reflect altered platelet adhesion and engagement with clotting factors [49,50].

A prospective study by Schmidt-Tanguy et al [49]. examined the role of hydroxychloroquine as secondary prophylaxis for recurrent thrombosis in primary APS. This small prospective, non-randomized trial enrolled 40 patients with primary APS and a history of VTE (arterial and obstetric morbidity were excluded). Patients were screened for traditional risk factors for thrombosis and genetic thrombophilia's and underwent baseline venous Doppler and D-dimer assessment. Twenty patients received HCQ (400 mg daily) in addition to a VKA (fluinidione), while the other 20 received VKA alone. The baseline characteristics for the 2 cohorts were similar and, importantly, were comparable in terms of the aPL profile, single or double aPL positivity, and aPL evolution over time. At the end of the 36-month trial, there were 2 recurrent VTE (30%) in patients receiving anticoagulation alone vs none in patients receiving HCQ and VKA. The percentage of time in the therapeutic INR range was high in all cases. Two patients (10%) in each cohort experienced minor bleeding. Though this was a small, non-randomized study with few thrombotic events, it was the first prospective trial to assess the role HCQ in addition to anticoagulation, and suggested a possible ancillary role for HCQ in secondary prevention of thrombosis.

Building upon this, Kravvariti et al [51] reported a pilot open-label prospective randomized clinical trial to evaluate the effect of HCQ on thrombosis prevention and aPL levels

in patients with primary APS. [51] Patients were followed prospectively for up to 3 years for development of thrombosis and assessment of aPL titers. All patients were continued on their existing anticoagulation regimens without modification. While initiation of immunosuppressive treatment was not allowed, patients on steroids at the time of enrollment were allowed to continue. Thrombotic events occurred in 7 of 50 (14%) patients in the trial – 6 in the standard of care cohort (4 patients on VKA and 2 patients on VKA plus low dose aspirin), and 1 in the HCQ plus standard of care arm (this patient later revealed they had discontinued HCQ). In the intention-to-treat analysis, HCQ use was associated with 85% reduction in the incidence rate of thrombosis (0.001 vs 0.008 for usual care, log-rank $P = .048$). In the Cox model, stratified by triple-positive aPL status and adjusted for other traditional risk factors for thrombosis, HCQ use was associated with a multivariate hazard ratio of 0.09 (95% CI = 0.011.–26, $P = .074$). Strengths of this trial include the prospective randomized design, a well-defined patient population inclusive of obstetric APS, and efforts taken to control for potential confounding and time-varying effects.

The ongoing HIBISCUS trial [50] is a multicenter, international double-blind RCT to evaluate the safety and effectiveness of HCQ in secondary prevention of obstetrical and thrombotic events in primary APS. This trial should further contribute to our understanding of the role of HCQ in this setting.

Rituximab for Non-Criteria Manifestations of Antiphospholipid Syndrome

Rituximab is a chimeric monoclonal antibody that binds to CD20 on B lymphocytes and results in their depletion. In mouse models of SLE-associated APS, B cell blockade prevented disease onset [52,53] and prolonged survival [53]. Case reports and small case series suggest a potential role for B-cell directed therapy in recurrent thrombotic APS [39], though rituximab has not been systematically studied for this indication.

Erkan et al [54] reported the results of the RITAPS trial (Pilot Study of Rituximab for the Anticoagulation Resistant Manifestations of Antiphospholipid Syndrome), a single-center phase II trial of rituximab for non-criteria manifestations of APS. The RITAPS trial was designed with the primary objective of evaluating the safety of rituximab in aPL-positive patients, and secondarily to assess the effect on non-criteria manifestations and the aPL profile. Of note, only approximately half of the patients in this trial met the revised Sapporo criteria. The non-criteria manifestations of enrolled patients included thrombocytopenia, cardiac valvular disease, skin ulceration, APS nephropathy, and/or cognitive dysfunction. Eligible patients received 1000 mg of rituximab on days 1 and 15, and were subsequently followed for up to 1 year. Nineteen patients were enrolled in the trial and 11 (58%) met criteria for primary APS. Twelve patients (63%) were triple positive for aPL. Rituximab did not significantly alter the aPL profile of patients: all patients with positive results of LAC, aCL, and/or anti-β2GPI IgG antibody tests at baseline had positive results at 24 weeks and 52 weeks. With regard to clinical end points, 2 patients had improvement in thrombocytopenia, while 2 had no response. No patients with cardiac valvular disease improved during the established follow up period. All 4 patients with skin ulcerations experienced a complete response, though 1 developed a recurrence. Three patients with cognitive dysfunction experienced remission with normalization of the cognitive impairment

index, and one had a partial response with >50% improvement. The authors conclude with appropriate caution given the small cohort that rituximab may be effective at controlling some of the non-criteria manifestations of APS.

The exploratory aims of the trial offer insights into the biological effects of rituximab in APS patients. Rituximab treatment predictably resulted in rapid B cell depletion within 2 weeks of the first infusion in all but 1 subject. B cell levels returned to baseline or normal levels, with significant inter-subject variability, over an interval from 6 to 24 months. One patient had a positive baseline human anti-chimeric antibody (HACA) test. At 36 weeks 9 (56%) of 16 patients had developed HACAs. Four of 6 (67%) patients with no response and 5 of the 11 (45%) patients with partial response, complete response, or recurrence demonstrated HACAs.

This trial remains one of the few prospective trials to systematically evaluate rituximab in APS. Although limited due to the small sample size, the trial offers a few key insights. First, the study demonstrated the safety of rituximab in APS. However, the response of aPL levels to rituximab was disappointing, with no substantial change in aPL profiles during 12 months of follow up; this suggests minimal or no effect on long-lived plasma cells or memory B cells. As the authors hypothesize, B cell effector function independent of antibody production may explain the interesting observation of some patients experiencing a clinical response in non-criteria manifestations without a substantial change in aPL profile. On the other hand, APS patients may display a heterogeneous antibody profile, and improvement in thrombocytopenia in this cohort may reflect reduction in levels of antibodies to "non-aPL" targets such as platelet glycoproteins; these responses are consistent with the 60% response rate to rituximab observed in immune thrombocytopenia (ITP). The most interesting responses were seen in skin ulceration where all patients had resolution of their lesions, and importantly, cognitive function where improvements were observed in aspects of attention, visuomotor speed, and flexibility.

Conclusions

Traditional management of APS remains anticoagulation. However, better and more durable treatment of this disorder will require a better understanding of the underlying immune dysregulation, the role of complement, and many other facets of the disorder that remain incompletely understood. The emerging treatment landscape in APS is in its infancy and the heterogeneity of both the patient population and the serologic characteristics of APS create challenges for the prospective study of novel treatment strategies. Further large-scale collaborative trials are needed to translate insights from preclinical and early clinical research into standard of care practice.

Funding

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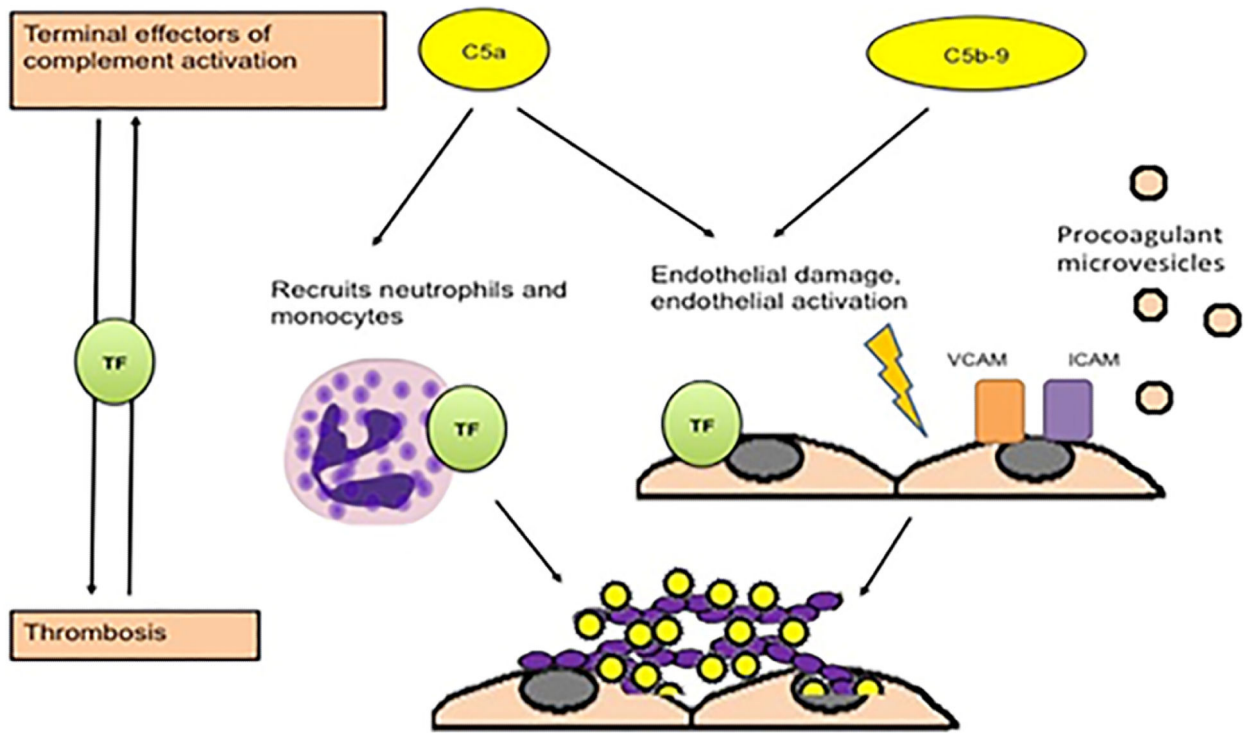
Fig. 1.
Potential mechanisms of thrombosis induced by aPL induced by complement, from
Chaturvedi, Brodsky and McCrae[26].
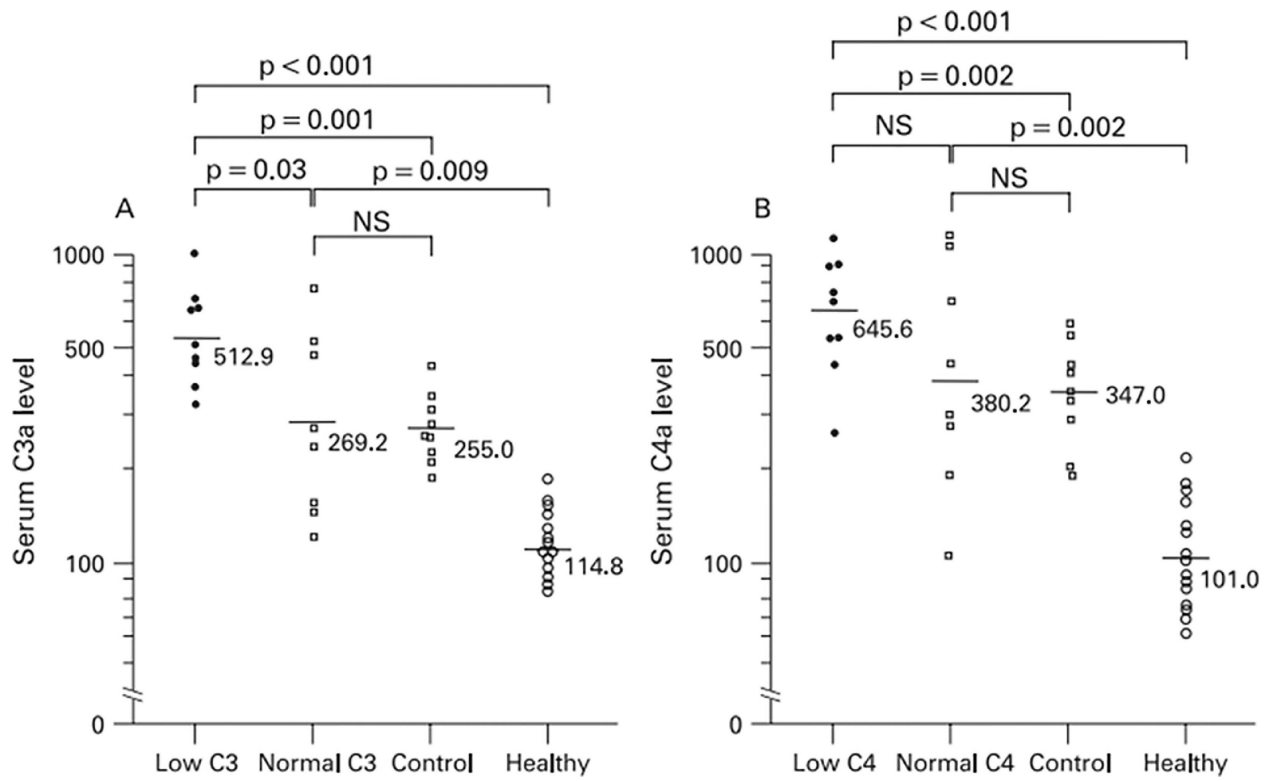
Fig. 2.
Serum C3a and C4a levels in 17 patients with primary APS, 9 patients with non-systemic SLE connective tissue diseases and 15 healthy volunteers, as reported by Oku et al.[36] Low C3/C4 and normal C3/C4 refers to the levels of C3 of C4 in the plasmas being assessed, since some patients with APS were found to have hypocomplementemia.
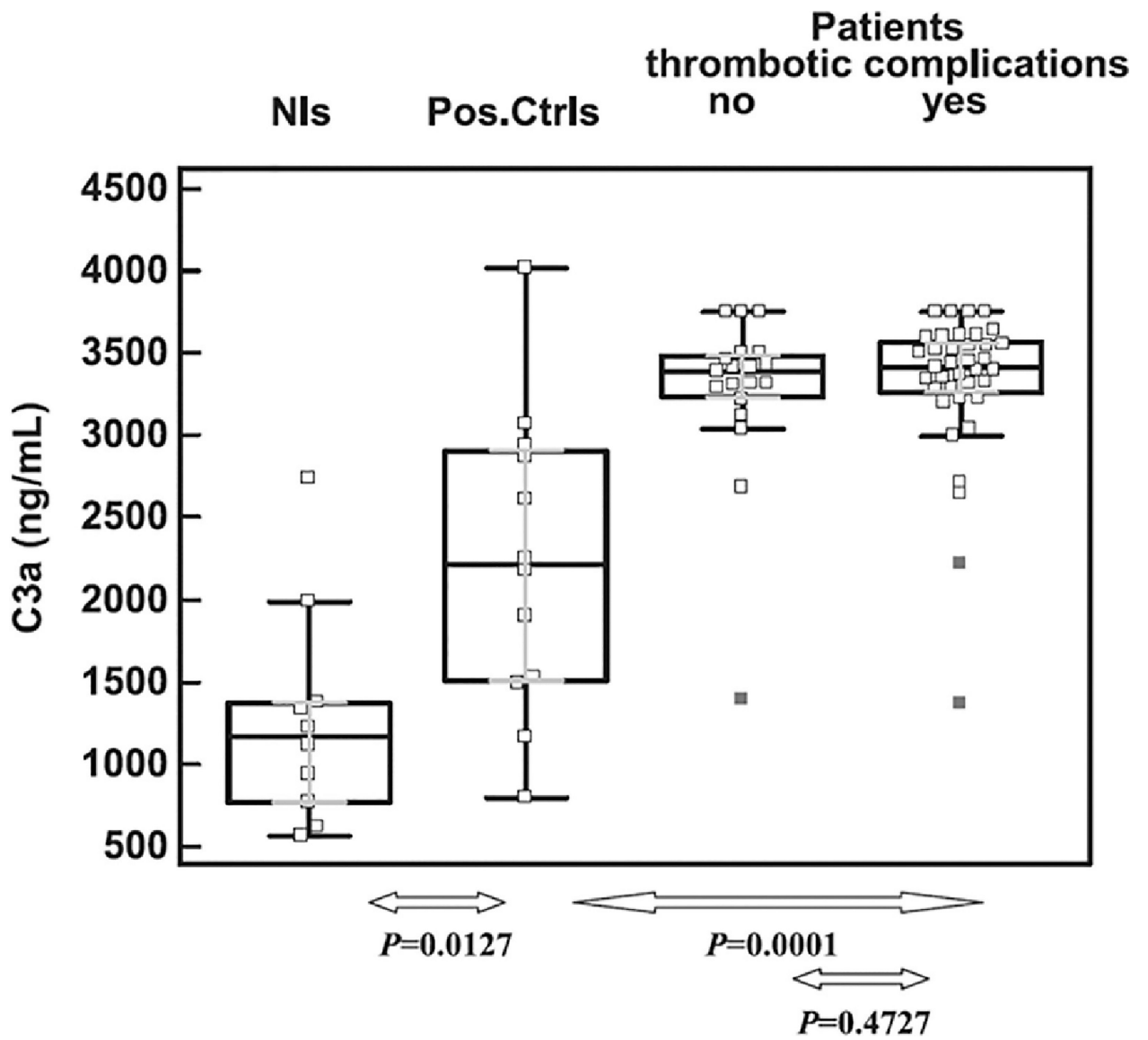
Fig. 3.
Relation between complement activation and aPL-associated thrombosis, from Devreese and Hoylaerts[37].
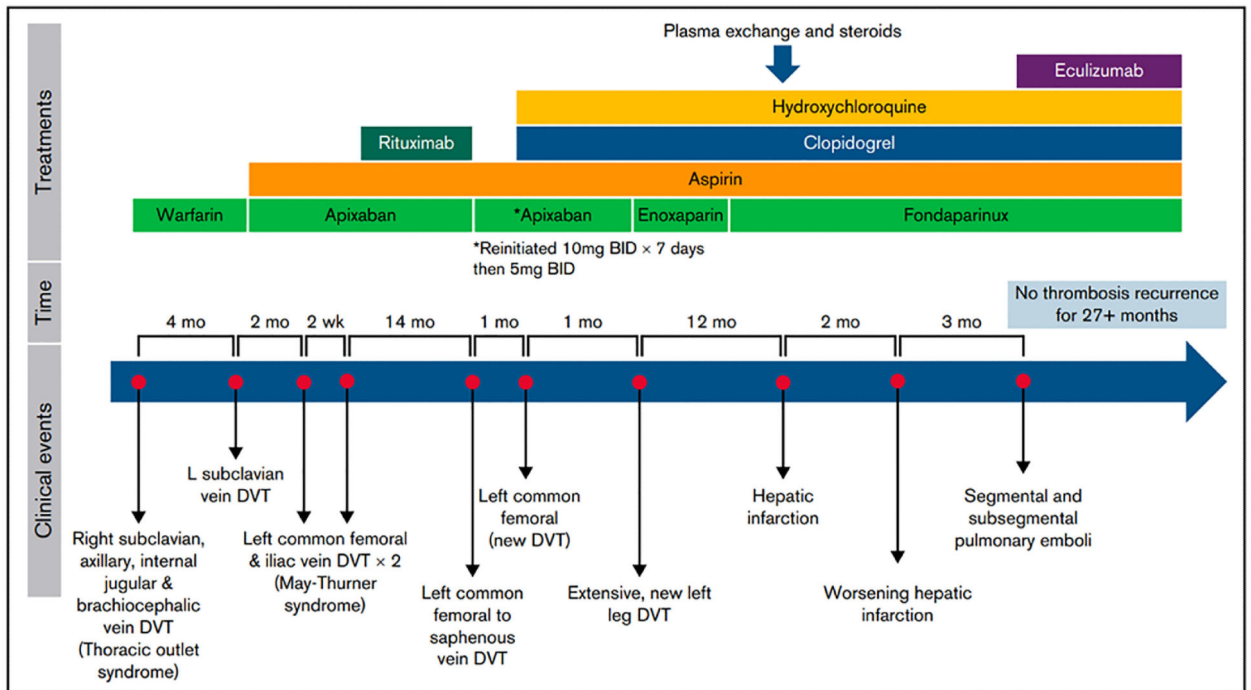
Fig. 4.
Clinical course and timeline of a case of refractory APS that ultimately responded to eculizumab, as reported by Hussain et al.[47]

Table 1

Summary of reports of eculizumab in patients with antiphospholipid syndrome.

	Patient	Prior therapies	Eculizumab dose/duration	Outcome
Shapira [55]	28 M with SLE, APS with PE, arterial thrombosis leading to leg amputation, and recurrent CAPS	Heparin, argatroban, fondaparinux, cyclophosphamide (CYC), steroids, IVIG, lepirudin, bivalirudin, aspirin, clopidogrel, plasma exchange (PEX)	Eculizumab 900 mg once, then 1200 mg biweekly for 1 y	Normalization of cytopenias and resolution of thrombotic events
Strakhan [43]	36 F with HTN, acute renal failure, stroke, acute coronary syndrome, and MAHA	PEX, steroids	Eculizumab 900mg weekly for 4 wk then 1200 mg biweekly	Gradual improvement of MAHA, continued dialysis
Appenzeller [56]	30 F with ITP and primary APS who developed CAPS after pregnancy	Hydroxychloroquine (HCQ), heparin, steroids, rituximab, PEX, immunoadsorption, dialysis	Eculizumab for 3 mo, mycophenylate, steroids	Resolution of thrombocytopenia and MAHA, with late partial relapse, dialysis dependent
Lonze [57]	2 patients with prior CAPS, undergoing renal transplant	Prednisone, rituximab, anticoagulation	Eculizumab, 900mg the day after transplant, then 1200 mg biweekly	Both with functioning allografts and no recurrence of thrombotic events, follow up 4 mo –4 y
Zikos [58]	47 M with primary APS, then CAPS with thrombocytopenia, multifocal thrombi including renal and hepatic infarcts	Heparin, PEX, IVIG, steroids, argatroban, heparin	Eculizumab 900mg weekly for 2 wk, then 1,200 mg q 7–10 d	Gradual improvement in cytopenias, ascites, and splenomegaly, no further thrombotic events for 16 mo of follow up, continued dialysis
Gustavsen [59]	22 F with arterial thrombosis and ischemic ulcerations during pregnancy	Warfarin, LMWH, aspirin	Eculizumab 600mg weekly for 2 wk in anticipation of Cesarean section	No further thrombosis, improvement in ischemic pain, no adverse fetal effects
Hussain [47]	18 F with triple positive APS with recurrent thrombosis, hepativ infarction, PE	enoxaparin, fondaparinux, apixaban, rivaroxaban, warfarin, aspirin and clopidogrel, HCQ, steroids, rituximab, PEX	Eculizumab 600mg weekly x4, then 900mg biweekly plus fondaparinux, aspirin, clopidogrel, hydroxychloroquine	No recurrence of thrombosis with 27 mo of follow up
Tinti [41]	54 F with primary APS with intestinal infarction, then CAPS with ischemic limb, acute bilateral effusions, acute decompensated heart failure, acute kidney injury	HCQ, steroids, warfarin, steroids, IVIG, PEX	Eculizumab 600mg weekly for 1 mo with steroids, warfarin, hydroxychloroquine	Rapid improvement in respiratory involvement, progressive improvement in thrombocytopenia, anemia, and serum creatinine, and normalization of C3 and C4 serum levels. No recurrence of thrombosis for 1 y
Chitalia [60]	Three cases of CAPS	All received steroids and anticoagulation, one additionally treated with rituximab, and one with PEX	Eculizumab dosing and regimen details not available	One with initial improvement in skin mottling and no further thrombosis but died during initial hospitalization (after 4 doses of eculizumab) due to septic shock; 1 discharged with maintenance eculizumab, length of follow up not available; 1 with resolution of CAPS and continues on maintenance eculizumab, length of follow up N/A
Guillot [42]	78 F with history of PE presents with CAPS with renal injury, hypertension and cerebral vascular lesions	Steroids, anticoagulation, PEX	Eculizumab 900mg weekly x 4, then 1200mg biweekly for 2 mo with steroids, anticoagulation and HCQ	No recurrence of CAPS in 12 mo of follow up
Chidharla [61]	64 F with triple positive APS develops acute encephalopathy and COVID associated CAPS with acute venous thrombosis, new ischemic stroke, adrenal hemorrhage	Dexamethasone, remdesivir, PEX, rituximab, IVIG	Eculizumab 900mg weekly x2	No recurrent thrombotic events at 1 mo follow up

	Patient	Prior therapies	Eculizumab dose/duration	Outcome
Skoczynska [62]	35 F with SLE and CAPS with severe TMA and respiratory, circulatory and renal failure	PEX, steroids, anticoagulation, dialysis	Eculizumab 900mg weekly for 1 mo, then 1200mg biweekly for 8 mo	Improvement in neurological and circulatory function, ongoing dialysis dependence, remission of CAPS at 9 mo follow up
Ruffatti [63]	32 F with pregnancy-associated CAPS with renal failure, respiratory and circulatory failure, ischemic digits	Anticoagulation, steroids, PEX, IVIG	1200mg weekly x3 then 900mg weekly x 6	Rapid remission of CAPS symptoms
Nauseef [64]	54 M with APS and Factor II G20210A carrier, and steroid-refractory ITP, develops CAPS with bilateral adrenal hemorrhage, acute thrombocytopenia, IVC thrombus and PE, and ear cartilage thrombosis	Steroids, IVIG, rituximab, oseltamivir, romiplostim, anticoagulation, HCQ	Eculizumab 900mg weekly x 4, then 1200mg biweekly x 6 mo	Found to have heterozygous deletion in CFHR3-CFHR1, no recurrence of thrombosis 1 y after cessation of eculizumab
Kello [65]	Case series of 9 patients with SLE and/or APS: 6 APS and 7 SLE, 4 SLE and APS	All APS patients received steroids and anticoagulation, 5 additionally received PEX, 2 cyclophosphamide, 1 mycophenolate mofetil, and 1 rituximab	Eculizumab duration ranged 3–60 mo	No recurrences of TMA, variable disease-free follow up after discontinuation from 1–30 mo, 100% survival at 3 mo, 2 subsequent deaths related to disconituation of dialysis
Rovere-Querini [66]	33 F with FVL, primary triple positive APS, prior PE and 2 miscarriages develops CAPS with acute hemorrage at 30 + 6 wk gestation with hemolytic anemia, thrombocytopenia, acute kidney injury	Warfarin replaced by LMWH during pregnancy, aspirin, HCQ, rituximab	Eculizumab 600mg hospitalization day 7 and 14, cesarean section day 9 due to thrombocytopenia.	Mild transient thrombocytopenia and transient inhibition of CH50 with low C3 in the newborn, with no adverse effects and spontaneous normalization
Kronbichler [67]	30 F with IgA deficiency, ITP, splenectomy, APS, SLE with pregnancy-associated CAPS with cerebral, myocardial, renal and pulmonary involvement	Steroids, rituximab, PEX (severe intolerance), immunoadsorption, dialysis	Eculizumab 900mg weekly x4, then 1200mg biweekly for 3 mo	Resolution of TMA, lupus flare while on eculizumab
Wig [68]	43 F with primary APS with thrombotic and pregnancy morbidity, with subsequent CAPS with HTN, intracranial hemorrhage, and recurrent thrombosis despite closely monitored anticoagulation	steroids, CYC, PEX, rituximab, IVIG, anticoagulation	Eculizumab 900mg once then 1200mg weekly x 6 until resolution of thrombocytopenia, then tapered 1200mg every other week, 900mg every other week, 900mg monthly	Improvement in thrombocytopenia, recovered of renal function and cessation of dialysis, reduction in steroids, functional improvement following strokes and living independently