Catastrophic Antiphospholipid Syndrome: Candidate Therapies for a Potentially Lethal Disease

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Annu. Rev. Med. 2017. 68:287–96

The *Annual Review of Medicine* is online at med.annualreviews.org

This article's doi: 10.1146/annurev-med-042915-102529

Keywords

antiphospholipid syndrome, CAPS, hydroxychloroquine, rituximab, eculizumab, sirolimus, defibrotide

Abstract

Catastrophic antiphospholipid syndrome (CAPS) is a potentially lethal disease that presents with rapidly progressive multiple organ thromboses. Anticoagulation, corticosteroids, intravenous immunoglobulin, and plasma exchange are the most commonly used treatments for CAPS patients. However, the high mortality despite these medications necessitates new treatment strategies. Following a brief review of current diagnostic and management strategies, we discuss the candidate therapies, i.e., hydroxychloroquine, rituximab, eculizumab, sirolimus, and defibrotide, that can be considered in CAPS patients refractory to traditional treatment.

INTRODUCTION

Antiphospholipid syndrome (APS) is characterized by thromboses and/or pregnancy morbidity associated with persistently positive antiphospholipid antibodies (aPL) [lupus anticoagulant (LA) test, anticardiolipin antibodies (aCL), and/or antiβ_2-glycoprotein-I antibodies (aβ_2GPI)] (1) (**Table 1**). APS classification is based on at least one of the clinical criteria and one of the laboratory criteria listed in **Table 1**. Thrombocytopenia, hemolytic anemia, nephropathy, cardiac valve disease, cognitive dysfunction, and skin ulcers, collectively known as "noncriteria" manifestations, can also occur in aPL-positive patients (2). A small percentage of APS patients develop life-threatening multiple organ thromboses, known as catastrophic APS (CAPS) (3, 4).

CAPS patients usually present with rapidly progressive thromboses resulting in multiple organ dysfunction syndrome, systemic inflammatory response syndrome, and thrombotic microangiopathy. "Definite" and "probable" CAPS are defined on the basis of the preliminary classification criteria listed in **Table 2** (5); however, some aPL-positive patients with multiple organ thromboses and/or thrombotic microangiopathies do not fulfill these criteria.

The purpose of this article is to review candidate therapies that can be considered in refractory CAPS patients. We offer only a brief overview of diagnostic challenges and current management strategies for CAPS patients because detailed information on these topics can be found elsewhere (6–9).

DIAGNOSTIC CHALLENGES

When a patient with multiple thromboses tests aPL positive for the first time, especially if non-aPL thrombosis risk factors exist, such as malignancy, surgery, or sepsis, the diagnosis of CAPS can be challenging. Thrombosis is usually multifactorial, and not every "positive" aPL test is clinically significant, e.g., single low-titer aCL and/or aβ_2GPI. In addition, CAPS is one of the conditions listed under "thrombotic storm" (10) (see sidebar Thrombotic Storm), which is a clinical umbrella term for extreme hypercoagulable conditions. Thus, the diagnosis of CAPS requires continuous

Table 1 Revised Sapporo classification criteria for antiphospholipid syndrome (1)

Clinical criteria	Laboratory criteria
1. Vascular thrombosis One or more clinical episodes of arterial, venous, or small-vessel thrombosis in any tissue or organ	1. Lupus anticoagulant present in plasma on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Hemostasis
2. Pregnancy morbidity (a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, *or* (b) One or more premature births of a morphologically normal neonate before the 34th week of gestation because of eclampsia, severe preeclampsia, or recognized features of placental insufficiency, *or* (c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded	2. Anticardiolipin antibody of immunoglobulin (Ig)G or IgM isotype in serum or plasma, present in medium or high titer (>40 GPL or MPL, or >99th percentile), on two or more occasions at least 12 weeks apart, measured by a standardized ELISA 3. Anti–β_2-glycoprotein I antibody of IgG or IgM isotype in serum or plasma (in titer >99th percentile) present on two or more occasions at least 12 weeks apart, measured by a standardized ELISA

Table 2 Preliminary classification criteria for catastrophic antiphospholipid syndrome (5)

Definite catastrophic antiphospholipid syndrome: all four criteria present	Probable catastrophic antiphospholipid syndrome
1. Evidence of involvement of three or more organs, systems, and/or tissues	1. Only two organs, systems, and/or tissues involved; criteria 2, 3, and 4 present
2. Development of manifestations simultaneously or in less than a week	2. Manifestation of a third event develops more than one week (but within one month) after presentation, despite anticoagulation; criteria 1, 3, and 4 present
3. Confirmation by histopathology of small-vessel occlusion[a]	3. No histopathological confirmation of small-vessel occlusion; criteria 1, 2, and 4 present
4. Laboratory confirmation of aPL[b]	4. No laboratory confirmation of aPL; criteria 1, 2, and 3 present

Abbreviation: aPL, antiphospholipid antibodies.
[a]Vasculitis may coexist, but significant thrombosis must be present as well.
[b]Finding of "positive aPL" twice 12 weeks apart. Note: The original Sapporo APS classification criteria required two positive aPL tests 6 weeks apart (62). The updated Sapporo APS classification criteria (1) changed this interval to 12 weeks.

assessment in patients with multiple organ thrombosis, as the disease can overlap with other conditions.

Diagnostic algorithms for CAPS provide a step-by-step approach in the assessment of patients with multiple organ thromboses (8):

1. Previous APS diagnosis and/or persistent, clinically significant aPL positivity is helpful for the CAPS diagnosis. However, half of CAPS patients do not have a history of APS or aPL positivity.
2. Three or more organ thromboses developing in less than a week is one of the requirements for definite CAPS classification. However, new thrombosis in only two organs (or even one

THROMBOTIC STORM

"Thrombotic storm" (10) is a clinical umbrella term for extreme hypercoagulable conditions such as atypical thrombotic thrombocytopenic purpura, cancer-associated thrombosis, heparin-induced thrombocytopenia, and catastrophic antiphospholipid syndrome. Clinical characteristics of a thrombotic storm include the following:

- Patient's age is typically <55 years
- Acute, ≥2 arterial and/or venous thromboemboli are present, with or without thrombotic microangiopathy (defined as microvascular thrombosis identified on tissue pathology)
- Individual thrombotic events occur typically in a compressed period of time (days to weeks) and may recur from time to time over years
- Thrombotic events frequently involve unusual sites, e.g., intra-abdominal and cerebral venous sinuses
- Progressive/early unexplained recurrence
- Refractory to acute therapy or atypical response to therapy
- Exacerbation of thromboembolic complications associated with subtherapeutic anticoagulation
- Frequently preceded by an initiating event or "trigger," e.g., pregnancy, surgery, trauma, infection and/or inflammatory state

organ with hematologic and/or microthrombotic manifestations) should also alert physicians to developing CAPS.

3. Microthrombosis is another requirement for definite CAPS classification. However, when a biopsy cannot be obtained for medical reasons, reassessment of the diagnosis should be considered when biopsy or new information becomes available.

CURRENT MANAGEMENT STRATEGIES

CAPS is a rare but challenging systemic disease. In addition to multiple organ thromboses, noncriteria manifestations of aPL can commonly occur. Bleeding and infections frequently complicate the disease course, requiring multiple deviations in the treatment plan and difficult decisions at times, e.g., continuation of anticoagulation despite bleeding. Thus, both diagnosis and management require a multidisciplinary team, including but not limited to specialists in rheumatology, hematology, intensive care, infectious disease, nephrology (and plasma exchange), and obstetrics when relevant. The team should meet at least once a day as the clinical course can change quickly in these patients.

Early treatment is vital for survival, in addition to elimination of precipitating factors, antibiotics for infections, and debridement of necrotic tissues. Anticoagulation, corticosteroids, intravenous immunoglobulin (IVIG), and plasma exchange are the most commonly used strategies for CAPS patients (11). In addition to the anticoagulation effect, heparin inhibits complement activation in mouse models (12); corticosteroids inhibit nuclear factor-κB, which is an important mediator in both systemic inflammatory response syndrome and aPL-mediated thrombosis; IVIG blocks pathological autoantibodies, increases clearance of pathological IgG, modulates complement, and suppresses pathogenic cytokines; and plasma exchange removes aPL (most likely transiently), as well as cytokines, tumor necrosis factor-α, and complement products (13). In patients with accompanying lupus or other vasculitis flare, cyclophosphamide can be added to the regimen (14, 15). In patients with low risk of bleeding, some physicians also add aspirin. The long-term management of CAPS patients who survive an acute event relies on warfarin; the role of direct oral anticoagulants is currently being investigated (16).

The CAPS Registry (**https://ontocrf.grupocostaisa.com/es/web/caps/home**) is a web-based data collection system created by the European Forum on Antiphospholipid Antibodies on the basis of the published CAPS cases and/or physician reports to the coordinating center (Hospital Clinic, Barcelona, Catalonia, Spain). Based on a descriptive analysis of the registry, the highest recovery rate is achieved by anticoagulation plus corticosteroids plus plasma exchange and/or IVIG (11). Even with this approach, the mortality rate remains high (30–50%) (17). Furthermore, anticoagulation, which is currently the mainstay of CAPS treatment, is commonly interrupted because of concomitant bleeding. Thus, additional new therapies are desperately needed for CAPS patients.

CANDIDATE THERAPIES FOR REFRACTORY PATIENTS

Definition of Refractory CAPS

CAPS is usually accompanied by comorbidities, which either trigger a CAPS event or develop during it, and which increase the risk of thrombosis and affect the prognosis. Thus, risk stratification and the optimal management of comorbidities such as septic shock are critical before considering candidate therapies for CAPS patients. In addition, a major bleeding event requiring the cessation of anticoagulation can have a major impact on prognosis; physicians should have a

lower threshold to use additional medications, including candidate therapies, for patients who are not anticoagulated.

Is There a Role for Immunosuppression in CAPS?

Antiphospholipid antibodies induce thrombosis through multiple immune mechanisms, so immunosuppression has been increasingly investigated in APS. β_2-glycoprotein-I (β_2GPI), which is the major target antigen in APS, exists in a circular form, then binds to phosphatidylserine (a negatively charged phospholipid) via β_2GPI surface receptors. After this binding, the circular β_2GPI opens up to expose Domain I, and aPL bind to β_2GPI, directly stimulating cells through surface receptors. The aPL can also stimulate cells indirectly by activating the classic complement pathway; the generation of C5a induces expression of adhesion molecules and tissue factor, activation of monocytes, polymorphonuclear cells, and platelets, and triggers the release of proinflammatory mediators as well as initiation of the proadhesive and prothrombotic state (18). Potential CAPS treatments based on these newly understood mechanisms are discussed below.

Hydroxychloroquine

Hydroxychloroquine (HCQ) is an antimalarial agent with anti-inflammatory properties, which is approved by the US Food and Drug Administration (FDA) for lupus but not for APS.

In aPL-injected mice (19), HCQ reduces the extent and the time of thrombus formation as well as the platelet activation. HCQ also reduces the attachment of aPL–β_2GPI complexes to phospholipid bilayers (20), reverses the binding of aPL to human placental syncytiotrophoblasts, restores annexin A5 expression (21, 22), and inhibits Toll-like receptors (23).

Historically, HCQ 600–1,200 mg daily prevented thrombosis after hip replacement (24). In lupus patients, HCQ protects against thrombosis via its effect on lupus activity and/or traditional cardiovascular disease risk factors (25). Although a limited number of small studies suggest that HCQ can be protective against thrombosis in aPL-positive patients without lupus, there are no randomized controlled trial results to support this finding (26, 27), and there are no data in CAPS patients.

In summary, despite the lack of strong clinical data in aPL-positive patients without lupus, HCQ is safe and reduces the risk of thrombosis in experimental models and lupus patients. Thus, although the short-term effects of HCQ during a CAPS event are unknown, it should be considered as an adjunctive treatment in refractory CAPS cases.

Rituximab

Rituximab is an anti-CD20 chimeric monoclonal antibody, which is currently FDA approved for rheumatoid arthritis, granulomatosis with polyangiitis (Wegener's granulomatosis), and microscopic polyangiitis (28).

In vitro experience indicates that B cells are involved in aPL-related clinical events (29, 30). Blocking B cell activating factor prevents disease onset and prolongs survival in APS murine models (31), and cytotoxic T lymphocyte antigen 4 immunoglobulin prevents initiation but not development of APS in the NZW × BXSB F1 APS mouse model (32). There are no mechanistic studies in rituximab-treated CAPS patients.

Several case reports (33–38) described rituximab use in APS patients with severe thrombocytopenia (39–42), hemolytic anemia (33), skin ulcers or necrosis (37, 43), aPL nephropathy (44), and CAPS (45, 46), with variable responses. An uncontrolled pilot study of 19 patients (with thrombocytopenia, aPL nephropathy, cardiac valve disease, skin ulcers, and cognitive dysfunction)

suggested that despite causing no substantial change in aPL profiles, rituximab may be effective in controlling some of the noncriteria manifestations of APS (47). There were no CAPS patients included in this study.

Lately, based on the analysis of the CAPS Registry (46), rituximab-treated acute CAPS patients (n = 20) had a 75% chance of recovery. Given the publication/selection bias associated with the CAPS Registry, along with the fact that the majority of patients received some combination of anticoagulants, corticosteroids, plasma exchange, and/or IVIG before or while receiving rituximab, it is difficult to evaluate the isolated antithrombotic effect of rituximab in CAPS patients.

In summary, despite the limited basic science and clinical experience, B cell inhibition may have a role in CAPS patients, especially in those with prominent hematologic and microthrombotic/microangiopathic manifestations.

Eculizumab

Eculizumab, a humanized monoclonal antibody against complement protein C5, is currently FDA approved for the treatment of paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome (48). Eculizumab reduces intravascular hemolysis and blocks complement-mediated pathogenesis, leading to a benefit in patients with microangiopathies.

Complement activation initiates and amplifies APS by endothelial cell activation, monocyte tissue factor expression, and platelet aggregation. Generation of C5a contributes to vascular inflammation (49, 50); C5a interacts with its receptor to promote recruitment and activation of neutrophils and monocytes, as well as activation of endothelial cells (51). Mice deficient in C3, C5, C6, or C5a receptor are resistant to aPL-induced endothelial cell activation (52). In addition, aPL-positive patients, with or without clinical manifestations of APS, show elevated circulating levels of Bb and C3a fragments (53). APS patients have elevated C3a levels in plasma without any correlation with thrombosis (54).

A recent review summarized six acute CAPS cases treated with eculizumab (four patients survived; two died), concluding that complement inhibition may have a role as an adjuvant or main therapy for APS patients refractory to anticoagulation. However, publication bias is a concern, as well as the lack of systematic clinical studies (18). In addition, Zikos et al. (55) reported a CAPS patient who showed progressive clinical and laboratory improvement upon initiation of eculizumab following a limited response to plasmapheresis, IVIG, high-dose corticosteroids, anticoagulation (argatroban and heparin followed by warfarin), and rituximab. The patient remained in remission for 16 months while on eculizumab.

An open-label interventional phase II prevention trial (NCT01029587) is investigating whether blocking the complement cascade with eculizumab in patients with a prior history of CAPS who are undergoing kidney transplant will lead to increased transplant success. Another open-label multicenter international phase IIa treatment trial (NCT02128269) is evaluating the safety and tolerability of an intravenous C5a inhibitor in persistently aPL-positive patients with at least one of the following noncriteria manifestations of APS: aPL nephropathy, skin ulcers, and thrombocytopenia.

In summary, eculizimab may have a role in refractory CAPS patients, especially in those with prominent features of thrombotic microangiopathy; however, more clinical data are needed before this medication can be recommended. The high cost of the medication limits its use.

Sirolimus

Sirolimus is FDA approved for the treatment of lymphangioleiomyomatosis and the prophylaxis of organ rejection in renal transplantation patients aged 13 years and older.

Sirolimus is the generic name for rapamycin, which is produced by fermentation of *Streptomyces hygroscopicus* (56). It modulates the activity of the mammalian target of rapamycin (mTOR) by binding FK binding protein, which results in inhibition of interleukin-2-mediated signal transduction, causing a cell cycle arrest in the G1-S phase and blocking the response of T and B cell activation by cytokines (56).

A recent study suggested that mTOR pathway blockade inhibits endothelial proliferation and thereby prevents aPL-related vasculopathy, which is characterized by vascular cellular infiltrates and fibrosis of the intima and media. In a small cohort of aPL-positive renal transplant recipients, patients treated with sirolumus (given to prevent graft rejection) developed significantly less vascular proliferation, as shown on posttransplant biopsies, and had no vascular lesions. Moreover, the rate of functioning allograft was significantly higher in this group (51). Also, in a substudy, the post mortem assessment of CAPS patients showed marked neointimal formation associated with severe constriction of the vessel lumens in both the carotid and left anterior descending arteries. Few of the neointimal cells that displayed the typical morphologic features of infiltrating inflammatory cells were also positive for the markers of mTOR pathway activation.

In summary, mTOR pathway blockade can be a promising target in CAPS, as it is in APS. However, further studies are needed to better clarify the potential beneficial effects of this immunosuppressive agent for the treatment of aPL nephropathy, arterial vasculopathy, and CAPS.

Defibrotide

Defibrotide was recently approved by the FDA for the treatment of adult and pediatric patients with hepatic veno-occlusive disease, also known as sinusoidal obstruction syndrome, with renal or pulmonary dysfunction following hematopoietic stem cell transplantation. Veno-occlusive disease has a complex pathogenesis that has not been fully elucidated. However, the disease starts with an injury to the hepatic venous endothelium (57), and defibrotide provides a beneficial effect by modulating vascular endothelial cells.

Defibrotide is an adenosine receptor agonist, which inhibits thrombin-induced platelet aggregation and thromboxane biosynthesis (58). It has antithrombotic, anti-ischemic, anti-inflammatory, and thrombolytic properties; however, it lacks significant systemic anticoagulant effects with no increased risk of bleeding (59). Defibrotide modulates tissue necrosis factor, endothelin, thrombin, and interleukin-2, as well as tissue factor secretion from monocytes (60).

Only one case report exists describing a CAPS patient who achieved a complete remission with defibrotide after a limited response to heparin, aspirin, and dipyridamole (61). Given that CAPS is a thrombotic disease with concurrent impairment of vascular endothelial cell functions (58), defibrotide can be a potential treatment for refractory CAPS patients by modulating these functions as well as inhibiting platelet aggregation and thromboxane production. With its recent FDA approval for veno-occlusive disease, further mechanistic and controlled studies are needed to evaluate defibrotide in treating CAPS.

CONCLUSION

In CAPS, the most severe form of APS, multiple organ thromboses occur and are usually accompanied by microthrombosis and hematologic manifestations. The clinical manifestations of CAPS may evolve gradually, commonly overlapping with other thrombotic microangiopathies, so diagnosis requires a high index of clinical suspicion. It is critical to initiate treatment urgently if the diagnosis of CAPS is clinically suspected, even without the confirmatory aPL tests. Anticoagulation, corticosteroids, IVIG, and plasma exchange are the most commonly used treatments for

CAPS patients. In parallel to our increased understanding of the aPL-mediated mechanisms, we believe that an immunosuppressive approach comprising what are now candidate therapies will eventually play a major role in the management of CAPS patients. Given that CAPS is relatively rare, only an international multicenter collaboration will help us identify the role of these agents.

DISCLOSURE STATEMENT

D.E. has received a research grant from Alexion Pharmaceutical and served on its advisory board.

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