blood®
Letter to *Blood*

TO THE EDITOR:

Patients with refractory catastrophic antiphospholipid syndrome respond inconsistently to eculizumab

Cécile M. Yelnik,[1,2] Sébastien Miranda,[3] Arsène Mékinian,[4] Estibaliz Lazaro,[5] Thomas Quéméneur,[6] François Provot,[7] Marie Frimat,[1,7] Sandrine Morell-Dubois,[2] Véronique Le Guern,[8] Eric Hachulla,[2] Nathalie Costedoat-Chalumeau,[8] and Marc Lambert[1,2]

[1]INSERM U1167, Lille, France; [2]Centre National de Référence Maladies Systémiques et Auto-Immunes Rares, Département de Médecine Interne et d'Immunologie Clinique, European Reference Network on Rare Connective Tissue and Musculoskeletal Diseases (ReCONNECT), Centre Hospitalier Université (CHU) Lille, Lille, France; [3]Département de Médecine Interne et de Médecine Vasculaire and Thrombosis Unit, INSERM U1096, Université Normandie de Rouen, Rouen, France; [4]Service de Médecine Interne, Assistance Publique-Hospitaux de Paris (AP-HP) Hôpital Saint-Antoine, Sorbonne Université, Paris, France; [5]Service de Médecine Interne, Centre de Référence des Maladies Auto-immunes Systémiques Rares de l'Est et du Sud-Ouest, Hôpital du Haut-Lévêque, Pessac, France; [6]Service de Néphrologie, Médecine Interne et Vasculaire, CH Valenciennes, Valenciennes, France; [7]Service de Néphrologie, CHU Lille, Lille, France; and [8]Service de Médecine Interne, Centre de Référence des Maladies Systémiques et Auto-Immunes Rares, INSERM U1153, AP-HP Hôpital Cochin, Université Paris Descartes-Sorbonne Paris Cité, Paris, France

Complement has been identified as a critical pathway for the development of obstetrical manifestations of the antiphospholipid syndrome (APS) and its life-threatening variant, catastrophic APS (CAPS).[1-4] We read with great interest the recently published study by Chaturvedi and colleagues that added important new insights into the understanding of complement involvement in CAPS.[4] Researchers have reported a genetic susceptibility in CAPS patients, with mutations in complement-regulating proteins that may explain the uncontrolled complement activation that triggers thrombotic storms. To date, long-term anticoagulation is the sole nonspecific treatment that has demonstrated efficacy in APS. Additional therapies, such as plasma exchange (PE), intravenous immunoglobulin, and corticosteroids are proposed to treat CAPS.[5,6] Despite this standard treatment, CAPS is still associated with significant mortality (up to 30% in the last update of the international CAPS registry).[6] Eculizumab, a monoclonal antibody against the terminal complement component C5, has been proposed as a rescue therapy in refractory CAPS. To date, data are restricted to 11 isolated case reports that indicated a dramatic improvement of CAPS after eculizumab.[7-17] With the growing evidence of complement involvement in CAPS and the recent publication of 2 systematic reviews on the efficacy of eculizumab, we can expect a larger off-label use of eculizumab without proper evaluation in this indication.[16,17] Given the potential side effects of the treatment, its cost, and restricted availability, there is a need to better evaluate the effectiveness of eculizumab in CAPS.

This retrospective cohort study, we enrolled all consecutive patients with CAPS who had been treated from 2012 through 2019 with eculizumab, in 5 French reference centers on rare autoimmune diseases (Bordeaux, Lille, Paris, Rouen, and Valenciennes). APS and CAPS were diagnosed according to international classification criteria.[5,18] Lupus anticoagulant, anticardiolipin antibody, and anti-β2-glycoprotein-1 antibody assays were performed according to the international guidelines for APS laboratory criteria. Responders to eculizumab were defined as survivors, with significant clinical improvement of CAPS-related organ failures after administration of eculizumab. A standardized case report form was used to collect data into a computer database. Data were anonymized and complied according to the requirements of the Commission Nationale Informatique et Liberté. The methods used to collect and analyze data were approved by the ethics committee (1889582 v 0), and research was conducted in accordance with the Declaration of Helsinki.

A total of 11 patients were included with a median age of 48 years. Demographic and clinical characteristics of the patients are described in Table 1. All patients were triple positive for antiphospholipids (aPLs) at APS diagnosis and at CAPS onset, as previously reported by Ruffatti et al.[19] Because a biopsy was performed in only 2 cases, the diagnostic of CAPS was definite only in those 2 patients; the 9 remaining patients were classified as probable CAPS. CAPS was newly developed in 2 patients and occurred after a median APS duration of 12 years in others. A triggering risk factor was identified in 10 cases: suboptimal anticoagulation in 4 cases, infection in 4 cases, and surgery in 2 cases. All patients presented with severe CAPS (a median of 5 organs or systems involved simultaneously). Despite full-dose anticoagulation (n = 11), corticosteroids (n = 11), and PEs (n = 10), their conditions continued to worsen (Table 1). Four patients had deep vein thrombosis that did not required thrombolysis. The delay between the CAPS diagnosis and the administration of the first eculizumab dose ranged from 3 to 100 days (median, 25 days). After eculizumab administration, all but 1 patient had undetectable complement activity (data were missing for 4).

Overall, 5 patients had significant improvement in the few days after the first dose of eculizumab. Compared with nonresponders, responders had a less severe history of thrombotic APS and a higher frequency of associated systemic lupus erythematosus. The number of organ failures was similar in both groups, with a higher number of patients who required hemodialysis before eculizumab in nonresponders. Responders had a lower platelet count and, more frequently, microangiopathic hemolytic anemia (MAHA). Among the 4 responders with renal

Table 1. Demographic and clinical characteristics of the study population

	Total (n = 11)	Responders (n = 5)	Nonresponders (n = 6)
Age, median (IQR), y	48 (24)	46 (40)	53 (23)
Female, n	8	4	4
APS duration, median (IQR), y	12 (15)	13 (37)	11 (10)
Inaugural CAPS	2	2	0
History of venous thrombosis	6	2	5
History of arterial thrombosis	3	1	2
History of CAPS	2	0	2
History of obstetrical manifestation	2	0	2
Associated systemic lupus	4	3	1
aPL triple positivity at diagnosis	11	5	6
CAPS clinical features			
Cardiac failure	6	3	3
Cutaneous (livedo reticularis, necrosis)	8	5	3
Renal failure	10	4	6
Cerebrovascular involvement	4	3	1
Venous thrombosis	4	1	3
Peripheral artery thrombosis	2	1	1
Adrenal ischemic hemorrhage	3	2	1
Diffuse alveolar hemorrhage	3	1	2
Liver infarct	2	1	1
Gastrointestinal involvement	3	1	2
Thrombocytopenia	11	5	6
Median (IQR) platelet count before, × 10^9/L	19 (96)	14 (54)	79 (207)
Median (IQR) platelet count after, × 10^9/L	89 (165)	89 (113)	111 (212)
MAHA	6	4	2
Dialysis			
Before eculizumab	4	1	3
After eculizumab (short term)	5	1	4
Therapy before eculizumab			
Anticoagulant therapy	11	5	6
PE	10	4	6
PEs, median (IQR)	7 (13)	8 (11)	5 (14)
Corticosteroids	11	5	6
IVIG	4	3	1
Rituximab	3	3	0
Other immunosuppressive drug*	2	2	0

Unless otherwise stated, the data are the number of patients.

IVIG, intravenous immunoglobulin.

*Endoxan and vinblastine.

failure, renal function recovered in 3 who were not on hemodialysis before eculizumab; the last patient continued to have dialysis-dependent renal failure. The median platelet count increased from 14 × 10^9/L (IQR 54) to 89 × 10^9/L (IQR = 113; Table 1). Responders were prescribed an eculizumab regimen consistent with the regimen generally used in atypical hemolytic uremic syndrome, with a median of 4 weekly injections of eculizumab, and a median delay from CAPS onset to the first administration of 45 (IQR = 51) days (Table 2). Long-term remission was achieved in 4 patients, and 1 patient had a CAPS relapse 1 year later.

The 6 nonresponders continued to deteriorate clinically despite treatment with eculizumab. Four patients died of uncontrolled CAPS-related multiorgan failure (Table 2). Among the 2 survivors, 1 patient improved after a rescue therapy with rituximab and IVIG, and the other experienced a CAPS relapse after renal transplantation and slowly improved after removal of the transplant.

Table 2. Eculizumab regimen and clinical outcomes of the study population

Patients sex, age (y)	CAPS features	Eculizumab regimen	Complement activity (CH50)	Platelet count	CAPS outcome	Long-term outcome
F, 46	Renal failure with cortical necrosis; colic and splenic infarcts; thrombocytopenia; MAHA; livedo reticularis	Started at day 45; 1 infusion of 900 mg	Before: 40 U/mL (N); after administration: <13 U/mL (undetectable)	Before C1: 14 × 10^9/L; after C1: 89 × 10^9/L	Partial remission	No relapse; hemodialysis after CAPS; follow-up, 3 y
F, 42	Renal and cardiac failures (LVEF 45%); deep vein and peripheral artery thrombosis; skin necrosis; thrombocytopenia; MAHA	Started at day 52; 900 mg/wk for 4 wk followed by 1 infusion of 1200 mg 7 d later	Before: normal; after administration: undetectable	Before C1: 66 × 10^9/L; after C1: 231 × 10^9/L	Symptoms worsened	Hemodialysis after eculizumab; death 4 mo later
M, 48	Renal failure; diffuse alveolar hemorrhage; deep vein thrombosis; thrombocytopenia; livedo	Started at day 10; 1 infusion of 1200 mg	Before: 46 U/mL (N); after administration: <13 U/mL (undetectable)	Before C1: 2 × 10^9/L; after C1: 4 × 10^9/L	Symptoms worsened	Improvement after rescue therapy with IVIG and rituximab; relapse 1 mo later; hemodialysis; follow-up, 5 y
F, 54	Renal failure with cortical necrosis (hemodialysis); thrombocytopenia; MAHA	Started at day 3; 900 mg/wk for 4 wk	Data missing	Before C1: 92 × 10^9/L; after C1: 190 × 10^9/L	Symptoms worsened; renal graft removed; slow improvement	No relapse; hemodialysis; follow-up, 4 y
F, 78	Renal failure with TMA; Multiple brain infarcts; livedo reticularis; thrombocytopenia; MAHA	Started at day 61: 900 mg/wk for 4 wk followed by 1200 mg every 15 d for 2 mo	Before: 50 U/mL (N); after administration: data missing	Before C1: 11 × 10^9/L; after C1: 142 × 10^9/L	Remission	No relapse; follow-up, 1 y
F, 61	Renal failure (hemodialysis) and ischemic myocarditis (LVEF 55%); deep vein thrombosis; adrenal ischemic hemorrhage; liver and brain infarcts; livedo reticularis; thrombocytopenia	Started at day 100; 900 mg/wk for 4 wk followed by 1200 mg every 15 d for 2 mo	Before: 62 U/mL (N); after administration: <13 U/mL (undetectable)	Before C1: 7 × 10^9/L; after C1: 70 × 10^9/L	Remission	CAPS relapse 1 y later; follow-up, 1 y
F, 25	Diffuse alveolar hemorrhage; myocardial infarction (LVEF 52%); brain infarcts; livedo reticularis and skin necrosis; thrombocytopenia	Started at day 19' 1 infusion of 900 mg	Before: 68 U/mL (N); after administration: data missing	Before C1: 106 × 10^9/L; after C1: 197 × 10^9/L	Remission	No relapse; follow-up, 1 y
M, 33	Cardiac shock (LVEF 10%; ECMO); renal failure; intestinal ischemic ulcerations; adrenal ischemic hemorrhage; peripheral artery thrombosis; livedo reticularis and skin necrosis; thrombocytopenia; MAHA	Started at day 39 900 mg/wk for 4 wk	Before: 39 U/mL (N); after administration: <13 U/mL (undetectable)	Before C1: 19 × 10^9/L; after C1: 43 × 10^9/L	Remission	No relapse; LVEF 39%; follow-up, 5 y
M, 67	Renal (hemodialysis) and cardiac failures (LEVF 22%); deep vein thromboses; diffuse alveolar hemorrhage; thrombocytopenia; livedo reticularis	Started at day 25; 1 infusion of 1200 mg	Before: 60 U/mL (N); after administration: 33 U/mL (N)	Before C1: 219 × 10^9/L; after C1: 32 × 10^9/L	Symptoms worsened	Death 6 d later

C1, first eculizumab administration; ECMO, extracorporeal membrane oxygenation; LVEF, left ventricular ejection fraction; N, normal value; TMA, thrombotic microangiopathy.

Table 2. (continued)

Patients sex, age (y)	CAPS features	Eculizumab regimen	Complement activity (CH50)	Platelet count	CAPS outcome	Long-term outcome
F, 44	Renal failure (hemodialysis); adrenal ischemic hemorrhage; thrombocytopenia MAHA	Started at day 21; 1 infusion of 900 mg	Before: 123 U/mL (N); after administration: <13 U/mL (undetectable)	Before C1: 10 × 10^9/L; after C1: 30 × 10^9/L	Symptoms worsened	Death 11 d later
F, 58	Renal and cardiac failures (LVEF 42%); liver and multiple brain infarcts; ischemic colitis; thrombocytopenia	Started at day 7; 900 mg/wk for 4 wk	Data missing	Before C1: 214 × 10^9/L; after C1: 248 × 10^9/L	Symptoms worsened	Death 33 d later

C1, first eculizumab administration; ECMO, extracorporeal membrane oxygenation; LVEF, left ventricular ejection fraction; N, normal value; TMA, thrombotic microangiopathy.

The median delay between CAPS onset and the first eculizumab injection was 15 (IQR 26) days, and patients received a median of 2.5 (IQR 3) injections.

We report for the first time, to our knowledge, a significant number of patients who did not respond to eculizumab. This difference highlights the potential publication bias of isolated case reports in which poor outcomes are less likely to be reported. Given the small sample size in our study, it is difficult to draw strong conclusions on the characteristics of patients who are more likely to respond. Our findings suggest that some manifestations improved more frequently; in particular, hematologic disorders were responsive. The delay between onset of CAPS and administration of eculizumab raises the question of the benefit of earlier administration, to avoid the occurrence of irreversible lesions, such as renal cortical necrosis that usually definitely alters renal function. Although the mechanisms by which aPLs activated the complement remain unclear, complement seemed to be almost constituently overactivated in CAPS. Chaturvedi et al reported that the sera of 6 of 7 patients with CAPS showed complement activation in functional assays.[4] They reported that activation of both the classic and alternative pathways of complement were involved in CAP, whereas only the classic pathway was involved in other patients with APS. Unfortunately, in our patients, only serum levels of complement products measured routinely were available (C3, C4, CH50), but those data did not enable proper assessment of the level of complement activation in each patient or evaluation of the response to treatment according to the level of complement overactivation. A research of rare germline variants in complement genes may be of interest, as those patients probably have a higher rate of complement activation. The question of a differential response to eculizumab according to the rate of mutations has to be further evaluated.

Our study had several limitations related to its retrospective and nonrandomized design. However, despite the small sample size, our study is the sole one that has reported data on a cohort of patients with CAPS who were treated with eculizumab.

To summarize, our findings suggest that patients with refractory CAPS respond inconsistently to eculizumab. However, eculizumab can successfully treat some critically ill patients and seems to be especially efficient in treating hematologic failure. The dramatic effect on thrombocytopenia may be of importance in decreasing the risk of bleeding and promoting maintenance of optimal anticoagulation. Given our findings, we suggest that eculizumab be used in refractory CAPS, in which thrombocytopenia and microangiopathic features are the main manifestations. Further studies are needed to better assess the drug's efficacy and safety and to identify the target population among patients with CAPS.

Acknowledgments

The authors thank the medical doctors of the centers for contributing to the antiphospholipid syndrome (secondary acute promyelocytic leukemia) cohort: Ygal Benhamou, Gaëlle Guettrot-Imbert, David Launay, Céline Lebas, Hélène Maillard, Nathalie Morel, Ryadh Pokeerbux, Sébastien Sanges, and Vincent Sobanski.

Authorship

Contribution: C.M.Y, and M.L. designed the research, collected and analyzed the data, and wrote the manuscript; and S.M., A.M., E.L., T.Q., F.P., M.F., S.M.-D., V.L.G., E.H., and N.C.-C. contributed to data collection and analysis and critically reviewed the paper.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

ORCID profiles: C.M.Y., 0000-0003-4260-5035; A.M., 0000-0003-2849-3049; T.Q., 0000-0001-8922-7727.

Correspondence: Cécile Marie Yelnik, Service Médecine Interne et de Médecine Polyvalente-post-Urgences, Hôpital Claude Huriez, CHU Lille, Rue Michel Polonovski, 59037 Lille Cedex, France; e-mail: cecile.yelnik@orange.fr.

Footnotes

Submitted 17 June 2020; accepted 3 July 2020; prepublished online on *Blood* First Edition 14 July 2020.

Original data are available by e-mail request to the corresponding author. Data from our SAPL cohort have been presented in other articles, but CAPS patients were not included in those reports, and the data in the present submission do not overlap those in the previous reports.

REFERENCES

1. Pierangeli SS, Girardi G, Vega-Ostertag M, Liu X, Espinola RG, Salmon J. Requirement of activation of complement C3 and C5 for antiphospholipid

antibody-mediated thrombophilia. *Arthritis Rheum*. 2005;52(7):2120-2124.

2. Shamonki JM, Salmon JE, Hyjek E, Baergen RN. Excessive complement activation is associated with placental injury in patients with antiphospholipid antibodies. *Am J Obstet Gynecol*. 2007;196(2):167.e1-167.e5.

3. Salmon JE, Heuser C, Triebwasser M, et al. Mutations in complement regulatory proteins predispose to preeclampsia: a genetic analysis of the PROMISSE cohort. *PLoS Med*. 2011;8(3):e1001013.

4. Chaturvedi S, Braunstein EM, Yuan X, et al. Complement activity and complement regulatory gene mutations are associated with thrombosis in APS and CAPS. *Blood*. 2020;135(4):239-251.

5. Asherson RA, Cervera R, de Groot PG, et al; Catastrophic Antiphospholipid Syndrome Registry Project Group. Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines. *Lupus*. 2003;12(7):530-534.

6. Rodríguez-Pintó I, Espinosa G, Erkan D, Shoenfeld Y, Cervera R; CAPS Registry Project Group. The effect of triple therapy on the mortality of catastrophic anti-phospholipid syndrome patients. *Rheumatology (Oxford)*. 2018;57(7):1264-1270.

7. Shapira I, Andrade D, Allen SL, Salmon JE. Brief report: induction of sustained remission in recurrent catastrophic antiphospholipid syndrome via inhibition of terminal complement with eculizumab. *Arthritis Rheum*. 2012;64(8):2719-2723.

8. Silva RA, Moshfeghi DM. Antiphospholipid antibody-associated choroidopathy. *Eye (Lond)*. 2014;28(6):773-774.

9. Kronbichler A, Frank R, Kirschfink M, et al. Efficacy of eculizumab in a patient with immunoadsorption-dependent catastrophic antiphospholipid syndrome: a case report. *Medicine (Baltimore)*. 2014;93(26):e143.

10. Strakhan M, Hurtado-Sbordoni M, Galeas N, Bakirhan K, Alexis K, Elrafei T. 36-year-old female with catastrophic antiphospholipid syndrome treated with eculizumab: a case report and review of literature. *Case Rep Hematol*. 2014;2014:704371.

11. Zikos TA, Sokolove J, Ahuja N, Berube C. Eculizumab induces sustained remission in a patient with refractory primary catastrophic antiphospholipid syndrome. *J Clin Rheumatol*. 2015;21(6):311-313.

12. Wig S, Chan M, Thachil J, Bruce I, Barnes T. A case of relapsing and refractory catastrophic anti-phospholipid syndrome successfully managed with eculizumab, a complement 5 inhibitor. *Rheumatology (Oxford)*. 2016;55(2):382-384.

13. Barratt-Due A, Fløisand Y, Orrem HL, et al. Complement activation is a crucial pathogenic factor in catastrophic antiphospholipid syndrome. *Rheumatology (Oxford)*. 2016;55(7):1337-1339.

14. Guillot M, Rafat C, Buob D, et al. Eculizumab for catastrophic antiphospholipid syndrome-a case report and literature review. *Rheumatology (Oxford)*. 2018;57(11):2055-2057.

15. Ruffatti A, Tarzia V, Fedrigo M, et al. Evidence of complement activation in the thrombotic small vessels of a patient with catastrophic antiphospholipid syndrome treated with eculizumab. *Autoimmun Rev*. 2019;18(5):561-563.

16. Tinti MG, Carnevale V, Inglese M, et al. Eculizumab in refractory catastrophic antiphospholipid syndrome: a case report and systematic review of the literature. *Clin Exp Med*. 2019;19(3):281-288.

17. Skoczynska M, Crowther MA, Chowaniec M, Ponikowska M, Chaturvedi S, Legault K. Thrombotic microangiopathy in the course of catastrophic antiphospholipid syndrome successfully treated with eculizumab: case report and systematic review of the literature. *Lupus*. 2020;29(6):631-639.

18. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost*. 2006;4(2):295-306.

19. Ruffatti A, De Silvestro G, Marson P, et al. Catastrophic antiphospholipid syndrome: Lessons from 14 cases successfully treated in a single center. A narrative report. *J Autoimmun*. 2018;93:124-130.

DOI 10.1182/blood.2020007499