

Clinical Utility and Potential Cost Savings of Pharmacologic Monitoring of Eculizumab for Complement-Mediated Thrombotic Microangiopathy

Meera Sridharan, MD, PhD; Ronald S. Go, MD; and Maria A.V. Willrich, PhD

Abstract

One of the treatment options for complement-mediated thrombotic microangiopathy (CM-TMA), also known as atypical hemolytic uremic syndrome, is the administration of the C5 complement inhibitor eculizumab. In vivo studies have reported a complete complement blockade with eculizumab serum concentrations above 50 $\mu\text{g/mL}$ in the case of atypical hemolytic uremic syndrome. The eculizumab trough levels and C5 functional activity were monitored in patients with CM-TMA being treated with eculizumab. For those with eculizumab trough concentrations of more than 100 $\mu\text{g/mL}$, the frequency of eculizumab 1200-mg doses was decreased. In this article, we describe the pharmacologic monitoring data with the use of C5 functional activity and mass spectrometric assessments of eculizumab to allow for a tailored eculizumab schedule for 10 patients with CM-TMA. In 9 out of 10 (90%) patients with a standard administration schedule, eculizumab trough concentrations were more than 100 $\mu\text{g/mL}$. At the time of the last eculizumab follow-up (median, 250 days; range, 85-898 days), the interval between eculizumab infusions was extended to every 3-6 weeks for 8 patients; no disease relapse was found with the modified dosing interval. Altering the administration of maintenance eculizumab from every 2-3 weeks to 3-6 weeks yields a savings of \$78,185 per patient for a 6-month eculizumab treatment course. Although larger standardized cohorts are necessary to confirm these findings, our data suggest that monitoring eculizumab levels in conjunction with C5 assessment allows for safe modification of eculizumab dosing and results in considerable cost savings.

© 2022 THE AUTHORS. Published by Elsevier Inc on behalf of Mayo Foundation for Medical Education and Research. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>) ■ *Mayo Clin Proc Inn Qual Out* 2022;6(5):458-464

From the Division of Hematology (M.S., R.S.G.) and the Department of Laboratory Medicine and Pathology (M.A.V.W.), Mayo Clinic, Rochester, MN.

Complement-mediated thrombotic microangiopathy (CM-TMA), also known as atypical hemolytic uremic syndrome (aHUS), is treated with the C5-complement inhibitor eculizumab. For adults, the standard eculizumab administration schedule is four 900-mg weekly infusions followed by 1200 mg every 2 weeks.¹ In vivo studies have demonstrated complement blockade with eculizumab serum concentrations of more than 50 $\mu\text{g/mL}$ for aHUS.²⁻⁴ In this article, we present data of monitoring C5 functional activity and eculizumab trough concentrations in 10 patients receiving eculizumab for CM-TMA.⁵ In addition, we provide data on physician-directed eculizumab discontinuation in this patient cohort.

PATIENTS AND METHODS

Laboratory databases were queried for patients with eculizumab levels and C5 activity since introduction of these assays in 2018. Inclusion criteria were patients with a clinical diagnosis of aHUS or CM-TMA receiving medical care at Mayo Clinic, Rochester, MN. Only patients with physician-ordered eculizumab trough levels were included.

Complement Serology and Eculizumab Assessment

AH50, C5 activity, and eculizumab assays are clinically available through Mayo Clinic Laboratories. AH50 is a measurement of the alternative pathway function using an enzyme-linked immunosorbent assay

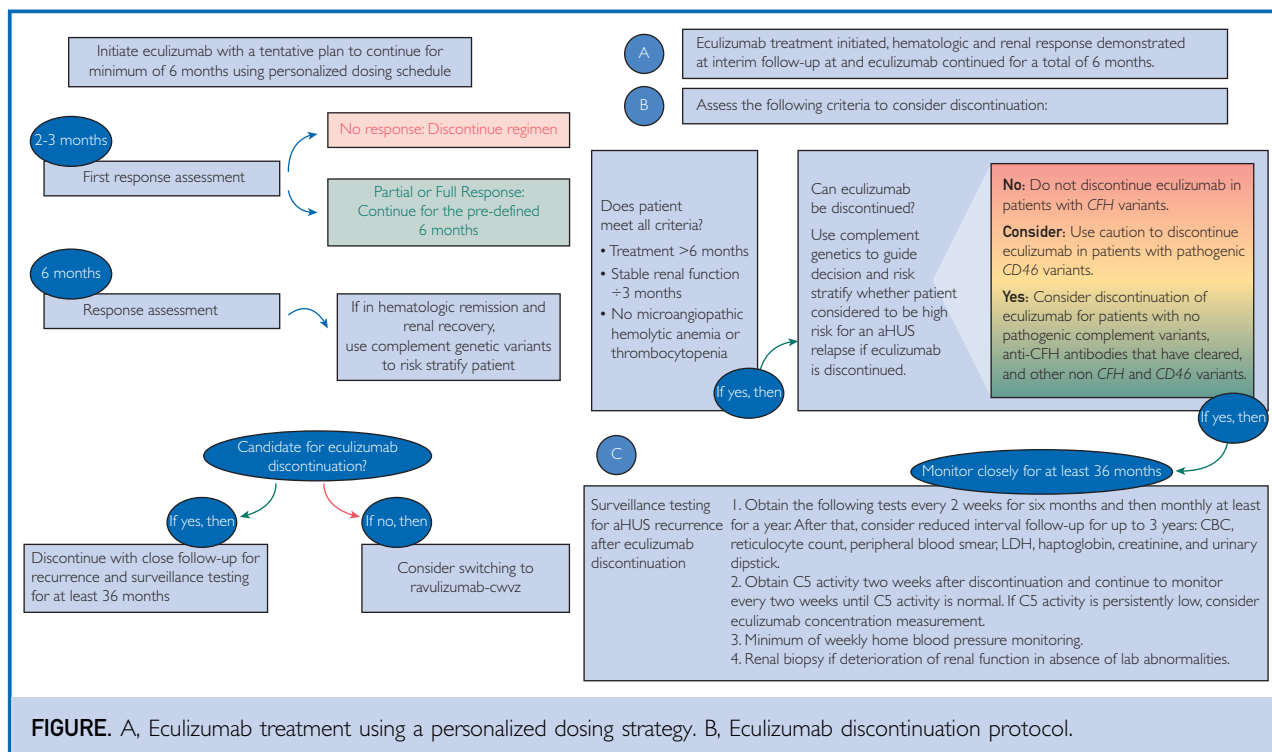


FIGURE. A, Eculizumab treatment using a personalized dosing strategy. B, Eculizumab discontinuation protocol.

(Wieslab, Svar Life Sciences).⁶ C5 activity is measured using a laboratory-developed test. The individual C5 function is assessed using a liposome immunoassay (Wako Autokit, Fujifilm Medical Systems USA, Inc.) in combination with C5-depleted human serum.⁷ Briefly, a mixture of C5-depleted serum and patient serum is added to the first reagent, which is composed of liposomes carrying dinitrophenyl (DNP) antigen on the surface and glucose-6-phosphate dehydrogenase in the interior. The second reagent is a solution of anti-DNP antibodies and nicotinamide adenine dinucleotide. Antibodies to DNP bind to the liposomes and are recognized by C1q in the serum to initiate the classical pathway activity. The complement membrane attack complex formed by C5b-C9 lyses the liposomes, releasing glucose-6-phosphate dehydrogenase to react with nicotinamide adenine dinucleotide. The rate of absorbance increase is measured at 340 and 700 nm. When eculizumab binds to C5 in patient serum, C5 function is below the reference interval (RI) or undetectable. In a series of 58 patients in whom C5 activity and eculizumab levels

were measured on the same specimens, when eculizumab concentrations were more than 100 $\mu\text{g/mL}$ ($n = 47$ samples), the C5 activity was undetectable in 34/47 (72%) of the samples and below RI for the other 13/47 (28%) of the specimens. All samples with eculizumab concentrations more than 100 $\mu\text{g/mL}$ had reduced or undetectable C5 activity. When eculizumab was measured between 35 and 100 $\mu\text{g/mL}$ ($n = 6$ samples), 67% (4/6) of samples measured below RI and 33% (2/6) within the test RI.⁵

Eculizumab concentration is measured by high-resolution mass spectrometry using a previously detailed⁵ laboratory-developed test that quantifies the signature κ light chains from the monoclonal antibodies. In this test, there is a pre-analytical enrichment of the serum sample, using IgG4 camelid beads as a capture, to decrease the nonimmunoglobulin protein content of the serum. After the immunoenrichment for IgG4, the samples are eluted from the IgG4 beads and reduced to break down the disulfide bonds of the IgG4 molecules, releasing the light chains from the heavy chains. The κ light chain of eculizumab has a

TABLE 1. Demographic Characteristics and Eculizumab and C5 activity Trough Levels^a

Case	Sex	Age at initiation of ECU (y)	Weight (kg)/BMI (kg/m ²)	ECU trough ^b (μg/mL)	C5 functional activity (U/mL) (RI: 29-53 U/mL)	Time to first ECU trough from initiation of ECU (d)	ECU Follow-up time (First ECU trough to last dose of ECU) (d)	Recommended ECU frequency at last ECU follow-up (wk)/ECU trough at last follow-up	Total Follow-up time (first ECU trough to last clinical visit) (d)	Using ECU at last clinical follow-up ^c /time (d) off ECU
1	F	64	58.4/24.4	412	<5	40	1095	5/167	1095	Yes
		Complement genetics ^d		VUS in <i>CFH</i> (c.1874-1G>C) and <i>CFB</i> (c.1143C>T)						
2	F	26	127/45.3	46	63	339	151 ^e	2/NA	697	No/546
		Complement genetics ^f		VUS in <i>CFH</i> (c.122C>T) and homozygous deletion of <i>CFHR1</i> likely ^g . Factor H antibodies were positive						
3	M	68	83/25.5	441	<5	620	347	5/139	542	No ^h
		Complement genetics ⁱ		No variant identified						
4	F	65	83.1/22.9	221	17	90	85	3/145	525	No/440
		Complement genetics ^f		No variant identified but <i>CFHR1/CFHR3</i> deletion possible ^j						
5	F	44	114/37.0	191	<5	282	595	3/130	988	No ^h
		Complement genetics ^d		Homozygous deletion of <i>CFHR1</i>						
6	F	72	55.7/22.0	187	6	68	126	3/158	353	No/227
		Complement genetics ^f		No variant identified						
7	M	20	66/24.2	464	<5	108	NA	Discontinue	42	No/27
		Complement genetics ^f		No variant identified but <i>CFHR1/CFHR3</i> deletion possible ^j						
8	F	22	55.3/20.7	453	<5	152	153	5/226	380	No/227
		Complement genetics ^f		No variant identified						
9	F	30	66/21.8	518	<5	45	142	4/381	779	No/637
		Complement genetics ^d		VUS in <i>CFI</i> (c.1534 + 5G>T), <i>C3</i> (c.463A>C), and <i>CFHR4</i> (c.1231C>T)						
10	F	54	73.2/27.2	459	<5	42	96	6/216	145	No/49
		Complement genetics ^f		No variant identified						

^aBMI = body mass index; ECU = eculizumab; NA = not applicable; RI = reference interval; VUS = variant of uncertain significance.

^bOur practice is to consider decreasing eculizumab frequency (by weekly intervals) if C5 is less than RI and eculizumab levels more than 100 μg/mL.

^cRefer to the Figure for details on our eculizumab discontinuation protocol.

^dGenes evaluated: *CFH*, *MCP* (*CD46*), *CFI*, *C3*, *CFB*, *CFHR1*, *CFHR3*, *CFHR4*, *CFHR5*, *THBD*, *PLG*, and *DGKE*.

^eDespite subtherapeutic eculizumab levels, patient was continued on standard eculizumab doses because of no evidence of relapse while additional evaluation was pursued.

^fGenes evaluated: *ADAMTS13*, *C3*, *CD46*, *CFB*, *CFD*, *CFH*, *CFHR1*, *CFHR3*, *CFHR5*, *CFI*, *DGKE*, *PLG*, and *THBD*.

^gNext generation sequencing revealed no coverage for the *CFHR1* gene. This lack of coverage may be indicative of a large homozygous deletion encompassing the *CFHR1* gene. However, the methodology used cannot confirm this.

^hPatient switched to ravulizumab.

ⁱGenes evaluated: *ADAMTS13*, *C3*, *CD46*, *CFB*, *CFH*, *CFHR5*, *CFI*, *DGKE*, *PLG*, *THBD*, and *MMACHC*.

^jNext generation sequencing revealed no coverage for the *CFHR1* and *CFHR3* genes for this individual. This lack of coverage may be indicative of a large homozygous deletion encompassing both the *CFHR1* and *CFHR3* genes. However, the methodology used cannot confirm this.

molecular weight of approximately 23,130 Da. Mass of this signature molecule is then identified and quantitated using mass spectrometry against a standard curve prepared with known concentrations of the eculizumab pharmaceutical preparations. The method has a lower limit of quantitation of 5.0 $\mu\text{g/mL}$.⁸

Protocol for Eculizumab Frequency Adjustment and Discontinuation

In our center, C5 activity and eculizumab levels are assessed before the second maintenance (1200 mg intravenously) dose of eculizumab and for those with C5 less than 29 U/mL and eculizumab more than 100 $\mu\text{g/mL}$, we decrease the frequency of subsequent 1200-mg eculizumab doses by 1-week increments. An eculizumab trough level of 100 $\mu\text{g/mL}$ was chosen because at this concentration C5 is consistently either undetectable or below RI. All patients are monitored this way for 6 months before considering eculizumab discontinuation (Figure A). Our institutional protocol is for a trial eculizumab discontinuation for patients who are in clinical remission without high-risk complement variants (Figure B). In patients in whom we do not recommend discontinuation, a physician-patient discussion regarding the continuation of the current protocol vs switching to ravulizumab-cwvz takes place.

Cost Savings Analysis

Cost savings analysis for modified eculizumab frequency was performed using Medicare reimbursement prices for medications and laboratory assays.

RESULTS

Baseline C5 Functional Activity and Eculizumab Trough Concentrations With Standard Eculizumab Dose Administration Schedule

Ten patients met the inclusion criteria, and eculizumab trough concentrations ranged from 46 to 518 $\mu\text{g/mL}$ (Table 1). Because of the variability in patient referral to our institution, there was no uniform time when eculizumab trough concentrations were obtained in relation to eculizumab initiation. C5 was less than RI and eculizumab trough concentrations were more than 100 $\mu\text{g/mL}$ in 9 of the 10

(90%) patients with standard administration schedules.

Modification of Eculizumab Dosing and Cost Savings Analysis

Using the described approach, at minimum, of those patients with adequate follow-up time, 8 out of 8 patients were able to be transitioned to every 3-week eculizumab dosing. At the time of the last eculizumab follow-up (median, 250 days; range, 85-898 days), eculizumab infusions were extended to every 3, 4, 5, and 6 weeks for 3, 1, 3, and 1 patient, respectively. There were no disease relapses with the modified dosing interval.

Altering eculizumab administration from every 2 weeks to every 3-4 weeks yields a savings of \$78,165-\$130,596 per patient for a 6-month eculizumab treatment course (Table 2A). Cost savings were estimated for each patient using the modified treatment protocol (Table 2B).

Eculizumab Discontinuation

Of the 9 patients with at least 2 months of follow-up, a trial of complement therapy discontinuation occurred in 8 patients after achieving hematologic and renal remission. In 227 days (range, 49-637 days) of follow-up after eculizumab discontinuation, 2 patients (case #1 and #5) required eculizumab reinitiation because of relapse. Both patients had initially been treated with standard eculizumab schedules, as their initial treatment predated the availability of C5 and eculizumab monitoring. After relapse, eculizumab was reinitiated using our personalized administration approach, and both patients achieved hematologic and renal remission. Given 2 previous episodes of TMA before the clinical diagnosis of CM-TMA, the decision was made to continue complement blockade indefinitely for case #3.

DISCUSSION

Atypical hemolytic uremic syndrome is a condition that occurs because of dysregulation of the alternative complement pathway and is treated by C5 inhibition with either eculizumab or ravulizumab-cwvz. The phase 2 clinical trials using eculizumab for the treatment of aHUS reported eculizumab trough concentrations of 93-205 $\mu\text{g/mL}$.³ The value of all

TABLE 2. Eculizumab With Modified Dosing Schedule and Estimated Cost Saving^a

A: Cost comparison of ECU with modified dosing schedule compared to standard dosing schedule						
Estimated total cost savings for 6 mo of ECU = [Cost of ECU (1200 mg) × (no. of every 2 wk interval doses in 5 mo) – [(cost of ECU (1200 mg) + cost of ECU monitoring assays) × (no. of every 3-4 wk interval doses in 5 mo)]]						
	Cost of ECU ^b induction (900 mg) for 4 weekly doses	Cost of ECU ^b (1200 mg)	Cost of ECU and C5 functional activity assays	No. of maintenance doses over 5 mo	Total maintenance cost	Total cost
Every 2 wk maintenance dosing	\$78,578	\$26,167.50	NA	10	\$261,675	\$340,253
Every 3-4 wk maintenance dosing	\$78,578	\$26,167.50	\$48.26 ^b	5-7	\$131,078- \$183,510	\$209,657-\$262,088
Estimated total cost savings for 6 mo of ECU treatment with every 3-4 wk maintenance schedule	\$78,165-\$130,596					
Estimated ravulizumab ^c cost for a 6-mo course	\$269,270					
B: Estimated individual patient cost savings						
Case	Recommended ECU administration schedule changes ^d	No. of ECU doses spared compared with the traditional every 2 wk maintenance schedule	Approximate cost saving	Long-term plan		
1	ECU every 3-5 wk indefinitely	8-12 doses/12 mo	\$220,488-\$331,311/y	Indefinite because of earlier relapse when ECU was discontinued		
2	Discontinue	NA	NA ^e	Discontinued ECU owing to subtherapeutic ECU level		
3	ECU every 5 wk	6 doses/6 mo	\$165,704	Indefinite complement inhibitor because of earlier relapse with prior TMA episodes. Note that patient has now transitioned to ravulizumab-cwvz		
4	ECU every 3 wk for 3 mo	2	\$54,880	Discontinued ECU 6 mo after initiation		
5	ECU every 2-3 wk indefinitely	Up to 8 doses/12 mo	Up to \$220,488/y while on ECU	Indefinite complement inhibitor because of earlier relapse when ECU was discontinued. Note that patient has now transitioned to ravulizumab-cwvz		
6	ECU every 3 wk for 4 mo	3 doses	\$82,538	Discontinued ECU 6 mo after initiation		
7	NA	NA	NA	At the time of initial ECU trough ECU was discontinued		
8	ECU every 3-4 wk for 3 mo; ECU every 5 wk for 3 mo	6 doses	\$165,704	Discontinued ECU 11 mo after initiation		
9	ECU every 3-4 wk for 4 mo	3 doses	\$82,731	Discontinued ECU 6.5 mo after initiation		
10	ECU spaced out by 1-wk intervals; last dose given 6 wk after last	5 doses	\$137,998	Discontinued after 6 mo total of ECU		

^aECU = eculizumab; NA = not applicable; TMA = thrombotic microangiopathy.

^bCost represents estimated Centers for Medicare and Medicaid (CMS) reimbursement rate; cost of eculizumab and ravulizumab include estimated CMS costs for infusion times.

^cGiven weight-based dosing of ravulizumab; estimated cost represents the cost of ravulizumab for a 70-kg individual.

^dIn our center, for those with C5 less than 29 U/mL and eculizumab more than 100 µg/mL, we decrease the frequency of 1200-mg eculizumab doses in weekly intervals. We make this assessment every time a patient is scheduled to receive eculizumab. For example, if a patient had been receiving infusions of eculizumab every 2 wk, if eculizumab levels are more than 100 and C5 functional activity is inhibited, the next infusion will be given in 3 wk. We continue to space out infusions as long as C5 is inhibited and eculizumab levels are more than 100. If a significant decline is noted in the eculizumab trough concentration but the C5 function is inhibited, we consider going back to the last frequency of administration until the eculizumab trough concentration stabilizes.

^eNo cost saving for this patient but highlights the importance of drug level monitoring because this patient was receiving subtherapeutic doses for an unknown period of time; therefore, the clinical benefit of the ECU doses received is uncertain.

levels above the minimum trough concentration of 50 µg/mL needed to achieve complement blockade suggested the opportunity to modify the standard doses of eculizumab when complement serology and eculizumab level monitoring became available.⁹ In our cohort, 90% of patients had eculizumab trough concentrations higher than 50 µg/mL.

Monitoring eculizumab levels adds value to patient care for several reasons. Most patients do not require eculizumab doses of 1200 mg intravenously every 2 weeks to achieve adequate C5 inhibition. This means less frequent infusion visits, which has the potential to impact the quality of life and result in significant cost savings. When using our protocol of a minimum of 6 months of eculizumab before discontinuation, decreasing the frequency of eculizumab to every 3 weeks rather than every 2 weeks led to a minimum cost saving of \$110,244. Further decrease in the frequency of eculizumab doses resulted in even higher cost savings (Table 2B).

Another benefit of eculizumab monitoring is the ability to determine when the residual effects of the C5 blockade have gone away. Because of the suprathreshold eculizumab levels in some patients with the standard dosing regimen, once discontinued, eculizumab may be present in vivo for several months. Given the approach by some centers, including ours, for close clinical monitoring after eculizumab discontinuation, it is important to recognize when eculizumab is no longer leading to C5 inhibition. For example, case #1 had initially been treated with eculizumab before our pharmacologic monitoring protocol and tailored dosing. Three months after eculizumab discontinuation, she had low AH50 and C5 as well as an eculizumab trough concentration of 117 µg/mL. AH50 was first detectable 2 weeks later, and 1 month after the initial increase in AH50, the patient had a clinical relapse of TMA and was restarted on eculizumab. It is important to recognize eculizumab persistence when developing strategies for surveillance of aHUS relapse.

The pharmacokinetics of eculizumab may differ between individuals for many reasons, including interindividual variability of C5 concentration and blood volume/body weight.¹⁰ Other studies have demonstrated similar findings of suprathreshold eculizumab levels in

adult and pediatric populations^{11,12}; yet, others have also demonstrated success in decreasing the frequency of eculizumab dosing by monitoring complement serology.¹³⁻¹⁵ Although other studies have reported the use of AH50 and total complement activity (CH50) to determine interval frequencies, ours is the first report using both C5 and mass spectrometric assessment of eculizumab to guide a personalized dosing strategy. We decided to implement C5 as a clinical test for eculizumab monitoring given its higher specificity.⁵ Although demonstrating inhibition of C5 is useful, it provides the clinician with no data regarding how close a patient's eculizumab level is to the lowest level needed to achieve adequate C5 inhibition. Obtaining eculizumab trough concentrations along with C5 allows for a more nuanced approach to eculizumab administration.

Although most patients in our cohort showed suprathreshold levels, one patient in our cohort (case #2) had subtherapeutic eculizumab. It is hypothesized that the reason for subtherapeutic levels is the nonweight-based approach for eculizumab administration. In pharmacokinetic studies of patients with aHUS and paroxysmal nocturnal hemoglobinuria, weight has been noted to be a parameter explaining interindividual variability.¹¹ Other studies have also suggested that Food and Drug Administration-approved doses may not be adequate for patients at high weight extremes.^{15,16} Pharmacokinetic modeling in one study showed that body weight and male gender increased eculizumab elimination clearance and suggested that trough concentrations of less than 100 µg/mL of eculizumab may be more likely in the case of the highest body-weight tested (90 kg).¹⁵

In addition to exploring a tailored approach to eculizumab dosing, we also describe our experience with eculizumab discontinuation. Of those discontinuing eculizumab, relapse occurred in 25% of patients. Both patients who relapsed were reinitiated on eculizumab within 48 hours of the first signs of TMA recurrence, and these patients once again achieved hematologic and renal remission at the restart of therapy. One of these patients has transitioned to ravulizumab-cwvz and the other patient (case #1) chose to remain on eculizumab (currently receiving treatment every 3-5 weeks).

Although larger standardized cohorts are necessary to confirm these findings, our data suggest that monitoring of eculizumab levels in conjunction with C5 allows for safe modification of eculizumab dosing and provides significant cost savings. In addition, we demonstrated that the safe discontinuation of eculizumab using a physician-directed monitoring system is practical and feasible. With the advent of longer-acting complement inhibitors such as ravulizumab-cwvz, it is important to consider the value of monitoring the drug level in personalized treatment strategies for patients. Ravulizumab-cwvz doses are weight-based¹⁷; therefore, drug levels may more closely approximate the minimal therapeutic trough levels needed to inhibit the complement; however, it will be important to characterize this further.

POTENTIAL COMPETING INTERESTS

Dr Sridharan has received honoraria from Alexion Pharmaceuticals Inc that includes: consulting or advisory.

ACKNOWLEDGMENTS

The authors thank Ms. Karin Braun, Development Technologist, Department of Laboratory Medicine and Pathology at Mayo Clinic, for assisting with figure creation for the Mayo Clinic eculizumab discontinuation protocol. M.S. designed the research, collected and analyzed the data, and wrote the manuscript; R.S.G. designed the research and edited the manuscript; M.A.V.W. designed the research, contributed to laboratory studies, and edited the manuscript.

Abbreviations and Acronyms: aHUS, atypical hemolytic uremic syndrome; CM-TMA, complement-mediated thrombotic microangiopathy; DNP, dinitrophenyl; RI, reference interval

Correspondence: Address to Meera Sridharan, MD, PhD, Mayo Clinic, 200 First Street, SW, Rochester, MN 55905 (sridharan.meera@mayo.edu).

ORCID

Meera Sridharan:  <https://orcid.org/0000-0001-7225-8228>; Maria A.V. Willrich:  <https://orcid.org/0000-0002-9318-7091>

REFERENCES

1. Alexion Pharmaceuticals, Inc. Soliris (eculizumab) prescribing information. US Food and Drug Administration. Accessed September 2021, http://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125166s426lbl.pdf. Accessed September 1, 2021.
2. Legendre CM, Licht C, Loirat C. Eculizumab in atypical hemolytic-uremic syndrome. *N Engl J Med*. 2013;369(14):1379-1380.
3. Legendre CM, Licht C, Muus P, et al. Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. *N Engl J Med*. 2013;368(23):2169-2181.
4. Wijnsma KL, Ter Heine R, Moes D, et al. Pharmacology, pharmacokinetics and pharmacodynamics of eculizumab, and possibilities for an individualized approach to eculizumab. *Clin Pharmacokinet*. 2019;58(7):859-874.
5. Willrich MAV, Andreguetto BD, Sridharan M, et al. The impact of eculizumab on routine complement assays. *J Immunol Methods*. 2018;460:63-71.
6. Mollnes TE, Jokiranta TS, Truedsson L, et al. Complement analysis in the 21st century. *Mol Immunol*. 2007;44(16):3838-3849.
7. Frazer-Abel A, Sepiashvili L, Mbughuni MM, Willrich MA. Overview of laboratory testing and clinical presentations of complement deficiencies and dysregulation. *Adv Clin Chem*. 2016;77:1-75.
8. Ladwig PM, Barnidge DR, Willrich MA. Quantification of the IgG2/4 kappa monoclonal therapeutic eculizumab from serum using isotype specific affinity purification and microflow LC-ESI-Q-TOF mass spectrometry. *J Am Soc Mass Spectrom*. 2017;28(5):811-817.
9. Goodship TH, Cook HT, Fakhouri F, et al. Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a "kidney disease: improving global outcomes" (KDIGO) controversies conference. *Kidney Int*. 2017;91(3):539-551.
10. Ricklin D, Barratt-Due A, Mollnes TE. Complement in clinical medicine: clinical trials, case reports and therapy monitoring. *Mol Immunol*. 2017;89:10-21.
11. Gatault P, Brachet G, Ternant D, et al. Therapeutic drug monitoring of eculizumab: rationale for an individualized dosing schedule. *MAbs*. 2015;7(6):1205-1211.
12. Volokhina E, Wijnsma K, van der Molen R, et al. Eculizumab dosing regimen in atypical HUS: possibilities for individualized treatment. *Clin Pharmacol Ther*. 2017;102(4):671-678.
13. Ardissino G, Tel F, Sgarbanti M, et al. Complement functional tests for monitoring eculizumab treatment in patients with atypical hemolytic uremic syndrome: an update. *Pediatr Nephrol*. 2018;33(3):457-461.
14. Cugno M, Gualtierotti R, Possenti I, et al. Complement functional tests for monitoring eculizumab treatment in patients with atypical hemolytic uremic syndrome. *J Thromb Haemost*. 2014;12(9):1440-1448.
15. Passot C, Sberro-Soussan R, Bertrand D, et al. Feasibility and safety of tailored dosing schedule for eculizumab based on therapeutic drug monitoring: lessons from a prospective multicentric study. *Br J Clin Pharmacol*. 2021;87(5):2236-2246.
16. Ring T. Eculizumab in atypical hemolytic-uremic syndrome. *N Engl J Med*. 2013;369(14):1377-1378.
17. Rondeau E, Scully M, Ariceta G, et al. The long-acting C5 inhibitor, ravulizumab, is effective and safe in adult patients with atypical hemolytic uremic syndrome naive to complement inhibitor treatment. *Kidney Int*. 2020;97(6):1287-1296.