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Case Report

Discontinuation of Eculizumab Maintenance Treatment for Atypical Hemolytic Uremic Syndrome: A Report of 10 Cases

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Atypical hemolytic uremic syndrome (aHUS) is a life-threatening thrombotic microangiopathy, and as many as 70% of patients with aHUS have mutations in the genes encoding complement regulatory proteins. Eculizumab, a humanized recombinant monoclonal antibody targeting C5, has been used successfully in patients with aHUS since 2009. The standard maintenance treatment requires life-long eculizumab therapy, but the possibility of discontinuation has not yet been tested systematically. We report the safety of discontinuing eculizumab treatment in 10 patients who stopped treatment with the aim of minimizing the risk of adverse reactions, reducing the risk of meningitis, and improving quality of life while also reducing the considerable treatment costs. Disease activity was monitored closely at home by means of urine dipstick testing for hemoglobin. During the cumulative observation period of 95 months, 3 of the 10 patients experienced relapse within 6 weeks of discontinuation, but then immediately resumed treatment and completely recovered. Our experience supports the possibility of discontinuing eculizumab therapy with strict home monitoring for early signs of relapse in patients with aHUS who achieve stable remission.

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INDEX WORDS: Atypical hemolytic uremic syndrome; eculizumab; discontinuation.

Atypical hemolytic-uremic syndrome (aHUS) is a rare, life-threatening, chronic thrombotic microangiopathy (TMA) that often is due to uncontrolled complement dysregulation[1-3]; it accounts for 10%-15% of all HUS cases in children, but also affects adults.[4-6] Approximately 60%-70% of patients with aHUS have mutations in the genes encoding complement factor H (CFH), factor I (CFI), membrane cofactor protein (MCP), factor B (CFB), thrombomodulin (THBD), and C3.[7-11] Anti-CFH antibodies also may contribute to the pathogenesis of the disease and often are associated with deletions in the CFH-related genes *CFHR3* and *CFHR1* (referred to as *CFHR3/R1*).[12]

For years, the only available treatment was plasma exchange, but outcomes were poor and up to 60% of patients with CFH mutations (the most severe form) reached end-stage renal disease shortly after onset.[13,14] Since 2009, aHUS has been treated successfully with eculizumab, a monoclonal antibody targeting C5 and preventing complement activation. Eculizumab treatment is associated with an increased risk of meningococcal infection, and mandatory vaccination only reduces the risk.[15] The drug was approved by the US Food and Drug Administration for use in aHUS treatment in September 2011, but the optimal treatment schedule has not yet been established.[16] A number of publications indicate that long-term therapy is necessary to prevent relapses, and the European Medicines Agency has approved life-long treatment.[2,3,17-21]

We describe 10 patients with aHUS who discontinued eculizumab maintenance treatment after achieving disease remission.

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Twenty-two patients with aHUS have started eculizumab treatment at our institution since 2010, all of whom were screened for complement dysregulation (*CFH*, *CFI*, *CFB*, MCP [encoded by the *CD46* gene], *C3*, *THBD* gene mutations, and anti-CFH antibodies). After TMA had remitted or, if the drug was used to prevent recurrences, several weeks after kidney transplantation, patients were offered the choice of continuing or discontinuing eculizumab treatment. Clinical remission was defined as normal platelet count, normal lactate dehydrogenase and haptoglobin levels, no detectable schistocytes, and normal or stable kidney function assessed in terms of serum creatinine level and/or urinary protein excretion. The rationale for discontinuation was to reduce the risk of meningococcal infection, minimize the treatment's impact on patients' quality of life, prevent the development of immune-mediated drug reactions, and reduce the considerable treatment costs. The potential benefits of treatment discontinuation and the risk of relapses with severe possible consequences were explained carefully to patients and/or their parents. Patients and/or parents also were informed that discontinuation was not the standard of care and that the likelihood of relapse was high. The risk of acute transplant rejection triggered by aHUS relapse was discussed when applicable.

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Table 1. Patients' Baseline Characteristics and Biomarkers of TMA Activity Before Eculizumab Discontinuation and at Last Available Observation

Patient No.	Age at aHUS Onset (y)	Sex	Complement Abnormality[a]	Relapse	Time Since Start of Eculizumab (mo)	Duration of Eculizumab Discontinuation (mo)	Scr (eGFR[b])		Platelet Count ($10^3/\mu L$)		LDH (IU/L)		Haptoglobin (mg/dL)		UPCR (mg/mg)	
							T1	T2	T1	T2	T1	T2	T1	T2	T1	T2
1	4.3	M	CFH (p.Ser1191Leu)	Yes	31.0	1.5	0.92 (49)	0.80 (58)	334	290	367	206	97	103	0.67	0.17
2	37.7	F	CFH (p.Arg1210Cys) + CFI (p.Asp519Asn) + THBD (p.Ala43Thr)	Yes	25.2	0.9	1.41 (44)	1.25 (51)	244	227	482	219	117	94	1.53	0.96
3	52.7	M	CFI (p.Ile140Thr)	No	24.3	22.7	1.03 (97)	1.00 (100)	180	256	467	371	312	292	NA	0.08
4	34.8	F	CFI (p.Gly269Ser)	No	21.5	10.1	2.72 (29)	2.54 (22)	281	286	406	403	98	88	1.38	0.70
5	2.6	M	CFI (p.Asp519Asn)	No	21.4	15.9	0.38 (132)	0.44 (117)	261	299	517	426	68	105	0.35	0.24
6	1.3	F	Homozygous deletion at *CFHR3/R1* locus	No	19.9	6.5	0.29 (128)	0.27 (138)	447	390	688	654	91	60	3.46	2.32
7[c]	19.1	M	Anti-CFH antibody (titer, 27 IU)	No	19.8	14.2	1.33 (72)	1.20 (79)	245	167	390	325	236	178	0.14	0.08
8	5.4	F	MCP (p.Phe175Val)	No	14.0	13.5	1.28 (36)	0.52 (89)	300	420	682	423	46	78	3.21	0.20
9	13.3	M	Anti-CFH antibody (titer, 100 IU) + homozygous deletion at *CFHR3/R1* locus	No	11.2	8.6	0.64 (110)	0.58 (122)	268	298	435	371	108	106	0.22	0.19
10	10.9	F	CFH (p.Gln950His) + homozygous deletion at *CFHR3/R1* locus + anti-CFH antibody (titer, 230 IU)	Yes	6.4	1.2	0.95 (73)	0.66 (105)	180	239	466	221	88	88	0.45	0.12

Abbreviations: aHUS, atypical hemolytic uremic syndrome; CFH, complement factor H; *CFHR3/R1*, CFH-related genes *CFHR3* and *CFHR1*; CFI, complement factor I; eGFR, estimated glomerular filtration rate (in mL/min/1.73 m^2); LDH, lactate dehydrogenase; MCP, membrane cofactor protein (encoded by the CD46 gene); NA, not available; Scr, serum creatinine (in mg/dL); T1, time of eculizumab discontinuation; T2, time of last follow up; THBD, thrombomodulin; UPCR, urinary protein-creatinine ratio.

[a]Mutations in CFH, CFI, THBD, and MCP are given at the protein level using 3-letter amino acid codes, eg, p.Ser1191Leu is a substitution of the serine at amino acid 1191 by leucine.

[b]GFR calculated using Schwartz formula in patients 18 years or younger and the 4-variable MDRD (Modification of Diet in Renal Disease) Study equation in patients older than 18 years.

[c]Eculizumab therapy was started as prevention of aHUS recurrence on kidney transplant.