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.

CASE REPORTS

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.

From the Center for HUS Prevention, Control and Management, Fondazione IRCCS Ca’ Granda, Ospedale Maggiore Policlinico, Milan, Italy.

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Address correspondence to Gianluigi Ardissino, MD, PhD, Center for HUS Control, Fondazione IRCCS Ca’ Granda, Ospedale Maggiore Policlinico, Via Commenda 9, 20122 Milano, Italy. E-mail: ardissino@centroseu.org
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<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age at aHUS Onset (y)</th>
<th>Sex</th>
<th>Complement Abnormality(^a)</th>
<th>Relapse</th>
<th>Time Since Start of Eculizumab (mo)</th>
<th>Duration of Eculizumab Discontinuation (mo)</th>
<th>Scr (eGFR(^b))</th>
<th>Platelet Count (10(^3)/m(L))</th>
<th>LDH (IU/L)</th>
<th>Haptoglobin (mg/dL)</th>
<th>UPCR (mg/mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.3</td>
<td>M</td>
<td>CFH (p.Ser1191Leu)</td>
<td>Yes</td>
<td>31.0</td>
<td>1.5</td>
<td>0.92 (49)</td>
<td>0.80 (58)</td>
<td>334 290</td>
<td>367 206</td>
<td>97 103</td>
</tr>
<tr>
<td>2</td>
<td>37.7</td>
<td>F</td>
<td>CFH (p.Arg1210Cys) + CFI (p.Asp519Asn) + THBD (p.Ala43Thr)</td>
<td>Yes</td>
<td>25.2</td>
<td>0.9</td>
<td>1.41 (44)</td>
<td>1.25 (51)</td>
<td>244 227</td>
<td>482 219</td>
<td>117 94</td>
</tr>
<tr>
<td>3</td>
<td>52.7</td>
<td>M</td>
<td>CFI (p.Ile140Thr)</td>
<td>No</td>
<td>24.3</td>
<td>22.7</td>
<td>1.03 (97)</td>
<td>1.00 (100)</td>
<td>180 256</td>
<td>467 371</td>
<td>312 292</td>
</tr>
<tr>
<td>4</td>
<td>34.8</td>
<td>F</td>
<td>CFI (p.Gly269Ser)</td>
<td>No</td>
<td>21.5</td>
<td>10.1</td>
<td>2.72 (29)</td>
<td>2.54 (22)</td>
<td>281 286</td>
<td>406 403</td>
<td>98 88</td>
</tr>
<tr>
<td>5</td>
<td>2.6</td>
<td>M</td>
<td>CFI (p.Asp519Asn)</td>
<td>No</td>
<td>21.4</td>
<td>15.9</td>
<td>0.38 (132)</td>
<td>0.44 (117)</td>
<td>261 299</td>
<td>517 426</td>
<td>68 105</td>
</tr>
<tr>
<td>6</td>
<td>1.3</td>
<td>F</td>
<td>Homozygous deletion at CFHR3/R1 locus</td>
<td>No</td>
<td>19.9</td>
<td>6.5</td>
<td>0.29 (128)</td>
<td>0.27 (138)</td>
<td>447 390</td>
<td>688 654</td>
<td>91 60</td>
</tr>
<tr>
<td>7(^-)</td>
<td>19.1</td>
<td>M</td>
<td>Anti-CFH antibody (titer, 27 IU)</td>
<td>No</td>
<td>19.8</td>
<td>14.2</td>
<td>1.33 (72)</td>
<td>1.20 (79)</td>
<td>245 167</td>
<td>390 325</td>
<td>236 178</td>
</tr>
<tr>
<td>8</td>
<td>5.4</td>
<td>F</td>
<td>MCP (p.Phe175Val)</td>
<td>No</td>
<td>14.0</td>
<td>13.5</td>
<td>1.28 (36)</td>
<td>0.52 (89)</td>
<td>300 420</td>
<td>682 423</td>
<td>46 78</td>
</tr>
<tr>
<td>9</td>
<td>13.3</td>
<td>M</td>
<td>Anti-CFH antibody (titer, 100 IU) + homozygous deletion at CFHR3/R1 locus</td>
<td>No</td>
<td>11.2</td>
<td>8.6</td>
<td>0.64 (110)</td>
<td>0.58 (122)</td>
<td>268 298</td>
<td>435 371</td>
<td>108 106</td>
</tr>
<tr>
<td>10</td>
<td>10.9</td>
<td>F</td>
<td>CFH (p.Gln950His) + homozygous deletion at CFHR3/R1 locus + anti-CFH antibody (titer, 230 IU)</td>
<td>Yes</td>
<td>6.4</td>
<td>1.2</td>
<td>0.95 (73)</td>
<td>0.66 (105)</td>
<td>180 239</td>
<td>466 221</td>
<td>88 88</td>
</tr>
</tbody>
</table>

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.

\(^-\)Eculizumab therapy was started as prevention of aHUS recurrence on kidney transplant.
Patients who chose to discontinue eculizumab maintenance treatment were monitored carefully using urine dipstick at home thrice weekly in order to detect disease reactivation early. In the event of detecting microscopic hematuria, patients were asked to return to the hospital immediately for further examination (including platelet count, hemoglobin, haptoglobin, lactate dehydrogenase, creatinine, and schistocyte levels, proteinuria, and dysregulated complement (genetic abnormalities and/or anti-CFH antibodies) and clearly had benefited from eculizumab therapy, having obtained clinical remission. Eight of the 10 patients had discontinued dialysis therapy, whereas the other 2 had never been dialyzed. Patients received eculizumab for a median of 5.6 (range, 0.4-14.2) months before its discontinuation. Figure 1 shows treatment management in each patient. Cumulative time off treatment was 95 (median, 9.3; range, 0.9-22.7) months.

In 5 cases, hemoglobinuria was detected at home by means of hemoglobin-positive urine dipstick. Subsequent blood and urine tests showed no association with signs of TMA in 2 of these patients and hemoglobinuria spontaneously subsided. In the 3 other patients, relapse was confirmed and eculizumab therapy was resumed. The relapses occurred within 6 weeks (mean, 37 days) of the last eculizumab dose, and peak serum creatinine levels at the time of relapse ranged from 2.3-3.4 mg/dL. All 3 patients experienced rapid remission (only 1 required hospitalization) and recovered completely, with serum creatinine levels returning to prediscontinuation values. The other 7 patients remained in remission with no signs of acute disease.

**DISCUSSION**

Our findings show that eculizumab maintenance treatment to prevent a relapse of aHUS can be discontinued and that discontinuation is relatively safe if specific measures to detect relapses early are systematically used. Discontinuing eculizumab therapy has been described previously in very limited experiences, with inconclusive results.22-26 The main rationale for discontinuing eculizumab therapy was to protect patients from the risk of the potentially devastating side effects of meningococcal infection, to which patients with complement deficiencies are exposed because of diminished capacity for complement-mediated lysis of bacteria.27,28 The risk of meningococcal infection due to eculizumab-induced complement is anything but negligible (1 event per patient per 20 years of treatment), and it also is reasonable to think that the infection is more severe in patients treated with eculizumab.

Eculizumab has become the frontline treatment for aHUS,7,29,30 and the standard schedule suggested for an adult patient includes an induction phase of 900 mg per week for 4 weeks, followed by 1,200 mg in week 5 and then 1,200 mg every 14 days as lifelong maintenance treatment.7 Eculizumab is highly effective; however, after aHUS is in stable remission, it may be difficult to motivate a patient to return to the hospital every other week of his or her life. Many of our patients were committed to discontinuing the drug therapy even though they had been informed that a relapse was very likely to occur eventually. After a patient has experienced a relapse, his or her commitment to regular drug infusions often becomes very strong. Paradoxically, the policy of discontinuation is made possible because of the efficacy of eculizumab itself, which means that a relapse is no longer the dramatic event it used to be when plasma exchange was the only therapy available.

Another reason for avoiding life-long maintenance treatment is to prevent other adverse events, such as immune-mediated drug reactions, including the theoretical risk of developing neutralizing anti-drug antibodies that ultimately would deprive the patient of a life-saving therapeutic resource. Additionally, eculizumab is among the most expensive life-long medical treatments. At a price of $5,617 per vial, the annual cost of standard maintenance treatment ranges from $100,860 (for body weight < 10 kg) to $578,100 (for an adult).30,32 The total cost per year of...
maintenance treatment for all 10 of our patients would have been more than $3.5 million, but our course led to a total saving of >$2.5 million.

All 3 patients who experienced relapse after eculizumab therapy discontinuation had CFH-related aHUS; therefore, knowing whether this gene is mutated may help predict the likelihood of a relapse. Although relapses were severe, resuming eculizumab therapy was effective immediately in controlling the disease, and serum creatinine levels returned to prediscontinuation values. We preferred using home urine dipstick to detect relapses rather than sophisticated but poorly accessible laboratory tests that can be performed only occasionally. The urine dipstick’s sensitivity and specificity cannot be calculated based on our limited data set, but all patients who experienced relapse were identified promptly (suggesting high sensitivity) and there were only 2 false-positive results (suggesting low specificity).

In conclusion, our experience supports the possibility of patients in stable remission discontinuing eculizumab treatment, but this decision may depend on the identified gene mutation. Such a policy also requires the full commitment of the patients, who need to be clearly informed about the risks involved and the importance of strict urine dipstick monitoring, particularly during acute intercurrent diseases. Better understanding of genotype/phenotype correlations in large data sets will certainly provide important clues about how to manage eculizumab maintenance treatment in such a way as to reduce the risks and costs of treatment while maximizing the benefits.

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REFERENCES


