Preservation of Renal Function in Atypical Hemolytic Uremic Syndrome by Eculizumab: A Case Report

Abstract

Genetic mutations in complement components are associated with the development of atypical hemolytic uremic syndrome (aHUS), a rare disease with high morbidity rate triggered by infections or unidentified factors. The uncontrolled activation of the alternative pathway of complement results in systemic endothelial damage leading to progressive development of renal failure. A previously healthy 8-month-old boy was referred to our hospital because of onset of fever, vomiting, and a single episode of nonbloody diarrhea. Acute kidney injury with preserved diuresis, hemolytic anemia, and thrombocytopenia were detected, and common protocols for management of HUS were followed without considerable improvement. The persistent low levels of complement component C3 led us to hypothesize the occurrence of aHUS. In fact, the child carried a specific mutation in complement factor H (Cfh; nonsense mutation in 3514G>T, serum levels of Cfh 138 mg/L, normal range 350–750). Given the lack of response to therapy and the occurrence of kidney failure requiring dialysis, we used eculizumab as rescue therapy, a monoclonal humanized antibody against the complement component C5. One week from the first administration, we observed significant improvement of all clinical and laboratory parameters with complete recovery from hemodialysis, even in the presence of systemic infections. Our case report shows that complement inhibiting treatment allows the preservation of renal function and avoids disease relapses during systemic infections. Pediatrics 2012;130:e1–e4
It is generally felt that atypical hemolytic uremic syndrome (aHUS) has heterogeneous causes. A genetic lack of complement inhibitors represents a major cause of aHUS, leading to uncontrolled complement activation with thrombotic microangiopathy. Plasma therapy (plasma infusion and/or plasma exchange) has empirically become the first-line treatment.\(^1\) The use of eculizumab (Soliris, Alexion Pharmaceuticals Cheshire, CT), a humanized monoclonal antibody against complement component C5, licensed for the treatment of paroxysmal nocturnal hemoglobinuria, has been recently approved for the therapy of aHUS in United States (September 2011) and in European Union (November 2011).

### PATIENT PRESENTATION

CD, a child born in April 2009, was admitted to our hospital in December 2009 for fever, vomiting, and a single episode of nonbloody diarrhea. The child presented the classic symptomatric triad of HUS: acute kidney injury with preserved diuresis, anemia, and thrombocytopenia (Table 1). The patient showed resistance to plasma infusion (21 infusions from January 3 to March 17, dosage: 10 mL/kg) and plasma exchange (9 sessions from March 20 to April 6 on alternate days). Because of the persistence of hypocomplementemia, we hypothesized that the patient had complement-associated aHUS. Mutation screening of complement regulator genes revealed a heterozygous complement factor H (Cfh) nonsense mutation 3514G>T (patient’s serum levels of Cfh 138 mg/L, normal range 350–750; Mario Negri Institute, Ranica, Bergamo, Italy). The mutation was inherited from the mother, who was asymptomatic without renal abnormalities, despite the presence of low levels of C3 and Cfh.

In March 2010, the clinical status of the patient worsened dramatically, with persistent vomiting, sweating, anorexia, and drowsiness without neurologic impairments. Hemodialysis was started (serum creatinine 2.51 mg/dL; serum urea nitrogen 79.9 mg/dL) because of the occurrence of congestive heart failure, and 3 packed red blood cell transfusions were administered. After consulting published reports on the use of eculizumab in aHUS,\(^2,3\) we obtained the authorization of the local ethical committee and the child’s parents for off-label use of this drug. Eculizumab was provided by Alexion and used as rescue therapy. It was administered in April after meningococcal vaccination. Plasma infusion and exchange were stopped after eculizumab administration. During the first month, it was administered on a weekly basis (300 mg, intravenously; patient’s weight 10 kg), then every 14 days for 2 months, and subsequently every 3 weeks up to the present. One week after the first administration, a significant improvement in the platelet count and lactate dehydrogenase values was already registered. Dialysis was discontinued 5 days after drug administration (creatinine 1.33 mg/dL; serum urea nitrogen 49 mg/dL). No additional packed red blood cell transfusions were necessary. Despite the onset of catheter-related sepsis by Staphylococcus aureus (June 2010), the overall improvement was progressive and persistent over 12 months (Table 1).

In September, the boy was admitted to nursery school, and no clinical relapses occurred, even in presence of 3 episodes of upper respiratory infections with fever.

### DISCUSSION

The pathogenesis of aHUS with factor H deficiency is due to the uncontrolled activation of the alternative pathway of complement resulting in systemic endothelial damage.\(^4\) The onset and relapses of aHUS are triggered by infection or unidentified factors. As was the case for our patient, there is usually a poor response to plasma therapy and a progressive development of renal failure.\(^1,4\) Between the different complement regulators screened in our patient and his relatives, we identified a single mutation in Cfh. This mutation (3514G>T) was originally described as a missense mutation of the last exon.\(^5\) Mutant protein has reduced binding to heparin, C3b/C3d, and endothelial cells. Heparin affinity chromatography revealed reduced binding of mutant protein to heparin, and surface plasmon resonance studies showed impaired binding to C3b and C3d.\(^6\) In addition, because the mutation was inherited by the healthy mother, our report confirms that this type of mutations have a penetrance of ~50%.\(^7\)

So far, the only therapeutic option available is early treatment with plasma infusion or plasma exchange at the onset of the disease,\(^1\) followed by a long-term

### TABLE 1 Main Laboratory Data

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</thead>
<tbody>
<tr>
<td>Hemoglobin g/dL (nv 12–18)</td>
<td>6.4</td>
<td>9.5</td>
<td>11.7</td>
<td>8.8</td>
<td>9.6</td>
<td>11.4</td>
</tr>
<tr>
<td>Haptoglobin g/L (nv 0.3–2)</td>
<td>0.08</td>
<td>0.07</td>
<td>0.07</td>
<td>0.69</td>
<td>0.93</td>
<td>0.95</td>
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<tr>
<td>Platelets (nv 150–450*10^12 mcr/L)</td>
<td>70</td>
<td>44</td>
<td>191</td>
<td>457</td>
<td>336</td>
<td>489</td>
</tr>
<tr>
<td>LDH UI/L (nv 300–800)</td>
<td>4577</td>
<td>3940</td>
<td>1125</td>
<td>770</td>
<td>581</td>
<td>540</td>
</tr>
<tr>
<td>Creatinine mg/dL (nv 0.4–0.8)</td>
<td>1.9</td>
<td>2.8</td>
<td>2.12</td>
<td>0.7</td>
<td>0.62</td>
<td>0.51</td>
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<tr>
<td>SUN mg/dL (nv 7.5–23.3)</td>
<td>77.5</td>
<td>55.6</td>
<td>35</td>
<td>31.3</td>
<td>24.2</td>
<td>17.7</td>
</tr>
<tr>
<td>Protein/creatinine ratio (nv &lt;0.20)</td>
<td>90</td>
<td>37.5</td>
<td>6.8</td>
<td>3.6</td>
<td>0.25</td>
<td>0.47</td>
</tr>
<tr>
<td>C3 g/L (nv 0.9–1.8)</td>
<td>0.54</td>
<td>0.45</td>
<td>0.48</td>
<td>0.69</td>
<td>0.58</td>
<td>0.78</td>
</tr>
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LDH, lactate dehydrogenase; nv, normal value; SUN, serum urea nitrogen.

* Pre-eculizumab.

\(^7\) 7 d from start of eculizumab.
prophylactic plasma therapy to prevent end-stage renal disease. Also if the guideline proposed had emphasized urgent and empirical plasmapheresis replacement with whole plasma fraction as the first option, patients with mutations that induce complete or partial factor H quantitative deficiency may be controlled by plasma infusions. Eculizumab is a recombinant humanized monoclonal antibody that specifically binds to the complement protein C5, inhibiting its cleavage by the C5 convertase, which prevents the generation of the terminal complement complex C5b-9. Because of the absence of complement inhibition in aHUS, permanent uncontrolled and excessive complement activation causes chronic platelet and endothelial cell activation, leading to thrombosis, inflammation, and occlusion of small vessels.

By reducing C5 activation in the absence of factor H, the use of eculizumab should be protective for host cells in aHUS. Moreover, eculizumab has been used in some cases of relapsing aHUS after kidney transplantation, and in few cases of a HUS in native kidney. Interestingly, eculizumab was also successfully used for the treatment of severe Shiga toxin–associated HUS in 3 children, each aged 3 years.

Unlike the majority of cases described in the literature in which this drug was introduced only after several relapses or in older patients, we found that eculizumab could be safely used in a 1-year-old patient during the first occurrence of aHUS. In the first case, the newborn with an early-onset of the disease (8 days) was treated with exchange transfusions followed by daily plasma infusions. At the fourth relapse, at 18 months of age, despite intensive plasma exchange (32 consecutive days), clinical response was poor until eculizumab was administered. Lapayraque then described a female child with an aHUS diagnosed at 7 months of age who was partially responsive to plasma therapy. All relapses of the disease were triggered by viral infections and managed by intensified plasma infusion. At age 7 years, after the tenth relapse and given the lack of response to plasma infusion, the patient was administered eculizumab with successful control of chronic thrombotic microangiopathy and a complete recovery of the renal function. Finally, Mache reported a case of a 17-year-old boy with relapsing unclassified aHUS and acute renal failure requiring hemodialysis. The plasma-exchange therapy was not effective in preventing HUS activity and chronic renal failure. The late use of eculizumab enabled to control microangiopathic hemolytic activity but could not prevent the development of end-stage renal failure, whereas early use of eculizumab may lead to a regression of fibrosis and thrombotic microangiopathy at the renal level.

Our case report shows that the use of eculizumab to inhibit the detrimental effects of complement on renal tissue helped preserve renal function and enabled to complete recovery from hemodialysis and protection from relapses, even during systemic infections. After administration of eculizumab, the child has been followed for 24 months without any relapse. Therefore, our experience suggests that eculizumab could be administered as first-line therapy in aHUS due to complement deficiencies. However, there are as yet no biomarkers advising when to stop treatment or to continue the drug administration as prophylaxis. We tried to stop eculizumab administration after 18 months of remission; however, after 45 days, the patient presented progressive reduction of platelet count and recurrence of proteinuria in the absence of any systemic symptoms. We thus reintroduced the drug, with immediate recovery of biochemical values. Therefore, this case report indicates that platelet count and proteinuria may be used as markers of early disease recurrence.

REFERENCES


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