Case Report: Benefits and Challenges of Long-term Eculizumab in Atypical Hemolytic Uremic Syndrome

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abstract

Atypical hemolytic uremic syndrome (aHUS) is caused by dysregulation of the complement system, leading to complement overactivation. A humanized anti-C5 monoclonal antibody, eculizumab, has been available for the treatment of aHUS since 2011. The long-term safety and efficacy of this novel drug in the pediatric population remain under review. We present a child with a hybrid CFH/CFHR3 gene who, having had multiple disease relapses despite optimal treatment with plasma exchange, commenced eculizumab therapy in August 2010. She remains relapse free in follow-up at 52 months, and treatment has been well tolerated. The risk of meningococcal disease during this treatment is recognized. Despite vaccination against meningococcal disease and appropriate antibiotic prophylaxis, our patient developed meningococcal bacteremia 30 months into treatment. She presented with nonspecific symptoms but recovered without sequelae with appropriate treatment. We recommend that children be vaccinated against invasive meningococcal infection before beginning eculizumab therapy and take appropriate antibiotic prophylaxis during treatment, and we suggest that vaccine responses should be checked and followed annually. Clinicians need to maintain a high index of suspicion for invasive meningococcal disease. Neither vaccination nor antibiotic prophylaxis provides complete protection in patients on eculizumab therapy. The appropriate dosage of eculizumab needed to achieve remission in aHUS in the pediatric population is unknown. Having achieved remission in our patient, we monitor eculizumab and CH50 levels to evaluate ongoing blockade of the terminal complement cascade. Such information may help guide dosing intervals in the future.

Atypical hemolytic uremic syndrome (aHUS) is a rare disorder characterized by thrombotic microangiopathy, thrombocytopenia, and renal failure. It is caused by dysregulation of the alternative complement pathway, leading to complement overactivation. The incidence of aHUS in the pediatric population is not well established, but recent data suggests an incidence of ~0.11 new cases per million population per year.1,2 aHUS is associated with significant morbidity and mortality, with ≤50% of cases progressing to end-stage renal disease or death.2,3 Approximately 60% of cases are associated with either an inherited or acquired abnormality of complement.4 Several mutations in genes responsible for the encoding of complement proteins have been identified in patients presenting with aHUS, such as mutations in CFH, factor I, membrane cofactor protein, thrombomodulin, C3, and factor B. Mutations in CFH account for ~25% of the genetic predisposition to aHUS.5

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Since 2011, eculizumab, a recombinant humanized anti-C5 monoclonal antibody, has been licensed to treat aHUS. It blocks activation of the terminal complement cascade and has been shown to be effective in treating aHUS. Earlier treatment with eculizumab leads to better preservation of renal function, and therefore early treatment in pediatric patients is recommended. In 2012, a hybrid $CFH/CFHR3$ gene consisting of $CFH$ exons 1 through 22 and $CFHR3$ exons 2 through 6 arising through microhomology-mediated deletion was identified in familial atypical hemolytic syndrome. Here we describe a 4-year experience of eculizumab treatment in an affected child from this family.

**CASE REPORT**

A previously well girl presented at 8 months of age with symptoms of bronchiolitis and associated fever. In addition to respiratory symptoms, she had 4 cm hepatomegaly. Laboratory investigations showed hemoglobin of 80 (96–148) g/L, platelet count of 99 (150–450) $\times 10^9$/L, and creatinine of 68 (15–50) $\mu$mol/L. Lactate dehydrogenase (LDH) was elevated at 5142 (230–600) U/L, with normal C3 and C4. Her urine had hematuria and proteinuria.

Renal biopsy demonstrated acute thrombotic microangiopathy (Fig 1). Screening for factor H and I autoantibodies was negative. Genetic testing showed a heterozygous deletion extending from $CFH$ intron 22 to the 5′ region of $CFHR3$, resulting in the formation of a $CFH/CFHR3$ hybrid gene. Of note, her mother developed severe preeclampsia at 31 weeks’ gestation and needed early delivery because of a rising creatinine. She had preeclampsia in a previous pregnancy. Her renal function deteriorated postpartum, necessitating acute hemodialysis and subsequent long-term peritoneal dialysis. Her LDH was 514 (50–150) U/L, with evidence of red cell fragmentation on blood film. Otherwise, there were no overt signs of HUS. Review of her renal biopsy showed subtle thrombotic microangiopathy with acute tubular necrosis. Genetic testing confirmed the same hybrid gene.

Our patient was initially treated with aggressive plasma exchange (PE) in the first 3 months (40 sessions) and was maintained on weekly PE over a period of 31 months, 212 sessions in total, as recommended by guidelines published by the European Study Group for Atypical HUS in 2009. She had adverse events on PE including electrolyte disturbances, hypocalcemia, venous access problems, and episodes of hypotension. She relapsed on multiple occasions, necessitating intensification of PE to stabilize hemolysis and creatinine in the setting of infections and vaccinations. This intensified regimen consisted of daily sessions for 5 days, alternate-day sessions for another 5 sessions, and weaning to once-weekly sessions when biochemical and clinical markers showed evidence of improvement (Fig 2).

In August 2010, she received her first dose of eculizumab, and PE was discontinued. She received 300 mg of eculizumab from initiation, with a dose adjustment to 600 mg for increased weight in August 2013. She has been treated with eculizumab for 52 months with complete remission and has not relapsed despite intercurrent illnesses. This information is highlighted in Fig 2, which illustrates hemoglobin, platelets, LDH, and creatinine levels over time, with multiple episodes of relapse demonstrated while on PE and her subsequent relapse-free course on a fortnightly eculizumab regimen.

She was vaccinated with both the quadrivalent meningococcal conjugate vaccine (serogroups A, C, W-135, and Y) and the meningococcal C vaccine before commencing treatment. After 30 months of treatment, she had an episode of meningococcal bacteremia. She was on amoxicillin prophylaxis for meningococcal disease at the time. She presented nonspecifically with fever, headache, and a macular rash. Her inflammatory markers were normal at presentation, but blood cultures were positive for *Neisseria meningitidis*, serogroup W135, at 28 hours, and blood polymerase chain reaction was also positive. The *N. meningitidis* strain showed intermediate penicillin sensitivity, with a minimal inhibitory concentration of 0.13 mg/L (sensitive <0.06 mg/L, resistant >0.25 mg/L). After 24 hours, inflammatory markers rise with neutrophilia of 18 (1.8–8.0) $\times 10^9$/L, C-reactive protein of 8.0 (0.06–0.25 mg/L).
169 (0–10) mg/L, and low platelets of 139 (150–450) \times 10^9/L. She did not develop proteinuria during this illness. She was treated with 7 days of intravenous ceftriaxone and made a full recovery.

After this illness, vaccine responses were found to be suboptimal, with serum bactericidal assay (rSBA) titers of 128, 2, 2, and 2 for serogroups A, C, W-135, and Y, respectively. An rSBA titer \( \geq 8 \) is considered protective (as quoted by the Meningococcal Reference Unit, Public Health England laboratories, Manchester). She has been revaccinated since this illness, with repeat vaccine responses in June 2014 showing protective levels with rSBA titers of 2048, 16, 2048, and 1024 for A, C, W-135, and Y, respectively.

Since commencing eculizumab treatment, she has had viral infections and vaccinations without relapses. We have reduced her antihypertensive treatment, and her creatinine has remained stable with no proteinuria. Figure 2 reinforces her stable course since eculizumab treatment commenced.

**DISCUSSION**

Atypical HUS is a rare condition associated with significant morbidity and mortality. While renal complications are most common, extrarenal disease occurs in \( \sim 20\% \) of cases, primarily neurologic and cardiovascular involvement. Eculizumab is an anti-C5 monoclonal antibody that prevents formation of the membrane attack complex and generation of C5b. Its use in aHUS was first reported in 2009. Although eculizumab has been licensed for use for \( >10 \) years in patients with paroxysmal nocturnal hemoglobinuria, experience in the pediatric population is limited.

There are no randomized controlled trials examining the treatment of aHUS. There are small case reports and case series and a prospective trial of patients who were successfully treated with eculizumab. Evidence suggests that earlier treatment leads to greater improvement in renal function and reversal of target organ damage. As in our case, many patients were able to discontinue plasma exchange after starting treatment. A systematic review article identified only 3 small uncontrolled studies indicating that eculizumab is effective in patients with aHUS, with a reduction in frequency of thrombotic microangiopathy events.

Data on the safety profile of eculizumab in aHUS are limited. The safety record in the short term is reassuring, with no cumulative toxicity noted. Case reports have been published with follow-up ranging from 1 to 3 years from initiation of treatment. Respiratory tract infections, hypertension, and gastrointestinal disturbances are the most common adverse events reported, and meningococcal septicemia has been described.

Administration of eculizumab in immunosuppressed patients may be complicated by meningococcal disease despite previous vaccination, as described in our patient. The bactericidal efficiency of the immune response is unknown in patients with complement deficiencies or under complement blockade, and the effectiveness of antibiotic prophylaxis may become problematic with the emergence of resistant strains going forward.

The recommended eculizumab level for complete blockage of C5 is not established in aHUS, because the

### TABLE 1 CH50 Levels and Concomitant Eculizumab Levels

<table>
<thead>
<tr>
<th>Date</th>
<th>CH50 (70%–130%)</th>
<th>Eculizumab Level*</th>
</tr>
</thead>
<tbody>
<tr>
<td>September 2, 2013</td>
<td>(&lt;10)</td>
<td>504</td>
</tr>
<tr>
<td>September 16, 2013</td>
<td>(&lt;10)</td>
<td>734</td>
</tr>
<tr>
<td>November 25, 2013</td>
<td>(&lt;10)</td>
<td>(&gt;800)</td>
</tr>
<tr>
<td>February 14, 2014</td>
<td>(&lt;10)</td>
<td>700</td>
</tr>
<tr>
<td>February 27, 2014</td>
<td>(&lt;10)</td>
<td>740</td>
</tr>
</tbody>
</table>

* Eculizumab level \( \geq 100 \mu g/mL \) for complete blockage as recommended by drug manufacturer, Alexion.
correlation between CH50 and eculizumab has not been documented in this disease. Previous studies have been carried out in the setting of paroxysmal nocturnal hemoglobinuria. The drug manufacturer (Alexion Pharmaceuticals, Cheshire, CT) recommends a level >100 µg/mL for complete blockage. During treatment, we monitored eculizumab levels and concomitant CH50 levels to ascertain whether complete blockage of the terminal complement cascade was achieved. Our patient had multiple eculizumab levels of >500 µg/mL despite being on the appropriate dose for age (Table 1). There are no studies with regard to reduction in dose or frequency if high levels persist. This highlights the need for more trials to determine appropriate pediatric dosages and assessment of treatment responses. Measurement of eculizumab levels, CH50, hemoglobin, platelets, LDH, and proteinuria may help validate dosing regimens in this population.

CONCLUSIONS
We report 4-year safety and efficacy of eculizumab in a 7-year-old girl with atypical HUS caused by a CFH/CFHHR3 hybrid gene mutation. In our experience, eculizumab is effective, safe, and well tolerated. Our patient has received eculizumab for 52 months on a fortnightly schedule, with no relapses and no side effects, even in the setting of infections and vaccinations, allowing cessation of plasma exchange therapy. We expect she will continue lifelong treatment. Notably, on presentation with meningococcal bacteremia, our patient had nonspecific symptoms. This observation highlights the need for a high clinical suspicion for invasive meningococcal disease, even with mild symptoms. All children should be vaccinated against meningococcal infection and treated with prophylactic antibiotics while on eculizumab therapy. In addition, children should have their vaccination titres checked annually, with advice to revaccinate children if immunity wanes. This is particularly true for children who have heavy proteinuria. Eculizumab levels, CH50, hemoglobin, platelets, LDH, and proteinuria should be studied to validate dosing regimens of eculizumab in this patient population.

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