Eculizumab is a safe and effective treatment in pediatric patients with atypical hemolytic uremic syndrome

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Atypical hemolytic uremic syndrome (aHUS) is caused by alternative complement pathway dysregulation, leading to systemic thrombotic microangiopathy (TMA) and severe end-organ damage. Based on 2 prospective studies in mostly adults and retrospective data in children, eculizumab, a terminal complement inhibitor, is approved for aHUS treatment. Here we prospectively evaluated efficacy and safety of weight-based dosing of eculizumab in eligible pediatric patients with aHUS in an open-label phase II study. The primary end point was complete TMA response by 26 weeks. Twenty-two patients (aged 5 months–17 years) were treated; 16 were newly diagnosed, 12 had no prior plasma exchange/infusion during current TMA symptomatology, 11 received baseline dialysis, and 2 had prior renal transplants. By week 26, 14 achieved a complete TMA response, 18 achieved hematologic normalization, and 16 had 25% or better improvement in serum creatinine. Plasma exchange/infusion was discontinued in all, and 9 of the 11 patients who required dialysis at baseline discontinued, whereas none initiated new dialysis. Eculizumab was well tolerated; no deaths or meningococcal infections occurred. Bone marrow failure, wrist fracture, and acute respiratory failure were reported as unrelated severe adverse events. Thus, our findings establish the efficacy and safety of eculizumab for pediatric patients with aHUS and are consistent with proposed immediate eculizumab initiation following diagnosis in children.

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Atypical hemolytic uremic syndrome (aHUS) is a progressive life-threatening thrombotic microangiopathy (TMA) associated with dysregulation of the complement alternative pathway.[1–3] Complement gene mutations (e.g., complement factor H [*CFH*], membrane cofactor protein [*MCP*], complement factor I [*CFI*], complement factor B [*CFB*], complement protein 3 [*C3*]), or factor H autoantibodies are identified in 50% to 60% of patients with aHUS.[4–6] Abnormalities in genes encoding thrombomodulin, plasminogen, and diacylglycerol kinase ε (DGKE)[7–9] occur in a small number of patients. Evidence of a genetic abnormality is not required for diagnosis.[4,10–13]

Although onset may occur at any age, 40% of patients develop aHUS by 18 years of age.[1,2,5] Clinical manifestations in children generally include anemia, thrombocytopenia, and acute kidney injury,[5] but peripheral gangrene,[14] arterial stenoses,[15] dilated cardiomyopathy, cardiorespiratory arrest,[16] and neurologic,[5,17] pulmonary,[11] and gastrointestinal complications[17] have been reported. Historically, aHUS was managed with plasma exchange/plasma infusion (PE/PI) and was associated with high morbidity and mortality rates,[1–3,5,18] with children having higher mortality than adults.[5] PE/PI may induce stabilization of hematologic parameters (but generally not significant renal function improvement),[19] is associated with complications, and impairs quality of life.[19,20]

The availability of eculizumab (Soliris, Alexion Pharmaceuticals, Inc., Cheshire, CT, USA)[21,22]— an anti-C5 monoclonal antibody and the first and only currently approved therapy for adult and pediatric patients—has profoundly changed aHUS management.[13,23] The efficacy and safety of

eculizumab was demonstrated in 2 prospective clinical trials of primarily adult patients with progressing TMA, long disease duration, and chronic kidney disease.[24,25] Use in children with aHUS is supported by case reports[13,16,26–37] and a retrospective study.[38,39] To further establish the efficacy and safety of eculizumab, a prospective clinical trial in patients with aHUS aged <18 years was conducted. Primary analysis results after 26 weeks of treatment are presented here.

RESULTS

Patients and treatment

Twenty-two patients were treated with eculizumab, and 19 (86%) completed the 26-week treatment period (Figure 1). Three patients discontinued treatment before week 26. Patients were exposed to eculizumab for a mean of 5.5 months (SD, 1.3 months).

Patients ranged in age from 5 months to 17 years (median age, 6.5 years) (Table 1). Median weight was 20 kg (range, 7−95 kg). Eleven (50%) had ≥1 identified complement gene abnormality or factor H autoantibody. One patient (5%) had a *DGKE* mutation. Six patients (27%; all <12 years of age) had a family history of aHUS. Sixteen patients (73%) were newly diagnosed. Ten patients (45%) received PE/PI at baseline. Overall, 18 patients (82%) had a baseline estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 m^2, including 10 patients (64%) who had an eGFR <15 mL/min

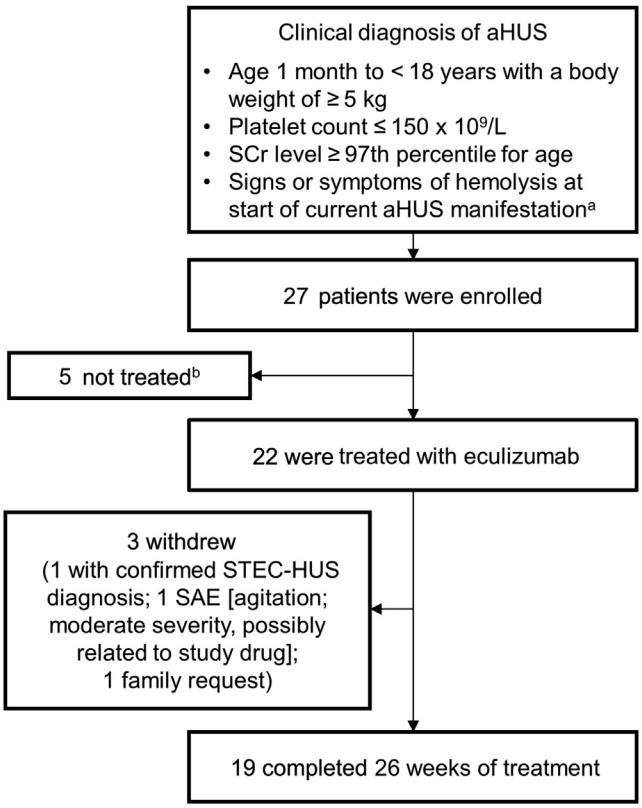

Figure 1 | Patient disposition. [a]LDH ≥ 1.5 × ULN; hemoglobin ≤ LLN; fragmented red blood cells with a negative Coombs test result. [b]One patient had a positive test for STEC infection, 1 had a normalized platelet count; 2 had a final diagnosis that was not aHUS, 1 had unspecified reasons. aHUS, atypical hemolytic uremic syndrome; LDH, lactate dehydrogenase; LLN, lower limit of normal; SAE, serious adverse event; SCr, serum creatinine; STEC, Shiga-like toxin-producing *Escherichia coli*; ULN, upper limit of normal.

Table 1 | Baseline demographics and disease characteristics

Variable	Intent-to-treat population (N = 22)
Median age at first infusion, yr (range)	6.5 (0.4–17)
Age range, n (%)	
1 mo to <23 mo (n = 5)	5 (23)
≥23 mo to <5 yr (n = 5)	5 (23)
≥5 to <12 yr (n = 8)	8 (36)
≥12 to <18 yr (n = 4)	4 (18)
Median weight, kg (range)	20 (7–95)
Female sex, n (%)	10 (45)
Race, n (%)	
Asian	2 (9)
Black or African American	0
White	18 (82)
Other	2 (9)
Patient-reported family history of aHUS, n (%)	6 (27)
Identified complement gene mutation, autoantibody, or polymorphism, n (%)	11 (50)
MCP[a]	3 (14)
CFH[b]	2 (9)
CFI[c]	2 (9)
CFH autoantibody	2 (9)
CFHR1/3 deletion (homozygous)	1 (5)
C3[d]	1 (5)
Identified *DGKE* mutation, n (%)[e]	1 (5)
Median duration from aHUS diagnosis until screening, mo (range)	0.6 (0–191)
Median duration of current manifestation to first dose, mo (range)	0.2 (0–4)
Newly diagnosed patients, n (%)	16 (73)
No PE/PI during current manifestation, n (%)	12 (55)
Dialysis at baseline, n (%)[f]	11 (50)
Previous renal transplant, n (%)	2 (9)
Mean platelet count, $\times 10^9$/l (SD)	88 (42)
Platelet count <150 $\times 10^9$/l, n (%)	22 (100)
Mean LDH level, U/l (SD)	1944 (1824)
LDH greater than ULN, n (%)	19 (86)
Mean hemoglobin concentration, g/dl (SD)	8.0 (1.5)
Mean serum creatinine level, mg/dl (SD)	1.7 (1.3)
Mean eGFR, ml/min per 1.73 m^2 (SD)	33 (30)
eGFR (ml/min per 1.73 m^2), n (%)	
<15	10 (46)
15–29	4 (18)
30–44	2 (9)
45–59	2 (9)
60–89	2 (9)
≥90	2 (9)

aHUS, atypical hemolytic uremic syndrome; *CFH*, complement factor H; *CFHR*, CFH-related protein; *CFI*, complement factor I; *DGKE*, diacylglycerol kinase ε; eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase; *MCP*, membrane cofactor protein; PE/PI, plasma exchange/infusion; ULN, upper limit of normal.
[a]*MCP* mutations: IVS3-2; p.Arg59Stop (c.175 C > T); p.Tyr189Asp (c.565 T > G).
[b]*CFH* mutations: p.Ser1191Leu and p.Val1197Ala; p.Ser1191Leu.
[c]*CFI* mutations: p.Ile340Thr (1019T > C) and p.Gly424Asp (1271G > A); p.Gly269Ser.
[d]*C3* mutation: p.Arg102Glyc (c.304C > G).
[e]After completion of the trial, patients with aHUS onset at <1 year of age and evidence of proteinuria (n = 3) were screened for *DGKE* mutations.
[f]Includes 1 patient who was receiving dialysis at baseline and discontinued dialysis during the baseline window before the first dose of eculizumab.