

# Critical appraisal of eculizumab for atypical hemolytic uremic syndrome

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**Abstract:** The biology of atypical hemolytic uremic syndrome has been shown to involve inability to limit activation of the alternative complement pathway, with subsequent damage to systemic endothelial beds and the vasculature, resulting in the prototypic findings of a thrombotic microangiopathy. Central to this process is the formation of the terminal membrane attack complex C5b-9. Recently, application of a monoclonal antibody that specifically binds to C5, eculizumab, became available to treat patients with atypical hemolytic uremic syndrome, replacing plasma exchange or infusion as primary therapy. This review focuses on the evidence, based on published clinical trials, case series, and case reports, on the efficacy and safety of this approach.

**Keywords:** acute kidney injury, ESRD, thrombotic microangiopathy, kidney, alternative complement pathway, complement blockade

## Introduction

This article is designed to provide a critical appraisal of the efficacy and safety of eculizumab in atypical hemolytic uremic syndrome (aHUS) in children and adults. We analyze published work based on the level of evidence from controlled trials through anecdotal case series and individual case reports. A MEDLINE search was performed to identify all relevant articles using the terms “atypical hemolytic uremic syndrome or aHUS” and “eculizumab.” We will review why it has become the treatment of choice for aHUS, and current limitations in the data.

Clinically, thrombotic microangiopathy (TMA) can occur in a number of diseases. However, the most commonly associated diseases are hemolytic uremic syndrome (HUS, either shiga-toxin-associated or aHUS), thrombotic thrombocytopenic purpura (TTP), and disseminated intravascular coagulation. HUS is characterized by the triad of microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and moderate to severe acute kidney injury, while TTP is defined by the pentad of MAHA, severe thrombocytopenia, fever, and, commonly, neurological impairment and milder acute kidney injury than in HUS, although such features may occur in HUS as well. Disseminated intravascular coagulation is rather distinct clinically, with the presence of an abnormal coagulation profile predominating, and often associated with sepsis.

aHUS is a prototypic TMA, caused by an inability to stop alternative pathway (AP) complement activation of the terminal membrane attack complex (MAC, C5b-9), thereby leading to damage of endothelial cell beds through the body, as well as the inability to block platelet and white blood cell activation in the circulation, which adds

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further to the microangiopathic process.<sup>1</sup> There is a clear genetic underpinning documented in nearly two-thirds of aHUS cases, relating to an inactivating mutation in proteins that downregulate AP activity (factor H, factor I, membrane cofactor protein [MCP or CD-46], thrombomodulin), or with an activating mutation in C3 or factor B that renders them constitutively overactive and not subject to modulation of activity, or through the formation of anti-factor H immunoglobulin G (IgG) antibodies (which commonly are associated with gene rearrangements or deletions in complement factor H [CFH]-related protein-1 and -3), all of which lead to AP generation of the MAC.

Additional cases of aHUS may be seen in a variety of circumstances that lead to AP complement overactivity coupled with the absence of sufficient regulation, including systemic lupus erythematosus, scleroderma, malignant hypertension, drugs,<sup>2-4</sup> and pregnancy, among other conditions. A recent study<sup>5</sup> of 193 patients that employed a high-throughput genetic screening process demonstrated the ability to find most mutations and raised the question of novel genetic variants in the pathogenesis of aHUS as well. The combination of a “predisposing factor” (genetic mutations/variants) with a “precipitating factor” (infection, drug, systemic disease, and others) may overcome the ability to control AP and, therefore, leads to the onset of aHUS. In a recent paper, Jodele et al<sup>6</sup> evaluated candidates for bone marrow transplant regarding genetic susceptibility to TMA and found that gene variants in complement regulators were more common among patients with transplant-associated TMA.

Common to aHUS, regardless of the cause, is the activation of the MAC, which starts with hydrolysis of complement factor C5 into C5a and C5b. The humanized monoclonal antibody, eculizumab, binds to the complement protein C5 with high affinity and inhibits its cleavage to C5a and C5b, thereby preventing the subsequent generation of the MAC. Eculizumab contains the murine complementarity-determining regions of the m5G1.1 monoclonal antibody, which were grafted onto the human framework light- and heavy-chain variable regions. The use of the germ line framework acceptor sequences was employed to minimize the potential for immunogenicity. The heavy-chain constant region of the parent antibody was replaced by components of both human IgG<sub>2</sub> and IgG<sub>4</sub> and, therefore, lacks the ability to activate complement and to bind Fc receptors. Such modifications should minimize the potential of eculizumab to induce pro-inflammatory responses.<sup>7,8</sup>

Eculizumab was approved in 2011 in the United States<sup>9</sup> and shortly thereafter in Europe.<sup>10</sup> Currently, the drug has

been used worldwide for the treatment of aHUS. A recent consensus document<sup>11</sup> almost uniformly recommended that, once the diagnosis of aHUS is made, eculizumab should be started immediately thereafter.

Reliable tools to monitor the response to eculizumab, outside of reversal of the clinical features of aHUS, are yet to be defined. In patients with paroxysmal nocturnal hemoglobinuria (PNH), a complement-mediated disease for which eculizumab was first approved, there seems to be a correlation between activity of 50% hemolytic complement (CH50) assay <10% and free eculizumab levels >50 µg/mL with efficacy of the drug in reducing hemolysis.<sup>12</sup> Although the use of CH50 is feasible in daily practice, there is no prospective data in patients with aHUS to confirm its usefulness, and a standard value to correlate with complement blockade is missing. In the National Health Service (NHS) Commissioning Policy on aHUS in England report,<sup>13</sup> monitoring was done by both CH50 and AP (AP50) hemolytic assay, where complete absence of hemolytic activity was used as criteria for adequate complement blockade. Based on these criteria, only two out of 43 patients treated needed increased dosing of eculizumab (one child and one adult post-transplant). Jodele et al<sup>14</sup> reported on the use of eculizumab to treat six children with severe hematopoietic stem cell transplant-TMA and adjusted the dose for a therapeutic level >99 µg/mL with resolution in four of six children. In this study, CH50 was used to monitor the level of complement blockade (CH50 level ≤4 complement activity enzyme units used in this series), and the authors found that children needed higher doses or smaller intervals of eculizumab infusions compared with the US FDA-approved regimen for children with aHUS. Two patients died despite dose intensification, but were critically ill.<sup>14</sup>

To assess the response to eculizumab in a different manner, and using retrospective data, Noris et al<sup>15</sup> documented a different biomarker of C5 blockade in patients with aHUS, using an ex vivo test that employed vascular endothelial cells that predicted clinical effectiveness of eculizumab in vivo and might guide drug dosing and/or timing. In this study, the authors demonstrated that aHUS patients with or without identified complement gene mutations or anti-CFH antibodies consistently and chronically activate complement on endothelium. Using an in vitro system with adenosine diphosphate-activated endothelial cell culture, blood samples from patients diagnosed clinically with aHUS, with or without overt TMA, induced more C3 and C5b-9 deposition than control sera, documenting the higher sensitivity (100%) of this ex vivo assay vs elevated plasma soluble (s)C5b-9 levels in detecting complement dysregulation in aHUS. In contrast,

this did not happen in patients with C3 glomerulopathy in which the AP is dysregulated in the fluid phase, reinforcing the concept of an endothelial-restricted complement deposition in aHUS. C5b-9 deposits were prevented by the anti-C5 antibody eculizumab. More work remains to understand what biomarker of disease activity and efficacy of eculizumab therapy might be appropriate. aHUS-associated mutant proteins may often effectively regulate complement in the fluid (blood) phase, which would explain the normal or near-normal circulating C3 levels in many mutation carriers. Gain-of-function mutations of CFB and C3 form a C3 convertase resistant to decay by endothelial cell/membrane-bound regulators. Such findings provide strong evidence that aHUS is a disease of unrestricted endothelial complement activation.

## Treatment of aHUS in the pre-eculizumab era

Following the landmark paper published by Bell et al in 1991,<sup>16</sup> plasma exchange/plasma infusion (PE/PI) became the initial treatment for most patients with aHUS. Initial reports<sup>17–19</sup> presented variable outcomes of patients with HUS in case series or reports in which laboratory assessments for differential diagnosis between shigatoxin HUS, aHUS, or TTP were not available. More recently, Noris et al,<sup>20</sup> in an analysis of 273 patients with either sporadic (n=191) or familial (n=82) aHUS and treated with PE/PI, found that two-thirds of adult patients had a bad outcome (dialysis or death) in a 3-year follow-up, which varied according to genotype. They reported a mortality rate of 8% and 11%, after first manifestation and 3 years of follow-up, respectively. Despite case reports of “good” outcomes with plasma therapy (three and five patients, respectively),<sup>21,22</sup> in a recent report from the French group (n=214 patients), the mortality rate was higher in children than adults (8% vs 2%) after 4 years of follow-up, with fatal outcomes, despite initial plasma therapy.<sup>23,24</sup> Cataland et al,<sup>25</sup> in a retrospective registry analysis of 19 patients diagnosed with aHUS, found that only six of the 16 patients treated with PE/PI had a complete hematologic and kidney recovery (and in contrast to seven of the nine patients treated with eculizumab). Although the genotype–phenotype correlation data indicate that *MCP* mutations are associated with a better prognosis than *CFH* mutations, this is not always straightforward, since there are patients who present severe and life-threatening manifestations with different degrees of response to plasma therapy independently of having an identifiable mutation or not.<sup>22,26,27</sup>

Among the potential risk factors for apheresis-related complications in low-weight patients, such as children

and small adults, are those related to the relatively large extracorporeal volume and the difficulties related to ensuring adequate vascular access. There is an almost 50% incidence of any adverse event including hypotension, symptomatic hypocalcemia, allergic reactions, and catheter-related thrombosis, and 1% death rate, in patients undergoing plasma-exchange therapies.<sup>28</sup>

De et al<sup>29</sup> published a review of 28 pediatric cases of aHUS with identified mutations who were treated with supportive measures, PE/PI, kidney transplant ( $\pm$ PE/PI), or liver/combined liver–kidney transplantation in the pre-eculizumab era. Overall, 13 of the 28 patients either died or had a relapse, and 15 recovered and were well until last follow-up (the latter included five patients with *MCP* mutations). Among the 20 patients with *CFH* mutations (homozygous or compound heterozygotes), ten either died or relapsed and ten recovered. Three patients with anti-factor H antibodies had poor outcomes (one needed dialysis and two had multiple relapses). The authors concluded that, despite major progress in the understanding of the underlying pathogenetic mechanisms, aHUS remains a severe childhood disease with potential adverse outcomes, including the development of end-stage renal disease (ESRD), disease recurrence after transplantation, and death.

## Analysis of the published data for eculizumab in aHUS

### Prospective controlled trials of eculizumab in patients with aHUS

In 2013, Legendre et al published the results of the first prospective trials of eculizumab in aHUS conducted in Europe and North America with patients 12 years of age or older.<sup>30</sup> These trials had followed upon dozens of anecdotal reports of the use of eculizumab for the treatment of aHUS, which we review later in this article.

Patients were enrolled in two prospective trials according to levels of kidney and hematologic abnormalities:

Trial 1 (“progressive TMA”): kidney impairment (creatinine  $\geq$  upper limit of normal [ULN]) and persistent thrombocytopenia ( $<150 \times 10^9/L$ ) with evidence of hemolysis (low haptoglobin, presence of schistocytes, or lactate dehydrogenase [LDH]  $\geq$  ULN) despite four or more sessions of plasma therapy (PE/PI).

Trial 2 (“longstanding TMA”): kidney impairment (creatinine  $\geq$  ULN) with evidence of hemolysis (low haptoglobin, presence of schistocytes, or LDH  $\geq$  ULN) and no platelet count decrease  $>25\%$  during 8 consecutive weeks during plasma therapy.

Among other inclusion criteria were a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) activity >5%, and shigatoxin negative in stools during enrollment screening. Gene mutations or anti-factor H antibodies were not a prerequisite.

While end points were different for each trial (Table 1<sup>30,31</sup>), common safety issues were assessed. Both groups received eculizumab for 26 weeks according to a previously predetermined dosing schedule<sup>9</sup> and were allowed to continue in an extension-phase study, with the 2-year follow-up results published recently by Licht et al.<sup>31</sup>

In the “progressive TMA trial,” the primary end point was to hinder “complement-mediated TMA,” defined by a composite measure (Table 1). At the beginning of the trial, 17 patients (one adolescent) were enrolled, and the median interval between diagnosis of aHUS and screening was 9.7 months. Time from onset of the then-prevalent manifestation of TMA to screening was 0.8 months.<sup>31</sup> Except for one patient, all received plasma therapy during the week before eculizumab was started. All patients had an eGFR (estimated glomerular filtration rate) below 60 mL/min/1.73 m<sup>2</sup> for 17 days (median duration), while eleven patients received dialysis either before or at first dose of eculizumab, with a median (interquartile range) duration of 22 (1–27) days. In this study, seven patients had prior kidney transplants. No mutations or factor-H antibodies were found in 24% of

patients. Patients received eculizumab ranging from 2 weeks to 90 weeks in duration (median 64 weeks on treatment), and 15/17 patients completed 26 weeks of treatment.

Complete TMA response (criteria described in Table 1) was reached by 65% and 76% of patients at week 26 and 2 years, respectively. Many additional analyses were performed based on the data in this trial. Half of the patients with thrombocytopenia at baseline had a normal platelet count after 1 week, which remained normal at week 26 in almost 90% of patients. Normalization of platelet count and LDH levels occurred in near 90% of patients, and the great majority of patients enrolled did not receive PE or PI for the entire duration of the study. After eculizumab treatment, kidney function improved progressively with an eGFR increase of 32 mL/min/1.73 m<sup>2</sup> from baseline to week 26. In 80% of patients, dialysis was discontinued, and they remained dialysis-free through the treatment period (26 weeks).

Among the 15 patients with aHUS who completed 26 weeks of eculizumab, 13 were enrolled in the extension phase.<sup>31</sup> At the 2-year time point, eleven of 13 patients remained on eculizumab (two had withdrawn because of decrease in kidney function). Platelet count was normalized in nearly 90% at the 1-year and 2-year cutoffs (two patients were withdrawn from the study before 26 weeks of treatment because of lack of improvement). Improvements in eGFR were maintained after the first year of this trial. eGFR increased from 33 mL/min/1.73 m<sup>2</sup> to 37 mL/min/1.73 m<sup>2</sup> between week 26 and the 2-year cutoff, with an absolute mean (SD) eGFR of 56 (40) mL/min/1.73 m<sup>2</sup> at 26 weeks, and 56 (30) mL/min/1.73 m<sup>2</sup> at the 2-year data analysis. Four of the five patients (80%) were able to stop dialysis (one before the first dose of eculizumab and three at a mean of 1 week after the starting on eculizumab). One patient needed to start dialysis during the 26-week study period (this patient discontinued the study and was not included in the 2-year analysis). Another patient started dialysis on study day 444, and also discontinued. In summary, two patients were on dialysis at the 2-year cutoff.<sup>31</sup> There was the same number of transplanted patients, and none lost their graft.

In the second controlled trial, comprising “patients with longstanding TMA,”<sup>30</sup> patients were eligible for study entry if they had kidney impairment, stabilization in platelet count for at least 8 weeks before the first dose of eculizumab, and received plasma therapy at least once every 2 weeks (but no more than three times per week). The primary end point (Table 1) for this trial was “TMA event-free status” for at least 12 weeks in duration. The interval between diagnosis and screening was longer (median, 48.3 months) than seen

**Table 1** Criteria for response to eculizumab in prospective trials

Inhibition of “complement-mediated TMA” (progressive TMA trial) <sup>30</sup>	TMA event-free status (longstanding TMA trial) <sup>31</sup>
Normal platelet count and normal LDH level sustained for at least two consecutive measurements over a period of at least 4 weeks	No decrease in platelet count of >25%, no plasma exchange or infusion use, no initiation of dialysis, and normalization of hematologic values (a normal platelet count and LDH level, sustained for at least two consecutive measurements over a period of at least 4 weeks)
Secondary end points included measures of renal function, changes in health-related quality of life, pharmacokinetics and pharmacodynamics, and safety and tolerability	Secondary end points included measures of kidney function, changes in health-related quality of life, pharmacokinetics and pharmacodynamics, and safety and tolerability

**Abbreviations:** LDH, lactate dehydrogenase; TMA, thrombotic microangiopathy.

in the progressive TMA trial discussed.<sup>30</sup> In the longstanding TMA trial, 35% of the participants had no identified mutation in AP complement or the presence of anti-factor H antibodies. The majority of patients had chronic renal disease (eGFR below 60 mL/min/1.73 m<sup>2</sup> for a median of 75 months before treatment with eculizumab; two patients on dialysis), and with the majority of patients being treated with plasma therapy for 10 months (median). Time from onset of the clinical manifestation of aHUS to screening was 8.6 months (median), and all patients received PE/PI before eculizumab. The median (range) duration of dialysis during the current manifestation was 1.7 (0.32–3) years. Eight patients had a prior kidney transplant.<sup>31</sup>

In this “longstanding TMA” trial, complete TMA response (criteria detailed in Table 1) increased from 25% at 26 weeks, to 55% at the 2-year cutoff. Treatment with eculizumab varied in length from 26 weeks to 74 weeks (median 62 weeks). By week 26, 80% of the patients met the primary study end point noted above; four patients did not achieve the proposed end point because of variations in platelet count, although levels were within normal limits. All patients stopped plasma therapy, and none started new dialysis.

After starting eculizumab, eGFR increased from 6 mL/min/1.73 m<sup>2</sup> to 9 mL/min/1.73 m<sup>2</sup> between baseline and week 60; the absolute mean (SD) eGFR also increased from 37 (21) mL/min/1.73 m<sup>2</sup> to 40 (18) mL/min/1.73 m<sup>2</sup> at the 2-year time point. Thereafter, initial eGFR improvements were maintained during the 2-year eculizumab treatment. Two patients required dialysis at baseline: one was on dialysis at the 2-year analysis, and the other received hemodialysis until renal transplantation (on day 217). During the 2 years of the study, one patient started dialysis (days 695–696) during admission for an intestinal hemorrhage and died of that complication. There were no new kidney transplants or graft losses.

Of the 20 patients (five adolescents) who completed the initial 26-week study, 19 entered the extension period, with eculizumab continued up to 78 weeks. Eighteen patients remained on treatment with eculizumab until the data analysis at 2 years.<sup>31</sup> The median (range) duration of eculizumab exposure in this trial was 0.31 (0.07–0.35) years.

Both in the “Progressing TMA trial” and in the “Longstanding TMA trial,” earlier initiation of eculizumab (time between the current manifestation and enrollment) was associated with a greater improvement in the eGFR. Eculizumab responses in the primary end points were seen in patients regardless of identified genetic mutations

or CFH autoantibodies, both in the initial and extension phases.<sup>30,31</sup>

In both trials, a significant improvement in health-related quality of life (QOL) was seen with eculizumab treatment.<sup>30</sup> Quality of life started improving after 1 week in the first trial and 3 weeks in the second trial, and was maintained over the 2 years of treatment.<sup>31</sup>

The dosing of eculizumab was designed to achieve a minimum blood concentration of 50–100 µg/mL to ensure complete complement blockade and to provide sustained low levels of free C5 and high levels of C5 cleavage suppression.<sup>30</sup> A biomarker of terminal complement activity remained inhibited over 2 years in both studies,<sup>31</sup> as measured by a modified CH50 assay (method not described).

### Open-label, single-group, multicenter, multinational clinical trial in adult patients

This clinical trial, performed after those discussed<sup>30,31</sup> and registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) as NCT01194973,<sup>32</sup> was conducted in adult patients with aHUS. This was a 26-week, open-label, nonrandomized, single-group, multicenter trial of eculizumab in patients with aHUS in which patients could continue to receive eculizumab in an extension phase. Adult patients (≥18 years of age) with a diagnosis of aHUS were enrolled at 23 centers in North America and Europe. Eligible patients had platelet counts <150×10<sup>9</sup>/L, hemoglobin levels ≤ the lower limit of the normal range, LDH levels ≥1.5 times above ULN, serum creatinine levels at or above ULN at screening, ADAMTS13 activity ≥5%, and no positive shigatoxin-producing *Escherichia coli* test. An identified complement gene mutation, associated polymorphism, or factor H autoantibody was not required. Patients were categorized according to whether they received PE/PI or not during the pretreatment period, defined as beginning on the start date of the current aHUS manifestation up to the first dose of eculizumab.

Forty-one adult patients with aHUS were treated; 38 (93%) completed the initial 26-week clinical study period and 21 (51%) continued treatment of 1 year during the optional extension period. Twenty patients (49%) had one or multiple identified mutations in complement genes and/or anti-factor H antibody. Thirty patients (73%) were enrolled during their first identified clinical TMA manifestation. At screening, the mean (SD) platelet count was 119.1 (66.1)×10<sup>9</sup>/L, mean haptoglobin was 0.6 (0.4) g/L, and mean LDH level was 492.9 (500.9) U/L. Thirty-five patients (85%) received PE/PI before eculizumab (mean, 9.6 sessions; range, 1–26) during the pretreatment period. Twenty-four patients (59%) were receiving dialysis at

baseline, and nine (22%) had a history of prior renal transplantation. Thirty-three patients (80%) had chronic kidney disease stage 4 or 5 (eGFR <30 mL/min/1.73 m<sup>2</sup>).

A prespecified exploratory analysis<sup>33</sup> was conducted as part of the trial to investigate the effect of terminal complement blockade on several biological markers associated with proximal and terminal complement overstimulation, inflammation, damage of endothelial cells, and coagulation markers, in addition to kidney injury, in patients with aHUS. Various biomarkers (plasma complement Ba, serum soluble tumor necrosis factor receptor-1 [sTNFR1], plasma prothrombin fragment 112 [F112], plasma thrombomodulin, urinary cystatin C, tissue inhibitor of metalloproteinases-1, b2-microglobulin [b2-M], liver fatty acid binding protein [L-FABP-1], creatinine, sC5b-9, and C5a) were used in this study, from either serum, ethylenediaminetetraacetic acid plasma, or urine samples obtained from patients with aHUS at baseline, before eculizumab treatment, and at weeks 1–3, 4–6, 12–17, 26–33, 38–42, and 49–54 during eculizumab treatment. Levels of plasma and serum markers were evaluated from healthy volunteers and patients with aHUS at baseline and at regular intervals during eculizumab treatment over the course of a 1-year period; markers in urine were evaluated over the course of 26 weeks of eculizumab treatment.

At baseline, all biomarkers were elevated significantly in the majority of patients with aHUS compared to levels measured in adult healthy volunteers; 69%–83% of patients with aHUS also showed significantly elevated levels of candidate renal injury biomarkers (ninefold to 48-fold higher than levels measured in healthy people). Levels of these biological markers were increased in patients who presented hematologic improvement from screening to the first dose of eculizumab, including those patients receiving plasma therapy.<sup>33</sup>

Eculizumab treatment reduced terminal complement activation (C5a and sC5b-9) and selected renal injury markers (clusterin, cystatin-C, b2-M, and L-FABP-1) to levels observed in the healthy volunteers. It also significantly reduced inflammation (sTNFR1), coagulation (prothrombin F112 and D-dimer), and endothelial damage (thrombomodulin) biomarkers compared to pretreatment levels (and frequently to levels seen in healthy individuals). Although AP activation and endothelial activation markers decreased, their mean levels were still elevated compared to healthy volunteers. This may reflect persistent complement activation in aHUS, even though terminal complement blockade with eculizumab was achieved.<sup>33</sup> There were no differences in biomarker assessment between patients who were or were not treated with plasma therapy before enrollment. Unfortunately, controls consisting of patients with similar degrees of chronic

kidney disease but without aHUS were not studied, so the meaning of the changes must be interpreted cautiously. At present, there is no uniformly agreed-upon biomarker of either disease activity or response to eculizumab.

### Anecdotal case reports of use of eculizumab in patients with aHUS

Tables 2<sup>34–49</sup> and 3<sup>22,50–78</sup> present the case reports of adult and pediatric patients with aHUS who received eculizumab according to the current label-approved schedule. We were able to find that 39 adults and 38 children were treated in the absence of a clinical trial in the published literature. Overall hematologic and kidney responses to eculizumab, as defined and judged by the authors of the case reports, were 90% and 56% for adults, respectively, and 100% both hematologic and kidney response in children receiving eculizumab. Where applicable, we describe the precipitating factor of ongoing TMA, herein termed the “complement-amplifying condition.” The reports in which eculizumab was used for diseases other than aHUS are not mentioned in this review. The reports in which eculizumab was used in a non-FDA-approved dosing schedule are mentioned in Table 4.

### Eculizumab and kidney transplantation

Recent studies have shown that the risk of post-transplant recurrence of aHUS is linked to the underlying genetic abnormality.<sup>79,80</sup> Higher risks are seen in patients with mutations in circulating complement proteins and regulators genes, in contrast to patients with mutations in *MCP* (*CD-46*) who generally, but not always (such as when the MCP mutation is combined with another mutation or high-risk polymorphism), achieve a good kidney transplant outcome. Recurrence of aHUS is shown to have dismal graft survival,<sup>80</sup> and led to the recommendation, therefore, in the pre-eculizumab era, that isolated renal transplantation was contraindicated in aHUS patients. Combined kidney–liver transplantation and prophylactic PE have been used to prevent post-transplant recurrences with variable outcomes.<sup>81</sup> More recently, evidence on the benefits of eculizumab in the prevention and treatment of aHUS recurrence has been demonstrated (Table 4).

### Retrospective, multicenter review of eculizumab use in renal transplant recipients

Zuber et al conducted a retrospective, multicenter study to assess eculizumab for the prevention or treatment of post-transplant manifestations in patients with aHUS.<sup>79,82</sup> From the 22 patients included in the study, 13 patients were enrolled

**Table 2** Anecdotal case reports using eculizumab in aHUS in adults

Author (year)	Population and complement-amplifying condition	Number of patients treated with eculizumab	Outcome with eculizumab
Sevinc et al (2015) <sup>46</sup>	Woman aged 32 years with plasma-resistant aHUS and infection	1	Hematologic recovery; stopped dialysis after 3 months
Thajudeen et al (2013) <sup>47</sup>	Man aged 51 years with eculizumab first-line treatment and trauma	1	Hematologic recovery; stopped dialysis after 2.5 months
Sengul Samanci et al (2015) <sup>45</sup>	Man aged 51 years with plasma-resistant aHUS and severe hypertension	1	Hematologic recovery; remained dialysis dependent
Rafiq et al (2015) <sup>42</sup>	Woman aged 59 years with recurrent TMA and accelerated hypertension/illicit drug use	1	Noncompliant and lost to follow-up
Nguyen et al (2014) <sup>39</sup>	Man aged 62 years with CKD3, DM2, and biopsy with IgA vasculitis relapse of TMA despite 14 days of PE and 1 month of rituximab	1	Hematologic recovery; remained dialysis dependent
Rigothier et al (2015) <sup>43</sup>	Adult with distal angiopathy and ESRD	1	Remission of distal angiopathy; hematologic recovery; successful kidney transplantation
Ohanian et al (2011) <sup>40</sup>	Woman aged 50 years with ischemic colitis and neurologic impairment	1	Renal and neurologic improvement after third dose; hematologic improvement after sixth dose
Salem et al (2013) <sup>44</sup>	Woman aged 66 years with shigatoxin-negative bloody diarrhea, seizures, and coma	1	Stopped dialysis after third dose; neurologic recovery at week 7
Povey et al (2014) <sup>41</sup>	Woman aged 21 years with neurologic involvement (PRES) and past history of TMA	1	Neurologic and hematologic recovery; stopped dialysis after 3.5 months
David et al (2013) <sup>36</sup>	Woman aged 23 years with SRD and TMA unresponsive to PE and steroids and third trimester of pregnancy	1	Hematologic and kidney recovery; complete resolution of SRD, and eyes remained stable at 2-month follow-up
Ardissino et al (2013) <sup>34</sup>	Woman aged 26 years with relapse of TMA after 39 sessions of PE during pregnancy and strong family history of aHUS	1	Eculizumab infused at 26th week of pregnancy with hematologic and kidney recovery; patient delivered a healthy baby girl at 38th week with no signs of TMA
Mussoni et al (2014) <sup>38</sup>			
Zschiedrich et al (2013) <sup>49</sup>	Woman aged 31 years with plasma-resistant postpartum aHUS	1	Eculizumab started at day 18 after diagnosis with full clinical resolution and creatinine 1.0 mg/dL
Tsai and Kuo (2014) <sup>48</sup>	aHUS was defined by MAHA, thrombocytopenia, and renal failure with plasma ADAMTS13 activity >10%. Other causes of the syndrome of MAHA and thrombocytopenia, such as DIC, systemic autoimmune disorders, lupus anticoagulants, metastatic neoplasms, shigatoxin, or neuraminidase-associated HUS, were excluded Case 1: patient presented with bloody diarrhea negative for shigatoxins Case 2: patient presented 3 months after undergoing autologous HSCT for advanced multiple myeloma Case 3: patient had recurrent episodes of severe hypertension accompanied by mild renal insufficiency and MAHA for 4.5 years before he was found to have aHUS Case 4: patient presented at 22 weeks of her third pregnancy and was initially assumed to have preeclampsia; however, her disease persisted after termination of pregnancy Case 5: patient had kidney biopsy performed for renal failure at 3 weeks after her seventh triweekly course of chemotherapy with gemcitabine and carboplatin for metastatic cholangiocarcinoma	5	After eculizumab infusion, platelet count began to exhibit steady increase within 3 days in each of the 5 courses in cases 1–4. No increase in platelet count occurred in case 5 while she was being treated with eculizumab. LDH normalized by day 14 in cases 3 and 4 and by day 70 in case 2; it did not normalize by day 21 in case 1 and by day 84 in case 5. Improvement of renal function by 1 stage was observed: By day 14 in case 4 By day 63 in case 3 By day 378 in case 2 (with further improvement by 1 stage by day 483)

(Continued)

**Table 2** (Continued)

Author (year)	Population and complement-amplifying condition	Number of patients treated with eculizumab	Outcome with eculizumab
Fakhouri et al (2014) <sup>37</sup>	19 patients who had received four or more weekly 900 mg infusions of eculizumab were identified through a query sent to all nephrology centers in France aHUS was defined as three or more of the following: acute kidney injury (serum creatinine >1.4 mg/dL [120 μmol/L]), mechanical hemolytic anemia, thrombocytopenia, and the presence of TMA features in a kidney biopsy specimen For first-line therapy, 16 patients underwent plasma exchange and 3 patients received eculizumab	19	Median time between aHUS onset and eculizumab therapy initiation was 6 days (range, 1–60 days), and median time to platelet count normalization after eculizumab therapy initiation was 6 days (range, 2–42 days). At the 3-month follow-up, 4 patients still required dialysis, 8 had non-dialysis-dependent CKD, and 7 had normalized kidney function. At last follow-up (range, 4–22 months), 3 patients remained dialysis dependent, 7 had nondialysis-dependent CKD (estimated glomerular filtration rate, 17–55 mL/min/1.73 m <sup>2</sup> ), and 9 had normal kidney function. Risks of reaching end-stage renal disease within 3 months and 1 year of aHUS onset were reduced by half in eculizumab-treated patients compared with recent historical controls
Ardissino et al (2014) <sup>35</sup>	Three cases of patients with aHUS and CKD (case 3 post-kidney transplant) who developed skin lesions that completely recovered when disease-specific treatment was established One patient responded to plasma therapy, and 2 also received eculizumab	2	Complete recovery of active skin lesions and hematologic parameters after eculizumab treatment

**Abbreviations:** ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; aHUS, atypical hemolytic uremic syndrome; CKD, chronic kidney disease; CKD3, chronic kidney disease stage 3; DIC, disseminated intravascular coagulation; DM2, type 2 diabetes mellitus; ESRD, end-stage renal disease; HSCT, hematopoietic stem cell therapy; HUS, hemolytic uremic syndrome; IgA, immunoglobulin A; LDH, lactate dehydrogenase; MAHA, microangiopathic hemolytic anemia; PE, plasma exchange; PRES, posterior reversible encephalopathy syndrome; SRD, serous retinal detachment; TMA, thrombotic microangiopathy.

in Europe<sup>82</sup> and nine were reviewed from the published literature.<sup>83–85</sup> Cases were reported in two groups: 1) patients who received eculizumab prior to transplantation to prevent subsequent TMA manifestations (n=9); and 2) patients who received eculizumab to treat post-transplant aHUS manifestations (n=13). Individual patient information describing eculizumab use prior to the transplantation is included in Table 4.<sup>52,53,73,79,82,86–98</sup>

### Use of eculizumab prior to transplantation (n=9)

Nine patients received eculizumab prior to transplantation to prevent post-transplant aHUS manifestations and allograft loss. Five patients had heterozygous mutations in *CFH*, three had a large *CFH/CFHR1* nonhomologous recombination, and one had a gain-of-function C3 mutation. Three patients had received four kidney transplants, all lost to post-transplant aHUS manifestations. Median age at time of present transplant was 9 years (range, 6.4–41.0 years). Two patients had preformed donor-specific antibodies with low titer (mean fluorescence intensity <1,000) at the time of transplantation. Strategy around the use of eculizumab consisted of one of the

following three methods: 1) PE started just before transplantation, then switched to eculizumab after transplantation (n=2); 2) eculizumab initiated 1 week or more before transplantation (n=2); and 3) eculizumab initiated ≤24 hours before transplantation with additional dose immediately before (n=1) or within 24 hours after (n=4) transplantation. Eight of nine patients treated with eculizumab maintained allograft function and experienced no additional post-transplant aHUS manifestations from 2–39 months of follow-up (mean 14.5 months). One allograft (case #8, Zuber et al<sup>82</sup>) was lost to immediate arterial thrombosis, despite undetectable CH50 activity. This patient was ultimately successfully retransplanted under peri-transplant eculizumab therapy.<sup>11</sup> No significant infectious complications were reported.

### Post-transplant treatment of aHUS with eculizumab (n=13)

From the 13 patients who received eculizumab to treat post-transplant aHUS, two received it because of intolerance to plasma therapy or convenience. Ten patients presented with plasma-resistant aHUS. One was treated with complement



**Table 3** Anecdotal case reports of use of eculizumab in children and adolescents with aHUS

Author (year)	Case presentation and complement-amplifying condition	Number of patients treated with eculizumab	Outcome with eculizumab
Diamante Chiodini et al (2014) <sup>60</sup>	Boy aged 8 years with shigatoxin-negative bloody diarrhea and severe neurologic impairment resistant to plasma therapy	1	Eculizumab started on day 37 with complete recovery of neurologic and hematologic parameters and improvement in kidney function (stopped dialysis after first dose)
Coppo et al (2015) <sup>58</sup>	Girl aged 4 years with lupus nephritis resistant to conventional therapy and features of aHUS	1	Prompt remission of vasculitis, proteinuria, and hematuria; normalization of renal function; 2 attempts to withdraw eculizumab followed by severe relapses and rescued by reinstating treatment; received eculizumab treatment for >17 months without relevant side effects.
Vaisbich et al (2013) <sup>77</sup>	Boy aged 14 months with aHUS, hypertension, and proteinuria	1	Hematologic improvement; stopped dialysis after second dose of eculizumab
Hisano et al (2015) <sup>65</sup>	Boy aged 4 years with aHUS, nonoliguric kidney injury, macrohematuria, and anti-factor H antibodies	1	Macrohematuria disappeared after second dose; discharged with complete hematologic and kidney resolution
Noone et al (2012) <sup>71</sup>	Boy aged 13 years with post-kidney transplant TMA, AMR, and aHUS	1	Kidney function recovery with AMR treatment and eculizumab; graft lost due to BK (polyomavirus) nephropathy
Cullinan et al (2015) <sup>59</sup>	Girl aged 8 months with aHUS and multiple TMA relapses treated with 212 sessions of PE; mother has aHUS	1	Patient treated with eculizumab for 52 months with complete remission and no relapses
Mache et al (2009) <sup>68</sup>	Boy aged 17.8 years with plasma-resistant aHUS	1	Hematologic recovery and partial kidney function improvement; eculizumab used only on relapses and progressed to ESRD
Belingeri et al (2014) <sup>54</sup>	Young male, first presentation at 6 months, remained with CKD until age 7 years, when PI was started because of relapses; remained with CKD, proteinuria, and hypertension	1	Eculizumab started at age 11 years with no more relapses; decrease in proteinuria, and no need for dialysis
Christmann et al (2014) <sup>57</sup>	Girl aged 5.5 months with aHUS and severe hypertension	1	Hematologic improvement on day 3; stopped dialysis 2 weeks after first dose
Dorresteyn et al (2012) <sup>61</sup>	Girl aged 6 years with aHUS treated initially with PE for 3 weeks, followed by PI; developed relapse during upper respiratory infection, and PE did not improve renal function despite platelet count normalization	1	Renal function started to improve 48 hours after first eculizumab dose; complete remission achieved until last follow-up 9 months later
Bekassy et al (2013) <sup>53</sup>	Girl aged 12 years with aHUS and kidney failure since age 20 months; bilateral nephrectomy and a lost graft due to aHUS; at 10 years of age, transient ischemic attack and occlusion of carotid arteries	1	Started eculizumab without overt TMA and despite being anephric. She received a successful kidney transplant and did not have progression of carotid lesions
Hu et al (2014) <sup>66</sup>	19-month-old girl with severe neurologic involvement and cardiomyopathy	1	Eculizumab infused 12 hours after admission. Normal echocardiography on day 15, stopped dialysis on day 18, and was discharged with mild hemiparesis, but completely alert
Tschumi et al (2011) <sup>76</sup>	Girl aged 9 years with plasma-dependent aHUS	1	Eculizumab started on day 126; PE was stopped and there were no relapses in 24 months of follow-up. Mild CKD due to fibrosis
Michaux et al (2014) <sup>70</sup>	Neonate aged 11 days with severe aHUS (myocardial impairment, respiratory failure, acute kidney disease requiring hemodiafiltration)	1	Early treatment with eculizumab as first-line therapy and completely recovered within 5 days. With >24 months of follow-up, renal function remains normal
Ohta et al (2015) <sup>72</sup>	Boy aged 4 months who developed aHUS; repeated plasma infusions and 9 sessions of plasmapheresis were ineffective. The patient initially required continuous hemodiafiltration and thereafter peritoneal dialysis	1	Eculizumab started on day 48 of diagnosis with improvement in hypertension, and dialysis was stopped on day 117. CKD2 at 17 months of follow-up

(Continued)

**Table 3** (Continued)

Author (year)	Case presentation and complement-amplifying condition	Number of patients treated with eculizumab	Outcome with eculizumab
Ariceta et al (2012) <sup>51</sup>	Boy aged 28 days with plasma-resistant aHUS. He developed multiple intestinal perforations and leg skin necrosis due to systemic TMA	1	Within 48 hours of first eculizumab infusion, the patient recovered from acute kidney failure, with complete hematologic remission 2 weeks later
Al-Akash et al (2011) <sup>50</sup>	Boy aged 15 years with aHUS since age 16 months, ESRD and two failed kidney transplants	1	Eculizumab used as rescue of aHUS after the third kidney transplant with complete recovery of renal function 3 weeks after the first dose
Roman-Ortiz et al (2014) <sup>73</sup>	Boy aged 9 years presented with aHUS at age 3; irreversible renal failure and uncontrolled severe hypertension with concentric left ventricular hypertrophy, recurrent acute pulmonary edema, and congestive heart failure despite 5 hypotensive agents and bilateral nephrectomy	1	Kidney transplant performed with prophylactic eculizumab; after 3 years of continuous use, hypertension is controlled, no left ventricular hypertrophy, no opportunistic infections, and negative clinical chemistry parameters for hemolysis
Cayci et al (2012) <sup>56</sup>	Girl aged 10 years with negative-culture bloody diarrhea and plasma-resistant aHUS	1	Eculizumab started on day 15 with diuresis improvement in 24 hours and complete hematologic and kidney recovery in 2 weeks
Lapeyraque et al (2011) <sup>67</sup>	Girl aged 7 years with aHUS. Weekly PI with short-term intensified PI during aHUS exacerbations was effective for 4.3 years; progressive mild renal failure (stage 2) and aHUS exacerbation unresponsive to intensified PI	1	Eculizumab was started with complete reversal of TMA after 1 week; no relapses and normal kidney function after 12 months of follow-up
Vilalta et al (2012) <sup>78</sup>	Girl aged 4 years with multiple severe clinical manifestations including acute kidney injury, dilated cardiomyopathy, and cardiorespiratory arrest; intense PE did not halt TMA manifestations	1	The initial single dose of eculizumab only temporarily improved the clinical symptoms of TMA; sustained improvement of renal, hematologic, and cardiac values were achieved only upon institution of chronic treatment with eculizumab (2.5 years)
Azukaitis et al (2014) <sup>52</sup>	Boy with first manifestation of aHUS at age 2 months and a relapse at age 10 months leading to ESRD despite PI. Remained hypertensive in dialysis and had convulsions at age 5.5 years, when stenosis of left carotid artery and bilateral middle cerebral arteries was diagnosed	1	At age 6.5 years received a kidney transplant under prophylactic eculizumab with no signs of post-transplant aHUS; evolved with seizures and cerebral ischemia on the fourth postoperative day, leading to death
Sharma et al (2015) <sup>75</sup>	Girl aged 28 days presented with plasma-resistant aHUS with gross hematuria and hypertension	1	After 1 dose of eculizumab, dialysis was discontinued and her hematologic parameters improved; after 11 months of follow-up, she remains on eculizumab and penicillin without recurrence of aHUS or any infectious complications
Besbas et al (2013) <sup>55</sup>	Newborn aged 5 days with aHUS and full renal and hematologic remission after PI. The patient was discharged with FFP infusions but subsequently developed 3 life-threatening disease recurrences at 1 month, 3 months, and 6 months of age. The last relapse presented with uncontrolled hypertension and impaired renal function while the patient was receiving FFP infusions	1	Five days following the first dose of eculizumab, renal and hematologic parameters returned to normal range and blood pressure normalized; FFP infusions were gradually decreased and stopped; at the time of the report, the patient was 20 months of age and currently on eculizumab treatment every other week with completely normal renal and hematologic parameters
Giordano et al (2012) <sup>62</sup>	Boy aged 8 months with aHUS resistant to 21 PI and 15 PE treatments	1	Eculizumab first dose at age 12 months with hematologic improvement in 1 week and dialysis cessation in 5 days; no relapses and no PE/PI needed
Schalk et al (2015) <sup>74</sup>	Boy aged 3 years with aHUS and frequent relapses requiring PI	1	Started eculizumab and continued presenting relapses despite complement blockade; the authors decided to administer the medication immediately in times of immunologic triggers, such as immunizations or infections; at the time of report, the patient had been in a stable condition with an eGFR of 90 mL/min/1.73 m <sup>2</sup> and no further TMA events for more than a year

(Continued)

**Table 3** (Continued)

Author (year)	Case presentation and complement-amplifying condition	Number of patients treated with eculizumab	Outcome with eculizumab
Gulleroglu et al (2013) <sup>64</sup>	Girl aged 11 years developed aHUS and was treated immediately with PE/PI. Although initial improvement in renal function was seen, patient showed progressing TMA despite daily PE, and neurologic manifestations developed after 1 month Girl aged 6 years developed cerebral TMA (seizures, vision loss, and nystagmus) 6 days after initial presentation and remained unresponsive to PE/PI	2	Treatment with eculizumab achieved complete control of neurologic symptoms within 24 hours and gradually normalized hematologic and renal parameters in both children
Malina et al (2013) <sup>69</sup>	Girl aged 4 years developed gangrene of the fingertips 2 days after initial presentation of aHUS. Renal function continued to decline despite daily PE, and she was started on peritoneal dialysis 5 days after admission. The distal tips of the left hand remained gangrenous with a line of demarcation. Three weeks later, she did not return for follow-up and died at home because of dialysis-related complications Another girl developed ESRD due to aHUS in the fourth month after birth. At age 9 months, she suddenly developed ischemic changes in fingers of both hands and several toes. The lesions progressed, and several fingertips became gangrenous despite intense PE therapy	1	Eculizumab was started on the second case and all non-necrotic digits rapidly regained perfusion. The 3 already gangrenous fingers healed with loss of the end phalanges; during maintenance, eculizumab aHUS activity subsided completely, and some late recovery of renal function was observed
Baskin et al (2015) <sup>22</sup>	Retrospective analysis of 15 children diagnosed with aHUS, which was defined as HUS negative for STEC Three patients had relapses, and 7 had a new diagnosis. Nine children had oliguria or anuria, and 8 required dialysis. Hypertension was observed in 6 patients. Neurologic involvement developed in 6 patients.	10	Ten were resistant to, or dependent on, plasma therapy and treated with eculizumab; following the start of eculizumab treatment, all patients achieved full recovery of renal function and hematologic parameters.
Gruppo and Rother (2009) <sup>63</sup>	Congenital aHUS: first manifestation at 8 days of life treated with PI; relapses at 3 months, 9 months, and 11 months of age; all treated with PI with good response after 2 weeks; fourth relapse at 18 months unresponsive to PE.	1	Eculizumab was initiated at day 35 of the fourth relapse with improvement in hemolysis in 48 hours and complete remission in 10 days (with no PE/PI)

**Abbreviations:** aHUS, atypical hemolytic uremic syndrome; AMR, antibody-mediated rejection; CKD, chronic kidney disease; CKD2, chronic kidney disease stage 2; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; FFP, fresh frozen plasma; PE, plasma exchange; PI, plasma infusion; STEC, shigatoxin-producing *Escherichia coli*; TMA, thrombotic microangiopathy.

blockade as first-line treatment. No mutations were found in two of the 12 patients screened. Overall, there were 17 renal transplants, and 14 had been lost by aHUS recurrence, two by vascular thrombosis, and one by chronic allograft nephropathy. The median interval between renal transplantation and recurrence was 2 months (from 3 days to 5 years). The delay between recurrence and treatment with eculizumab was 30 days (from 1 day to 14 months).

Donor-specific antibodies were not detected in any patient, and histological findings of TMA were present on biopsy in 77% of patients (of which one only exhibited

signs of antibody-mediated rejection). All but three patients were maintained on eculizumab until last follow-up. Two patients who received a single dose of eculizumab presented a relapse after aHUS remission, but this did not resolve with eculizumab reintroduction; the patients progressed to ESRD. In all patients, there was good hematologic response (defined by the authors), as well as kidney function improvement. In the patients unresponsive to plasma therapy, renal function recovery was inversely proportional to the delay in starting eculizumab therapy, as few patients had kidney function benefit when the drug was started after 1 month.

**Table 4** Summary of case reports describing eculizumab both prior to and post-transplant to prevent TMA complications

Author (year)	Mutation status	Patient history	Transplant and post-transplant course	Eculizumab dosing	Outcome after starting eculizumab
Zimmerhackl et al (2010) <sup>88</sup>	CFH mutation	The patient was diagnosed with aHUS at age 4 years and treated with intermittent followed by continuous PD. Rapid deterioration of renal function at age 9 years required switch to HD.	First transplant from DD at age 9 years with daily PE on days 0–9.	Eculizumab 600 mg Q2W starting post-transplant on day 10 (ongoing).	No TMA complications reported over the next year with normalization of C3 levels, platelets, and haptoglobin. SCr of 46 $\mu\text{mol/L}$ reported at last follow-up of 39 months.
Zuber et al (2012) <sup>82</sup>			Good graft function with high urine output and normalization of SCr reported within 48 hours post-transplant.		
Noris and Remuzzi (2013) <sup>79</sup>					
Legendre et al <sup>80</sup>					
Weitz et al (2011) <sup>96</sup>	CFH mutation	The patient was diagnosed with aHUS at age 6 months. Sudden presentation of TMA resulted in progression to ESRD within 2 months despite PE.	First transplant from DD at age 7 years without PE.	Eculizumab 600 mg on days –17, 0, and 1. Eculizumab 600 mg was administered 3 more times to suppress elevated C5b-9 levels.	No TMA complications reported over the following 7 months with normal SCr levels and no evidence of hemolysis.
Zuber et al (2012) <sup>82</sup>			Good graft function reported with SCr and urea rapidly falling to normal levels.	Maintenance with eculizumab 300 mg QW, then Q2W (ongoing).	SCr of 44 $\mu\text{mol/L}$ reported at last follow-up of 23 months.
Noris and Remuzzi (2013) <sup>79</sup>		The patient was maintained on dialysis for 7 years.			
Nester et al (2011) <sup>91</sup>	CFH/CFHR1 hybrid	The patient initially presented with aHUS at age 8 years and progressed to ESRD.	Second transplant from LNRD at 12 years old with PE sessions on days –7 and –1.	Eculizumab 900 mg on days –7 and –1 (after PE) and post-transplant on days 7 and 14.	No TMA complications reported over the following 4 months with continuously declining SCr and normalization of hemolytic markers.
Zuber et al (2012) <sup>82</sup>		Biopsy-confirmed TMA complications occurred 25 months after first transplant, and the patient initiated PE and HD.	Graft function was established within hours of transplantation.	Maintenance with 900 mg Q2W thereafter (ongoing).	SCr of 70 $\mu\text{mol/L}$ reported at last follow-up of 16 months.
Noris and Remuzzi (2013) <sup>79</sup>					
Krid et al (2012) <sup>88</sup>	CFH/CFHR1 hybrid	The patient initially presented with aHUS at age 4 years and rapidly progressed to ESRD despite PE.	First transplant from DD at age 7.5 years without PE/PI.	Eculizumab 600 mg 2 hours before surgery and on day 1. Subsequent 600 mg doses administered QW for the first month and Q2W thereafter (ongoing).	Mixed rejection reported at 3 months post-transplant with biopsy-proven resolution at 15 months post-transplant.
Zuber et al (2012) <sup>82</sup>			Graft function was established within hours of transplantation with rapid normalization of SCr, platelets, and Hb.		No TMA complications reported over the following 16 months with normal SCr levels.
Noris and Remuzzi (2013) <sup>79</sup>					
Zuber et al (2012) <sup>82</sup>	Complex CFH/CFHR1 hybrid	Patient diagnosed with aHUS at age 17 years and had no prior transplant history.	First transplant from DD at age 18 years with 6 PE sessions from days 0 to 5.	Eculizumab (dose not reported) started day 5 (ongoing).	No TMA complications and SCr of 87 $\mu\text{mol/L}$ reported at last follow-up of 14 months.
Noris and Remuzzi (2013) <sup>79</sup>					
Zuber et al (2012) <sup>82</sup>	C3 mutation	The patient was diagnosed with aHUS at age 10 months and had no prior transplant history.	First transplant from DD at age 6.4 years without PE/PI.	Eculizumab (dose not reported) started at time of renal transplant (ongoing).	No TMA complications and SCr of 44 $\mu\text{mol/L}$ reported at last follow-up of 4.5 months.
Noris and Remuzzi (2013) <sup>79</sup>					

Zuber et al (2012) <sup>82</sup> Noris and Remuzzi (2013) <sup>79</sup>	<i>CFH</i> mutation	The patient was diagnosed with aHUS at age 1 year and had no prior transplant history.	First transplant from DD at age 9 years without PE/PI.	Eculizumab (dose not reported) started at time of renal transplant (ongoing).	No TMA complications and SCr of 58 µmol/L reported at last follow-up of 4 months. CH50 remained below detection level with Q2W eculizumab maintenance.
Zuber et al (2012) <sup>82</sup> Noris and Remuzzi (2013) <sup>79</sup>	<i>CFH</i> mutation	The patient was diagnosed with aHUS at age 3 years. One previous transplant was lost to aHUS.	Second transplant from DD at age 18 years with 1 PE session before the first eculizumab dose.	Eculizumab (dose not reported) started at time of renal transplant (discontinued).	Early arterial thrombosis occurred on day 1, and the graft was lost at day 3 post-transplant. This patient was ultimately successfully retransplanted under peritransplant eculizumab therapy.
Zuber et al (2012) <sup>82</sup> Noris and Remuzzi (2013) <sup>79</sup>	<i>CFH</i> mutation	The patient was diagnosed with aHUS at age 33 years. Two previous transplants were lost to aHUS.	Third transplant from DD at age 41 years without PE/PI.	Eculizumab (dose not reported) started at time of renal transplant (ongoing).	Mixed rejection at 6 weeks post-transplant with biopsy-proven resolution 15 days later. No TMA complications and SCr of 176 µmol/L reported at last follow-up of 2 months.
Xie et al (2012) <sup>97</sup>	<i>CFH</i> mutation	The patient was diagnosed with aHUS at age 30 years and progressed to ESRD despite PE/PI.	First transplant from LNRD at age 31 years with PE on days -7 and -1. Graft function was established promptly after transplantation and SCr decreased from 10.8 mg/dL to 0.8 mg/dL at day 4.	Eculizumab 900 mg on day -7 and 1,200 mg on day -1 after PE. Post-transplant dosing was 900 mg QW for 2 weeks followed by 900 mg Q2W (ongoing).	No TMA complications reported with SCr of 0.88 mg/dL at last follow-up of 1 year.
Ažukaitis et al (2014) <sup>52</sup>	<i>C3</i> mutation	The patient initially presented with aHUS at age 2 months. 10 months later a second TMA complication resulted in ESRD despite PI, and the patient started on PD. The patient experienced a stroke at age 5.5 years associated with suspected Moyamoya syndrome. The stroke resolved, and no neurologic complications were reported over the next year.	First transplant from DD at age 6.5 years without PE/PI. SCr decreased rapidly following transplant with no evidence of TMA.	Eculizumab 600 mg 5 hours before transplant, 300 mg 16 hours later, and 300 mg 5 days later.	Seizures occurred 4 days post-transplant, with massive irreversible ischemic lesions in the middle cerebral arteries. Neurologic status worsened and the patient died on post-transplant day 9 with well-functioning kidney grafts and no evidence of TMA. Author's comment: "Whether the arterial stenoses could have been prevented by the initiation of eculizumab treatment at diagnosis of aHUS and the long-term maintenance of treatment is an open question."

(Continued)

Table 4 (Continued)

Author (year)	Mutation status	Patient history	Transplant and post-transplant course	Eculizumab dosing	Outcome after starting eculizumab
Parikova et al (2015) <sup>92</sup>	CFH mutation	The patient was diagnosed with aHUS at age 43 years and progressed to ESRD despite PE.	First transplant from LNRD at age 45 years without PE. Graft function was established immediately after transplant with rapid decrease in SCr from 10.6 mg/dL to 1.9 mg/dL by post-transplant day 4.	Eculizumab 900 mg QW initiated 2 months prior to transplant for 5 weeks, followed by 1,200 mg Q2W thereafter. 1,200 mg administered on the day of surgery prior to reperfusion and 900 mg 24 hours post-transplant. Induction with 900 mg QW for 4 weeks was repeated on post-transplant day 14 due to evidence of microangiopathic hemolysis and increased blood pressure. Maintenance with 1,200 mg Q2W (ongoing).	The patient had marked improvements in mental status and blood pressure after initiating eculizumab. No TMA complications reported with stable SCr of 1.7 mg/dL at 18 months post-transplant.
Ranch et al (2014) <sup>94</sup>	CFH mutation	The patient presented with aHUS at age 7 months and was maintained on chronic dialysis for 2 years.	First transplant from DD at age 3 years without PE/PI. Graft function was established post-transplant with good urine output and SCr decreasing from 5.75 mg/dL to 2.73 mg/dL at 2 hours post-transplant.	Eculizumab initiated 7 months prior to transplant, with 600 mg initial dose followed by 300 mg 1 week later and 300 mg Q2W thereafter. 300 mg administered a few hours prior to surgery and 2 days post-transplant. Induction with 600 mg QW for 2 weeks was repeated on post-transplant day 8 due to surgery-associated complement activation. Maintenance with 300 mg Q2W (ongoing).	Stable allograft function and complete terminal complement blockade with no evidence of TMA complications were reported at last follow-up.
Alasfar and Alachkar (2014) <sup>97</sup>	CFH mutation	The patient presented at age 25 years with aHUS and biopsy-confirmed TMA. Despite PE/PI, the patient progressed to ESRD and became HD-dependent.	First transplant from LNRD at age 28 years without PE/PI. Graft function was established immediately post-transplant with SCr decreasing to 1.0 mg/dL.	Eculizumab 1,200 mg initiated 24 hours prior to transplant. Induction with 900 mg QW for 4 weeks followed by maintenance with 1,200 mg Q2W starting week 5 (ongoing).	Stable allograft function and no evidence of TMA complications at last follow-up.

Alasfar and Alachkar (2014) <sup>87</sup>	Mutations in two <i>CFHR</i> genes	The patient presented at age 23 years with aHUS. Despite PE/PI, the patient progressed to ESRD and became dialysis-dependent. First transplant from LNRD was lost 2 years post-transplant due to TMA complications despite PE/PI.	Second transplant from DD at age 33 years without PE/PI. No evidence of hemolysis at time of transplant.	Eculizumab 1,200 mg 24 hours prior to transplant. Induction with 900 mg QW for 4 weeks followed by maintenance with 1,200 mg Q2W starting week 5 (ongoing).	Excellent allograft function and SCr of 0.5 mg/dL reported at last follow-up of 6 months.
Tran et al (2014) <sup>95</sup>	<i>CFH</i> mutation	The patient presented at age 11 months with aHUS and progressed to ESRD despite PE/PI. The patient experienced a cerebrovascular event with neurodevelopmental devastation and multiple episodes of peritonitis while on PD and was intolerant to HD.	Liver-kidney transplant performed at age 5 years from DD. PE was administered prior to surgery. Both organs functioned immediately post-transplant with decrease in SCr from 7.3 mg/dL to 2 mg/dL.	Eculizumab (dose not specified) prior to, and following, surgery (ongoing).	Biopsy performed 6 months post-transplant showed no evidence of rejection or TMA complications. SCr was reported stable between 0.5 mg/dL and 0.7 mg/dL with 19 month follow-up.
Matar et al (2014) <sup>90</sup>	No identified mutation	The patient progressed to ESRD due to aHUS diagnosed at age 45 years. The patient received a prior kidney transplant from a DD, which was lost to aHUS.	Second kidney transplant from LRD at age 51 years without PE/PI.	Eculizumab (dose not specified) started 24 hours prior to surgery and continued for 6 months (discontinued).	The patient maintained allograft function and had no reported TMA complications with 34 months of follow-up. SCr was 1 mg/dL and eGFR was 58 mL/min/1.73 m <sup>2</sup> at 1 year post-transplant.
Matar et al (2014) <sup>90</sup>	No identified mutation	The patient progressed to ESRD due to aHUS diagnosed at age 37 years.	First kidney transplant from LRD at age 38 years without PE/PI.	Eculizumab (dose not specified) started 24 hours prior to surgery and continued for 6 months (discontinued).	The patient maintained allograft function and had no reported TMA complications with 26 months of follow-up. SCr was 1.1 mg/dL and eGFR was 80 mL/min/1.73 m <sup>2</sup> at 1 year post-transplant.
Matar et al (2014) <sup>90</sup>	No identified mutation	The patient progressed to ESRD due to FSGS diagnosed at age 13 years. The patient received a prior kidney transplant from an LRD, which was lost after 9 years to aHUS.	Second kidney transplant from LNRD at age 40 years without PE/PI.	Eculizumab (dose not specified) started 24 hours prior to surgery and continued for 6 months (discontinued).	The patient maintained allograft function and had no reported TMA complications with 21 months of follow-up. SCr was 1.3 mg/dL and eGFR was 45 mL/min/1.73 m <sup>2</sup> at 1 year post-transplant.

(Continued)

Table 4 (Continued)

Author (year)	Mutation status	Patient history	Transplant and post-transplant course	Ecilizumab dosing	Outcome after starting ecilizumab
Matar et al (2014) <sup>90</sup>	2 CFH mutations	The patient progressed to ESRD due to aHUS diagnosed at age 10 months. The patient received 3 prior kidney transplants, which were all lost to aHUS. The first allograft from a DD failed after 2 years, the second allograft from an LRD failed after 4 years, and the third allograft from an LRD failed after 5 years.	Fourth kidney transplant from LNRD at age 27 years without PE/PI.	Ecilizumab (dose not specified) started 24 hours prior to surgery and continued as lifelong therapy (ongoing).	The patient maintained allograft function and had no reported TMA complications with 21 months of follow-up. SCr was 0.9 mg/dL and eGFR was 80 mL/min/1.73 m <sup>2</sup> at 1 year post-transplant.
Akchurin et al (2015) <sup>86</sup>	CFH	The patient presented at age 5 years and progressed to ESRD by the age of 6. While on dialysis, the patient experienced severe hypertension, seizures, PRES, pulmonary edema, and cardiac complications.	The patient received a nonrelated living donor kidney at the age of 10 years.	600 mg for 7 days and 1 day prior to transplant (induction dose for body weight between 20 kg and 30 kg). The third and fourth doses were given 1 week and 2 weeks post-transplant, after which dosing was transitioned to every other week.	The patient maintained allograft function and had no reported TMA complications with 9 months of follow-up. The patient had urine output immediately after the transplant, and by post-transplant day 2 the serum creatinine was 53.04 μmol/L.
Roman-Ortiz et al (2014) <sup>73</sup>	CFH/CFHR1 hybrid gene	The patient presented with aHUS at age 3 years with irreversible renal failure, uncontrolled hypertension with concentric left ventricular hypertrophy, recurrent acute pulmonary edema, and congestive heart failure despite 5 hypotensive agents and bilateral nephrectomy.	Deceased donor kidney transplant was performed at age 6.	600 mg ecilizumab pretransplant and a second dose within 24 hours of transplantation. Four additional weekly doses followed by fortnightly doses thereafter.	The patient maintained allograft function and had no reported TMA complications with 36 months of follow-up. The dose was adjusted for body weight to 900 mg per fortnight.
Mallett et al (2015) <sup>89</sup>	Unknown	Patient presented with a history of aHUS and previous graft loss to aHUS.	Second transplant with LRD.	Dosing with ecilizumab 900 mg/wk for 4 weeks followed by 1,200 mg fortnightly ongoing were added to standard treatment with prednisolone, tacrolimus, and mycophenolate.	The patient maintained allograft function and had no reported TMA complications with 29 months of follow-up (creatinine 116 μmol/L).
Pellicano et al (2013) <sup>83</sup>	CFH	Patient aged 24 years was diagnosed with aHUS in April 2008. PE and corticosteroids were used with no improvement in kidney function, and HD was initiated 1 month later. The patient had inherited the CFH mutation from	In September 2011, the patient received a living-related donor kidney transplant.	Ecilizumab 900 mg was given 1 week before the surgery with a further dose of 1,200 mg administered during the post-transplant period. Ecilizumab continued at 900 mg/week for 4 weeks	The patient maintained allograft function and had no reported TMA complications with 15 months of follow-up. The recipient continues to receive maintenance treatment with ecilizumab (1,200 mg) every 2 weeks.



<p>her asymptomatic mother, but her father had no relevant aHUS risk factors. Therefore, he was selected as a suitable living kidney donor.</p>		<p>(the first dose on the day after the procedure). In the fifth week, the dose and interval were increased to 1,200 mg eculizumab every 2 weeks.</p>
<p>Patient aged 12 years developed renal failure at the age of 20 months. She underwent bilateral nephrectomy and renal transplantation but lost the transplant due to recurrences. She was on hemodialysis for 7 years. At age 10 years, she developed a TIA and eculizumab was subsequently initiated.</p>	<p>The patient underwent a successful kidney transplant 9 months later.</p>	<p>The patient maintained allograft function and had no reported TMA complications with 12 months of follow-up. No progression of vascular occlusion was noted within 1 year after the TIA by repeated imaging.</p>

**Abbreviations:** aHUS, atypical hemolytic uremic syndrome; CFB, complement factor B; CFH, complement factor H; CFHR, complement factor H-related; DD, deceased donor; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; FSGS, focal segmental glomerulosclerosis; Hb, hemoglobin; HD, hemodialysis; HUS, hemolytic uremic syndrome; LNRD, living nonrelated donor; LRD, living related donor; PD, peritoneal dialysis; PE, plasma exchange; PI, plasma infusion; PRES, posterior reversible encephalopathy syndrome; QW, once per week; Q2W, once every 2 weeks; SCr, serum creatinine; TIA, transient ischemic attack; TMA, thrombotic microangiopathy.

Two patients presented with a pulmonary infection by *M. tuberculosis* and *H. influenza*, respectively, and one patient had hypogammaglobulinemia (history of prior splenectomy and use of rituximab), but good outcome with antibiotics and subcutaneous immunoglobulin.

## Retrospective single center case series of eculizumab use in renal transplant recipients

Matar et al<sup>90</sup> reported a retrospective study of 12 consecutive patients with an established diagnosis of aHUS who underwent at least one kidney transplant at a single institution between 2003 and 2013. Diagnosis of primary aHUS was confirmed by evidence of thrombocytopenia, hemolytic anemia, acute renal failure, normal ADAMTS13 levels, and negative for shigatoxin-producing *E. coli*-HUS.

Six patients had an established diagnosis of aHUS as their primary disease prior to their first transplant, three patients were diagnosed with aHUS post-transplant, two patients had an unclear diagnosis as the cause of the primary disease, and one patient was diagnosed with focal segmental glomerular sclerosis as their primary disease. All patients had genetic testing for complement mutations: six patients (50%) had identified complement mutations, including four with *CFH* mutations, one with an *MCP* mutation, and one with a *THBD* mutation. The 12 patients received a total of 23 kidney transplants. Six patients had only a single transplant, three patients had two transplants each, and three patients had more than two transplants. Four patients considered at high risk of post-transplant TMA complications received eculizumab starting 24 hours prior to transplantation. Individual patient information is included in Table 5. All patients maintained allograft function, and there were no reported TMA complications with 21–34 months of follow-up.

## Retrospective, multicenter review of eculizumab use for aHUS in England

Sheerin et al<sup>13</sup> reported on the use of eculizumab commissioned by NHS England in 2013 for both new patients with aHUS and long-duration aHUS, including those who underwent renal transplantation. Overall, 43 patients received eculizumab: 15 (35%) were <18 years (eleven male, four female); 28 (65%) were adults (nine male, 19 female); 23 (53%) had active progressing TMA, and 20 (47%) had a long duration of aHUS. At the time of publication, 31 (72%) patients were receiving ongoing eculizumab. Three of 14 (21%) patients who discontinued eculizumab had subsequent

**Table 5** Summary of case reports describing interrupted eculizumab use

Author (year)	Mutation status	Patient history	Transplant and post-transplant course	Time from TMA to eculizumab	Eculizumab dosing	Post-eculizumab course
Nurnberger et al (2009) <sup>83</sup>	CFH and CFHR1 mutations	The patient developed ESRD due to aHUS and received 5 years of dialysis. At age 25 years, the patient underwent DD kidney transplant, which was lost due to TMA complications presenting 5 weeks post-transplant, despite PE. Dialysis was resumed for 7 years.	Second renal transplant from DD at age 37 years. TMA complications presented 6 weeks post-transplant following 3 episodes of cellular rejection requiring additional tacrolimus. Platelet counts and renal function worsened despite 4 PE sessions. SCr prior to eculizumab was 1.49 mg/dL.	5 days	Eculizumab 600 mg (single dose).	Haptoglobin normalized after 8 days, platelet counts and SCr improved. Renal function reported stable at 8-month follow-up. After eculizumab discontinuation, TMA complications presented at 21 months, resulting in graft loss.
Larrea et al (2010) <sup>106</sup> Loirat et al (2016) <sup>111</sup>	No identified mutation	The patient presented postpartum at age 20 years with biopsy-confirmed aHUS and progressed to ESRD and HD dependence.	First renal transplant from DD at age 22 years. The patient presented 12 days post-transplant with elevated SCr, thrombocytopenia, hemolytic anemia, and biopsy evidence of TMA, despite daily PE. SCr prior to eculizumab was 4.69 mg/dL.	9 days	Eculizumab 600 mg (single dose).	Hemolysis and platelets improved 36 hours after first dose, with normalization of renal function and platelet counts at 4 days. TMA complications presented at 11.5 months, and eculizumab was reinitiated with resolution of manifestations. Graft was lost after second eculizumab cessation following humoral rejection.
Alachkar et al (2012) <sup>89</sup>	No identified mutation	The patient presented at age 27 years with acute kidney injury, thrombocytopenia, and hemolytic anemia. Despite	Second renal transplant from living donor at age 32 years. Proteinuria developed at	2 weeks	Eculizumab 900 mg QW followed by 1,200 mg Q2W with 600 mg supplemental dose after each PE session (8 months).	Steady renal improvement and discontinuation of HD. Laboratory and clinical parameters normal over

<p>PE and high-dose corticosteroids, the patient progressed to ESRD and started on HD. Two years later, the patient received LRD transplant that was lost to aHUS 2 months post-transplant, despite PE.</p>	<p>28 days post-transplant, and biopsy showed evidence of TMA 10 weeks later. Renal function and hematologic parameters deteriorated despite PE. Oliguria and fluid overload developed, and HD was initiated.</p>	<p>8 months of treatment. TMA complications reported 5 months after discontinuation. Eculizumab restarted with improvement in SCr and Hb. Tubular necrosis developed 2 weeks later due to complications of an endovascular procedure, and graft was lost at 2 years post-transplant.</p>	
<p>The patient presented postpartum with aHUS. One previous kidney transplant lost to aHUS.</p>	<p>Second renal transplant received at age 43 years. TMA complications presented 8 days post-transplant. SCr prior to eculizumab was 1.99 mg/dL.</p>	<p>Hematologic parameters normalized, and SCr progressively improved. 3 months after eculizumab discontinuation, TMA complications presented following influenza vaccination. Eculizumab was resumed every other month. SCr was 1.39 mg/dL with 14 months of follow-up.</p>	<p>1 day</p>
<p>The patient progressed to ESRD secondary to diabetes mellitus and remained on dialysis for 3.5 years.</p>	<p>Combined pancreatic and renal transplant received at age 34 years. TMA complications presented 8 days post-transplant with worsening renal function despite daily PE. Biopsy showed features of</p>	<p>Eculizumab 1,200 mg followed by a 900 mg dose 1 week later (2 doses).</p>	<p>6 days</p>

(Continued)

Table 5 (Continued)

Author (year)	Mutation status	Patient history	Transplant and post-transplant course	Time from TMA to eculizumab	Eculizumab dosing	Post-eculizumab course
Wilson et al (2011) <sup>108</sup>	No identified mutation	The patient had ESRD due to diabetic nephropathy.	AMR and TMA. SCr prior to eculizumab was ~5 mg/dL. Combined pancreatic and renal transplant received from DD at age 46 years. Evidence of renal dysfunction reported 26 days post-transplant. Biopsies showed borderline rejection on days 21 and 25, and evidence of TMA seen on day 41. Renal function continued to deteriorate despite 18 cycles of PE over 3 weeks.	3 weeks	Eculizumab 900 mg QW for 4 weeks (4 doses).	Platelet count and Hb increased within 24 hours of starting eculizumab. Renal function reportedly improved with 1 year of follow-up.
Matar et al (2014) <sup>90</sup>	CFH mutation	The patient progressed to ESRD due to aHUS diagnosed at age 36 years. The patient received 2 prior kidney transplants, both lost to aHUS. The first allograft from a DD never functioned post-transplant, and the second allograft from an LRD was lost after 6 months.	Third kidney transplant from LRD at age 38 years without PE/PI. TMA complications occurred at 6 years and 7 years post-transplant following bacterial infections.	Not reported	Eculizumab (dose not specified) was administered with PE/PI after each TMA complication. Lifelong therapy was initiated after the second TMA complication (ongoing).	Both TMA complications responded to eculizumab with restoration of graft function and normalization of laboratory parameters. The patient maintained allograft function and no further TMA complications were reported. SCr was 0.9 mg/dL and eGFR was 91 mL/min/1.73 m <sup>2</sup> at 1-year follow-up.

Matar et al (2014) <sup>90</sup>	No identified mutation	The patient progressed to ESRD due to aHUS diagnosed at age 28 years. The patient received 1 prior kidney transplant from LRD that was lost to aHUS after 1 year.	Second kidney transplant from LNRD at age 33 years without PE/PI. TMA complications occurred at 3 months and 17 months post-transplant.	Not reported	Eculizumab (dose not specified) was administered with PE/PI after each TMA complication (discontinued).	Both TMA complications responded to eculizumab. Allograft was lost at 23 months due to contrast nephropathy and acute tubular injury. SCr was 2.1 mg/dL and eGFR was 27 mL/min/1.73 m <sup>2</sup> at 1-year follow-up. The patient did not recover allograft function and the graft was lost after 7 months.
Matar et al (2014) <sup>90</sup>	2 <i>CFH</i> mutations	The patient progressed to ESRD due to an unclear primary diagnosis with hypertension.	First kidney transplant from DD at age 57 years without PE/PI. TMA complications occurred at 3 months post-transplant.	Not reported	Eculizumab (dose not specified) was administered with PE/PI (discontinued).	
Kransdorf et al (2014) <sup>105</sup>	No identified mutation	aHUS after heart transplantation in a woman aged 40 years.	Preoperative laboratory studies showed normal renal function, normal platelet count, and mild anemia (Hb 10.6 g/dL). After a 10-hour surgery, the patient returned to the intensive care unit, where she was noted to have TMA.	4 days	900 mg followed by 3 additional doses of eculizumab on a weekly basis, then every 2 weeks.	Renal function improved and renal replacement therapy was discontinued on POD 18. She was discharged home on POD 22. At 14 months post-transplant she developed acute kidney injury and underwent a renal biopsy to exclude recurrent aHUS. Histopathology showed moderate tubular injury without evidence of TMA. Eculizumab infusions were discontinued at that time. She had no further evidence of aHUS.

(Continued)

Table 5 (Continued)

Author (year)	Mutation status	Patient history	Transplant and post-transplant course	Time from TMA to ecilizumab	Ecilizumab dosing	Post-ecilizumab course
Pu and Sido (2014) <sup>07</sup>	Not identified	Patient aged 85 years with TMA after diarrhea with <i>Pseudomonas aeruginosa</i> but shigatoxin negative. She was aggressively treated with systemic antibiotics but developed mental status changes with seizure activity requiring protective intubation and acute renal failure needing HD.	NA	Not described	Ecilizumab was administered 2 weeks after patient received meningococcal vaccine.	Her mental status, seizure activity, and kidney function dramatically improved after several doses of ecilizumab. She was extubated and stopped HD after 2 weeks and 4 weeks of starting ecilizumab therapy, respectively. Twelve weeks after receiving ecilizumab therapy, she developed sepsis originating from a urinary tract infection. She was treated with intravenous antibiotics, and her ecilizumab was discontinued. She has been off ecilizumab for 12 months with a normal CBC profile, mental status, and kidney function.
Kourouklaris et al (2014) <sup>04</sup>	Not performed	31-week-pregnant young woman (aged 23 years), free of previous medical history, was admitted for an urgent cesarean section due to preclampsia and presented with postpartum TMA. Intensive PE treatment	NA	Not described	900 mg weekly ecilizumab for 4 weeks, followed by 1 dose of 1,200 mg. A 6-week interruption of ecilizumab treatment occurred due to drug accessibility, and the patient was managed with dialysis. Three months later, ecilizumab	Following 2 doses of ecilizumab, the patient presented with pneumonia), cardiac failure, and hypertensive crisis. She received treatment with antibiotics, diuretics, and antihypertensives,



Table 5 (Continued)

Author (year)	Mutation status	Patient history	Transplant and post-transplant course	Time from TMA to eculizumab	Eculizumab dosing	Post-eculizumab course
Cañigral et al (2014) <sup>100</sup>	No identified mutation	Daily PE with fresh frozen plasma was started on day 7 for 5 days, with an initial hematologic response without renal improvement.	NA	Not described	Eculizumab was administered following an induction schedule at a dose of 900 mg IV per week for 4 weeks, followed by maintenance at a dose of 1,200 mg every 2 weeks. Apheresis was discontinued before the first dose of eculizumab.	a dose of 900 mg twice weekly, with complete recovery of renal function and no signs of hemolysis by week 4 of treatment. After 11 months, eculizumab was discontinued and close monitoring was performed. One year after eculizumab discontinuation, the patient remains well with normal renal function, no need for antihypertensive drugs, and no signs of aHUS recurrence. In the first week, after initial induction dose, the platelet count increased above $150 \times 10^9/\mu\text{L}$ . Creatinine and anemia diminished progressively. In outpatient follow-up, complete remission with normalization of creatinine levels was obtained after 2 doses of maintenance treatment. Eculizumab was discontinued after 6 months of treatment. One year after diagnosis, the



<p>day with no response. ADAMTS13 activity was completely normal and the patient was diagnosed as having aHUS.</p>	<p>A previously well female infant born to healthy, nonconsanguineous parents presented to her local hospital at the age of 4 months and was diagnosed with aHUS.</p>	<p>NA</p>	<p>7 days</p>	<p>300 mg of eculizumab 7 days after admission, followed 7 days later by a further dose and then doses at 3-week intervals.</p>	<p>patient remained in complete remission.</p> <p>She was discharged on hospital day 14, immediately after the second eculizumab infusion. The plasma LDH level remained persistently elevated, despite ongoing eculizumab therapy. The alternative, classical, and mannose-binding lectin complement pathways were all suppressed to &lt;20% of normal activity (as assessed by CH50 and AP50 hemolytic assays), confirming drug action. The high levels of sC5b-9 were interpreted as indicating ongoing dysregulated complement activation. The dose was increased to 300 mg Q2W when the patient weighed only 9 kg, instead of adhering to the 10 kg limit recommended by the manufacturer. Six weeks after increasing the dose</p>
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(Continued)

Table 5 (Continued)

Author (year)	Mutation status	Patient history	Transplant and post-transplant course	Time from TMA to eculizumab	Eculizumab dosing	Post-eculizumab course
Xie et al (2012) <sup>97</sup>	Heterozygous nonsense mutation in <i>CFH</i> reduced <i>CFH</i> plasma levels	Female patient aged 31 years with aHUS and acute kidney injury low C3 level and progression to ESRD despite plasma therapy and corticosteroids.	Pre-transplant: C5 functional activity and sMAC were suppressed after eculizumab infusion. Intraoperatively, she received a unit of platelets and a unit of packed RBCs because Hb fell from 8.4 g/dL to 6.2 g/dL. Post-transplant, her Hb fell from 8.3 g/dL to 5.9 g/dL and LDH was consistent with low-grade hemolysis. Haptoglobin remained normal, LDH remained mildly elevated for several days. sMAC remained low	Pretransplant	First dose of eculizumab (900 mg) intravenously after apheresis 1 week before transplantation; a second dose of 1,200 mg eculizumab was given after apheresis the day before transplantation. She completed induction phase with two weekly doses, then switched to maintenance phase every 2 weeks.	frequency, the sC5b-9 concentration remained elevated at 167 ng/mL 2 weeks after the preceding dose. A trough plasma eculizumab concentration was then measured and found to be satisfactory at 347.2 µg/mL, with levels of >99 µg/mL considered to be therapeutic. The simultaneous plasma LDH was 734 IU/L. CMV infection that responded to valgancyclovir. One year after kidney transplantation, no anemia or hemolysis and serum creatinine was 0.88 mg/dL. On maintenance dose with undetectable CH50.

<p>after surgery and functional C5 and CH50 levels were undetectable. Urine output increased and creatinine decreased preoperatively to 0.8 mg/dL by POD day 4.</p>	<p>NA</p>	<p>6 days</p>	<p>Initially eculizumab 900 mg Q4W. On week 5, she commenced maintenance therapy starting at 1,200 mg Q2W. Due to nausea and vomiting, the maintenance dose was reduced to 600 mg weekly (beginning with dose 7). After receiving 600 mg weekly for 9 doses, eculizumab was then reduced to 600 mg Q2W.</p>	<p>Six months after the initial diagnosis, the patient continued to have improved renal function on maintenance doses of eculizumab as low as 600 mg Q2W.</p>
<p>Ohanian et al (2011)<sup>40</sup></p>	<p>Unknown</p>	<p>A previously described woman aged 50 years with aHUS had a remarkable recovery with eculizumab, which safely reversed profound neurologic damage and eliminated the need for dialysis.</p>		

**Abbreviations:** ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; aHUS, atypical hemolytic uremic syndrome; AMR, antibody-mediated rejection; CBC, complete blood count; CFb, complement factor B; CFH, complement factor H; CFHR, complement factor H-related; CMV, cytomegalovirus; DD, deceased donor; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; Hb, hemoglobin; HD, hemodialysis; IV, intravenous; LDH, lactate dehydrogenase; LNRD, living nonrelated donor; LRD, living related donor; MCP, membrane cofactor protein; NA, not applicable; PE, plasma exchange; PI, plasma infusion; POD, postoperative day; QW, once per week; Q2W, once every 2 weeks; Q4W, once every 4 weeks; RBC, red blood cell; SCr, serum creatinine; sMAC, soluble membrane attack complex; TMA, thrombotic microangiopathy.

TMA complications and recommenced therapy with eculizumab (including two patients on dialysis who did not recover renal function but had ongoing hemolysis).

At the moment of publication, there were 45 patients (43 adults/two children) on dialysis in England whose primary diagnosis was aHUS. Mutations were identified in 32 (71%) of patients. Of the 13 patients without an identified mutation, five (38%) had lost a previous transplant to recurrent disease. This suggests that in these individuals there is an as-yet unidentified inherited or acquired factor that caused recurrent disease. The majority had not been wait-listed due to risk of subsequent TMA manifestations, and wait listing was made possible with the introduction of the NHS England Commissioning Policy for aHUS.

#### Use of eculizumab prior to renal transplantation

In the report by Sheerin et al,<sup>13</sup> from April 1, 2013, to March 31, 2014, nine of 45 (20%) aHUS patients received a renal transplant with eight (89%) receiving eculizumab prior to transplantation. One patient received eculizumab for subsequent TMA in the early postoperative period, and all of these renal transplant recipients had good transplant outcomes and continue to receive eculizumab.

#### Treatment of prevalent patients not on dialysis

Of the eleven patients with long-duration aHUS who were not on dialysis, eight received eculizumab to prevent further relapses. One of these was a patient with a known *CD46* mutation who had recurrent episodes of pancreatitis that did not respond to eculizumab, which was withdrawn. Three were transplant patients—one started eculizumab 29 months after transplant when a biopsy undertaken for progressive decline in transplant function showed evidence of a chronic TMA with graft function improvement after eculizumab; two other transplant patients (deemed to have typical HUS) developed a TMA in the graft early after transplantation leading to a revised primary renal diagnosis of aHUS, both of whom had good outcome with eculizumab treatment.

## Case reports of kidney transplant patients with aHUS treated with eculizumab

Cases describing use of eculizumab in patients with aHUS prior to transplant and long-term use after kidney transplantation to prevent TMA and therefore the risk of allograft loss are summarized in Table 5.<sup>11,40,82,83,90,97,99–108</sup> Of the 26 cases backed with adequate follow-up information, 24 patients (92%) remained free of TMA complications with stable graft

function at last follow-up (range, 3 days to 39 months). We refer you to the full publications for complete details.

Limited patient-level information was available in the case series presented by Sheerin et al;<sup>13</sup> therefore, these are not presented in Table 5.

## Safety

Terminal complement activity (MAC) is required for protection from invasive meningococcal disease, and use of eculizumab would heighten the exposure of patients to this risk. Immunization is required by regulatory authorities for the use of eculizumab, and antimicrobial prophylaxis is suggested in the early days after such immunization (on label). In the prospective trials,<sup>30</sup> meningococcal infection, infection-related serious adverse events, and deaths were not reported, and this continued throughout the extension study.<sup>31</sup> In trial 1 (“progressive TMA”), serious adverse events were reported in all patients, one of which was considered severe (hypertension in a chronically hypertensive patient). In trial 2 (“longstanding TMA”), half of the patients had serious adverse events. All serious adverse events related to eculizumab had resolution without interruption of the drug. Beyond the 26th week of treatment, no new adverse events were reported and were similar among different subgroups, including transplant recipients. It is noteworthy that adverse events were reported to diminish over time from week 26 to the 2-year cutoff, and no new or cumulative adverse events were noted.<sup>31</sup>

In the series published by Sheerin et al<sup>13</sup> regarding the NHS England Commissioning Policy for aHUS, there were no meningococcal infections described in 43 patients treated with eculizumab and vaccinated according to local guidelines.

The presence of non-neutralizing human anti-human antibodies was confirmed in one patient in trial 1 who received a single dose of eculizumab and discontinued following diagnosis of systemic lupus erythematosus (an exclusion criterion).

In a 10-year-old boy with aHUS and heterozygous factor H mutation who received eculizumab to avoid recurrence of aHUS in the renal allograft, protective serum bactericidal antibody titers ( $\geq 1:8$ ) were seen after kidney transplantation under immunosuppressive therapy with mycophenolate mofetil, tacrolimus, steroids, and eculizumab over a 27-month observational period. This case illustrates that a humoral immune response to conjugate meningococcus C vaccination may occur and be maintained despite chronic renal disease, kidney transplantation, immunosuppressive

drugs, and immunomodulatory therapy with eculizumab. However, it remains unclear whether serologically defined protective serum bactericidal antibody titers mediate true protection from invasive meningococcal disease in an immunocompromised patient, particularly if undergoing treatment with a complement inhibitor.<sup>109</sup>

A 24-year-old man with diarrhea found to have acute renal failure with MAHA was diagnosed with aHUS. He was initiated on PE and hemodialysis. On day 6, he was started on eculizumab. His renal function progressively improved. His main complication during eculizumab therapy was hypertension-related posterior reversible encephalopathy syndrome.<sup>110</sup>

The complement system plays a vital role in preventing life-threatening infections by ensuring optimal functioning of the host immune system. Its dysregulation has been implicated in causing glomerular, hematologic, and transplant-related disorders. Vellanki and Bargman<sup>111</sup> describe a very rare case of *Aspergillus niger* peritonitis in an ESRD patient on peritoneal dialysis receiving maintenance eculizumab therapy for aHUS. Given that murine models with the same defect as that induced by eculizumab are vulnerable to invasive aspergillosis, it is suggested that the fungal peritonitis in this patient was the result of the eculizumab therapy.<sup>111</sup>

The long-term safety and efficacy of eculizumab in the pediatric population remain under review. Cullinan et al<sup>59</sup> presented the case of a child with a hybrid *CFH/CFHR3* gene who, having had multiple disease relapses despite optimal treatment with PE, commenced eculizumab therapy in August 2010. She remained relapse-free in follow-up at 52 months, and treatment has been well tolerated. Despite vaccination against meningococcal disease and appropriate antibiotic prophylaxis, the patient developed meningococcal bacteremia 30 months into treatment. She presented with nonspecific symptoms but recovered without sequelae with appropriate treatment. The authors suggest vaccination, antibiotic prophylaxis, and annual monitoring and follow-up of vaccine responses.<sup>59</sup>

A recently published case series in a pediatric population<sup>112</sup> described a possible relationship of liver injury with the use of eculizumab in eleven children treated with this drug for aHUS in a single center. Elevated liver enzymes were reported in seven children (ages 6–11 years) after starting eculizumab infusions to treat aHUS. Liver enzyme thresholds for drug-induced liver injury (international patterns) were exceeded in five cases, all of which were classified as mixed hepatocellular/cholestatic. Other causes for liver injury such

as infections were excluded. One patient developed tender hepatomegaly and a 20-fold liver enzyme elevation after starting eculizumab. Recurrent liver injury following resumption of treatment with eculizumab led to its discontinuation and conversion to plasma therapy. Thus, hepatotoxicity in patients treated with eculizumab for aHUS should be monitored. Despite this clinical finding, further research is necessary to characterize the mechanism of potential hepatotoxicity and also to identify patients at risk.<sup>112</sup>

Eculizumab has been used in pregnant women successfully, albeit with PNH<sup>113</sup> and not aHUS. Recently, a case report of safe use of eculizumab in a 26-week pregnant woman with aHUS was described.<sup>38</sup>

## Dose modification or eculizumab discontinuation

In the prospective trials,<sup>31</sup> the six patients in trial 1 (“progressive TMA”) and two patients in trial 2 (“longstanding TMA”) discontinued treatment with eculizumab, with no overt TMA reported up to 8 weeks after withdrawal.

In a separate cohort, Cugno et al<sup>114</sup> used a complement activity assay (Wieslab) to measure alternative lectin–mannose and classical pathways in patients receiving eculizumab. Complement activity was completely suppressed at 1 week, 2 weeks, and 3 weeks after the last eculizumab infusion but only partially suppressed after 4 weeks.

The largest case series of eculizumab discontinuation was provided by Ardissino et al<sup>115</sup> and Carr and Cataland,<sup>116</sup> who published the outcome of eculizumab discontinuation in ten patients aiming at minimizing adverse reactions, including meningitis risk and infusion discomfort, and reducing costs. Patient monitoring was home-based and consisted of urine dipstick testing for blood. During the 95 months of observation, one-third of the patients experienced a relapse (median within 1.5 months), but recovery after eculizumab was restarted. More recently, Ardissino et al<sup>117</sup> published the results of longer follow-up period after discontinuation, and a report of six additional cases. Patients had received eculizumab for a median of 4.3 months (range, 0.5–14.4 months). Eight patients were able to discontinue dialysis therapy, whereas the other eight had never been dialyzed. During a cumulative time off treatment of 243 months, five patients experienced relapse, identified by means of regular home urine dipstick testing, within 6 months of the last eculizumab dose (an average of one relapse per 49 months off therapy). In these patients, eculizumab therapy was restarted, followed by rapid improvement in serum creatinine levels and proteinuria to or below baseline values, and maintained every 3 weeks or

4 weeks based on global complement activity. Eleven patients remained in remission with no signs of acute disease.

The authors concluded that, in aHUS, it is possible and relatively safe to discontinue eculizumab therapy. They discourage discontinuation of eculizumab therapy in kidney transplant recipients with *CFH* mutations and patients with glomerular filtration rates below 20 mL/min/1.73 m<sup>2</sup>. In patients with anti-*CFH* antibodies, one should consider discontinuation of eculizumab therapy when the antibody titer is <2.5 times ULN. Regular home urine dipstick monitoring is suggested for early identification of relapses, especially during acute illnesses and when patients feel unwell.

After the publication of this case series, Wetzels and van de Kar<sup>118</sup> added data for eculizumab treatment discontinuation in patients with aHUS and a *CFH* mutation. In their report, the authors treated four such patients who were plasma-resistant or -dependent and received eculizumab in accordance with FDA-proposed schedules. By local protocol, treatment is discontinued after 4–6 months if disease activity has disappeared and kidney function has improved and stabilized for at least 4–6 weeks. Eculizumab treatment was withdrawn in three of four patients, two of whom had no signs of disease activity as of their respective 11-month and 17-month follow-ups. Recurrent disease developed in one patient 3 months after eculizumab therapy discontinuation. When they compared these patients with those of Ardissino et al,<sup>117</sup> they noted a difference in the location of the *CFH* mutations, suggesting that patients with a mutation in exons 19 or 20 may be more prone to recurrence.

There are reports of temporary use of eculizumab in drug-induced TMA. Faguer et al<sup>3</sup> published on use of seven doses of eculizumab starting 30 days after mitomycin C-induced TMA with reversal and no relapse after 1 year of follow-up. At the same time, Gilbert et al<sup>2</sup> published the case of a 2-year-old patient with TMA after cisplatin therapy for neuroblastoma for whom eculizumab was administered for 2 months—there was a relapse 2 months after stopping eculizumab, and the patient was found to have a pathogenic variant in CD46, resuming treatment with complement blockade with good outcome.

Case reports of discontinuation of eculizumab in patients with aHUS are summarized in Table 5.

## Failure of response to eculizumab: possible underlying mechanisms

When patients fail to respond to eculizumab or have frequent episodes of overt hemolysis during treatment, it is important to address the underlying mechanism of resistance, especially associated conditions that enhance complement responses

such as infections, drugs, chemotherapy, or surgery, among others.

Mechanisms of TMA not primarily related to complement defects have been described in poor responders to eculizumab, such as methylmalonic aciduria and homocystinuria type C protein mutations with elevated homocysteine levels, which may occur even in adult-onset aHUS<sup>119</sup> and in a case of monoclonal proteinuria.<sup>120</sup>

Although the underlying mechanism is still unknown, Schalk et al<sup>74</sup> described a 3-year-old boy with aHUS due to a novel heterozygous truncating complement Factor H mutation in combination with other changes known to be associated with an increased risk for aHUS. Despite eculizumab treatment and maximal suppression of the classical and alternative complement pathways, C3d and sC5b-9 remained consistently elevated and were confirmed by augmented serum-induced endothelial C5b-9 deposits. The patient showed repeated relapses, reflected in ongoing activation in vivo, despite the full inhibition of global AP activity (CH50, APH50) in vitro. The authors state that no laboratory-confirmed parameter definitively reflects the situation on endothelial cells, where microangiopathy is localized. Nevertheless, the initial diagnosis of nonresponse was made on the basis of persistently low C3 (which is commonly seen after treatment), as well as other parameters not acceptably reliable. Insufficient data are given to judge whether relapses were indeed relapses or not.

In a cohort of 345 Japanese patients with PNH who received eculizumab, eleven patients had a poor response. All of them had a single missense C5 heterozygous mutation, whose prevalence among the patients with PNH (3.2%) was similar to that among healthy Japanese persons (3.5%), and which was also identified in the Han Chinese population. A patient of Asian ancestry in Argentina who had a poor response had a very similar mutation. Both C5 (with and without the mutation) caused hemolysis in vitro, but only C5 without the mutation was able to bind to and have its hydrolysis prevented by eculizumab.<sup>121</sup> To date, similar mutations in C5 have not been described in patients with aHUS.

## Summary and conclusion

The molecular understanding of the mechanism of TMA related to aHUS has led to the novel therapeutic application of a C5 inhibitor, eculizumab. Controlled clinical trials, following upon dozens of case reports and a few case series, confirm that aHUS may be controlled in the overwhelming majority of patients and likely at a higher frequency than with PE alone by historical database comparisons. Recent consensus guidelines and our extensive review support that

the drug has become the treatment of choice for patients of all ages with aHUS.

Despite the impressive clinical outcomes using eculizumab in a variety of circumstances in patients with aHUS that were summarized in our review, there remain absent biomarkers of disease diagnosis, ongoing clinical activity, or response to the drug. As with all pharmacologic agents, risks and side effects may occur; however, in aHUS, these are largely outweighed by efficacy.

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