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Eculizumab: A Review of Its Use in Atypical Haemolytic Uraemic Syndrome

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Abstract The recombinant humanized monoclonal antibody eculizumab (Soliris®) is a complement inhibitor that is indicated for use in the treatment of atypical haemolytic uraemic syndrome (aHUS). This article reviews the clinical efficacy and tolerability of eculizumab in the treatment of patients with aHUS, as well as summarizing its pharmacological properties. Intravenous eculizumab inhibited complement-mediated thrombotic microangiopathy in patients aged ≥12 years with aHUS, according to the results of two noncomparative, multinational, 26-week, phase II trials. At 26 weeks, the platelet count was significantly increased in patients with progressing thrombotic microangiopathy despite plasma exchange/infusion, and thrombotic microangiopathic event-free status was achieved in 80 % of patients with a long disease duration and chronic kidney disease who received long-term plasma exchange/infusion. Renal function and health-related quality of life also improved with eculizumab therapy in both studies. Outcomes were maintained or further improved throughout 2 years of follow-up. Eculizumab was also effective in adult and paediatric patients with aHUS, according to the results of additional prospective or retrospective trials. Intravenous eculizumab was generally well tolerated in patients with aHUS. Eculizumab is associated with an increased susceptibility to meningococcal infection, so patients should be immunized with meningococcal vaccine. In conclusion, eculizumab is a valuable new agent for use in the treatment of aHUS.

Eculizumab in atypical haemolytic uraemic syndrome (aHUS): a summary

Inhibits complement-mediated thrombotic microangiopathy in patients with progressing thrombotic microangiopathy despite multiple plasma exchanges/infusions, as shown by significant increases in platelet count

Inhibits complement-mediated thrombotic microangiopathy in patients with long aHUS disease duration and chronic kidney disease managed with long-term plasma exchange/infusion, as shown by the absence of thrombotic microangiopathic events, permitting the discontinuation of plasma exchange/infusion

Improves renal function, with earlier intervention associated with greater improvements in estimated glomerular filtration rate

Improves health-related quality of life

Outcomes maintained or further improved throughout 2 years of follow-up

Generally well tolerated in patients with aHUS

Immunization with meningococcal vaccine recommended ≥2 weeks before administration of the first dose of eculizumab, although prophylactic antibacterials can be administered to patients who receive eculizumab <2 weeks after meningococcal vaccination

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1 Introduction

Atypical haemolytic uraemic syndrome (aHUS) is a genetic, life-threatening, chronic disease of complement-mediated thrombotic microangiopathy, often characterized by microangiopathic haemolytic anaemia (with high lactate dehydrogenase [LDH] levels and reduced or undetectable haptoglobin levels), thrombocytopenia and acute renal failure [1–5]. aHUS is a disease that affects both paediatric patients and adults [4], and usually describes cases of haemolytic uraemic syndrome that are not caused by Shiga toxin-producing micro-organisms [6, 7]. Although rare, aHUS has a poor prognosis and is associated with high morbidity and mortality [1, 7]. In one study, progression to end-stage renal disease was seen in 56 % of adults with aHUS within the first year [8].

aHUS is associated with uncontrolled activation of the alternative complement pathway, which leads to damage to endothelial cells and thrombotic microangiopathy [4, 6]. Although lesions most commonly affect the kidneys, there may be multiorgan involvement, with peripheral thrombi and cardiovascular, gastrointestinal, pulmonary and neurological complications all reported in patients with aHUS [9, 10]. In approximately 60–70 % of cases, the activation of the alternative complement pathway seen in aHUS is associated with identified mutations in complement regulators or activators and/or autoantibodies against these proteins, resulting in chronic disease [11].

The underlying genetic abnormality affects not only disease outcome, but also the response to renal transplantation and plasma therapy [1]. For example, 60–70 % of patients with a mutation in the gene encoding complement factor H (CFH) develop terminal renal failure within 1 year of diagnosis and 75–90 % develop clinical manifestations of aHUS following renal transplantation [1, 10]. By contrast, 80–90 % of patients who have an isolated membrane co-factor protein (MCP) mutation will achieve resolution of clinical manifestations without plasma therapy, although subsequently, patients will frequently display additional clinical manifestations of aHUS [1, 10]. MCP mutations occur in 10–15 % of patients with aHUS [10]. It should be noted that while plasma exchange/infusion may transiently normalize haematological measures in patients with aHUS, it does not treat the underlying systemic disease, and outcomes remain poor [8, 10, 12].

There has been a severe, previously unmet need for new treatment options in aHUS [12]. Blockade of terminal complement activation represents a rational approach to the treatment of aHUS. The complement inhibitor eculizumab (Soliris®) prevents the formation of the terminal complement complex C5b-9 via specific, high-affinity binding to complement protein C5 [7]. Eculizumab is approved for the treatment of aHUS in a number of countries worldwide, including the EU, the USA, Japan, Canada, Australia, Iceland, Norway, Israel, Switzerland, Colombia and Russia [13–16]. Specifically, eculizumab is approved for the treatment of aHUS in the EU [13], and for the treatment of patients with aHUS to inhibit complement-mediated thrombotic microangiopathy in the USA [14] (see also Sect. 6).

This article reviews the clinical efficacy and tolerability of eculizumab in the treatment of patients with aHUS, as well as summarizing its pharmacological properties. Discussion of the use of eculizumab in its other approved indication, the treatment of paroxysmal nocturnal haemoglobinuria [17], is beyond the scope of this review.

2 Pharmacodynamic Properties

This section provides a brief overview of the mechanism of action and pharmacodynamic effects of eculizumab in patients with aHUS. Some of the data concerning its pharmacodynamic effects were obtained from case reports in adult [18–28] and paediatric [6, 24, 29–35] patients with aHUS, including renal transplant recipients who experienced post-transplant aHUS [6, 19–21, 23, 24, 27, 28, 30, 32, 35]; some of these patients had experienced at least one prior graft loss [19, 21, 24, 28, 30].

The recombinant humanized monoclonal IgG2/4κ antibody eculizumab comprises murine complementarity-determining regions grafted onto a human heavy and light chain antibody framework (Fig. 1) [13, 17].

Eculizumab is a complement inhibitor [14]. It binds to the complement protein C5 with high affinity (Kd of 120 pmol/L), inhibiting the cleavage of C5 to C5a (a potent proinflammatory mediator) and C5b, thereby preventing the generation of the terminal complement complex C5b-9 and blocking complement-mediated thrombotic microangiopathy [14, 17, 36, 37].

The critical role of C5 activation in the development of aHUS was shown in a murine model that functionally mimics the CFH mutations seen in patients with aHUS [38]. Renal histology remained normal over 8 months of follow-up in mice with the CFH mutation and concomitant deficiency in C5. By contrast, spontaneous renal disease developed in mice with the CFH mutation and sufficient C5, and these mice were hypersensitive to experimentally triggered renal injury; the hypersensitive response was specifically dependent on C5 activation [38].

In patients with aHUS, pharmacodynamic activity was directly correlated with serum eculizumab concentrations, and essentially complete blockade of terminal complement activity was seen at maintenance trough serum eculizumab concentrations of 50–100 μg/mL (see also Sect. 3) [13].

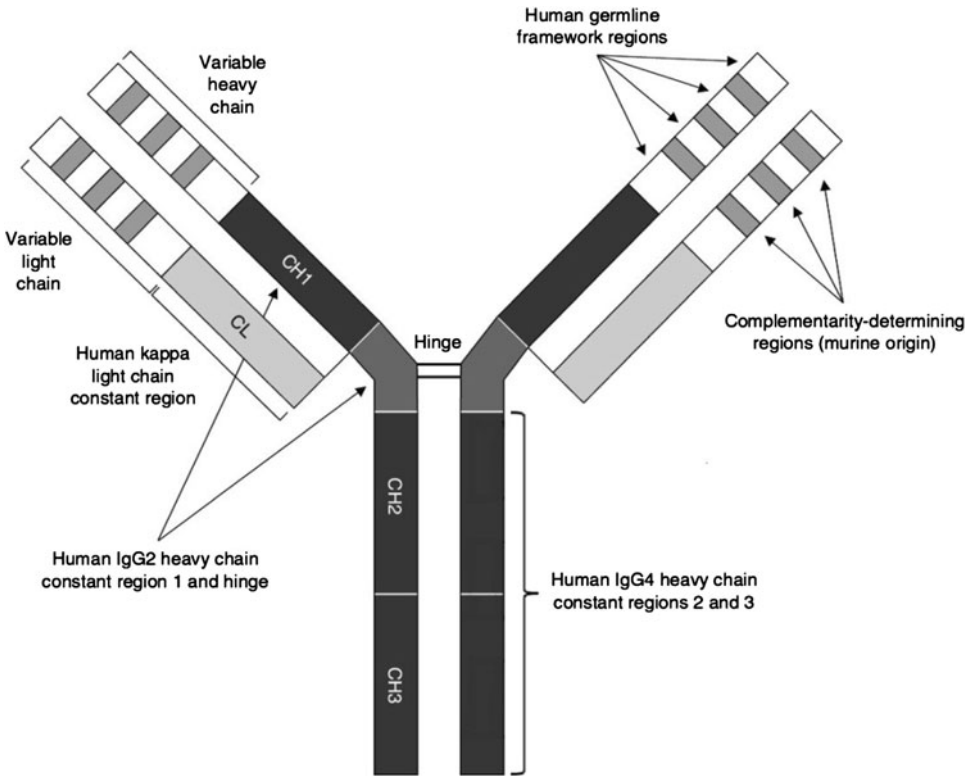

Fig. 1 Structure of the humanized monoclonal antibody eculizumab [17]

Indeed, rapid and sustained reductions in terminal complement activity were seen in patients with aHUS who received recommended dosages of eculizumab [13]. For example, in patients with aHUS who received eculizumab in the two pivotal clinical trials (see Sect. 4 for further details), complement activity was significantly ($p < 0.001$) reduced within 1 h of starting treatment with eculizumab, and inhibition of terminal complement activity was maintained over 2 years of eculizumab treatment [5, 39].

Case reports also showed that eculizumab completely blocked terminal complement activity in patients with aHUS [19, 29, 31], with associated resolution of haemolysis [19, 20, 31, 32]. Haemoglobin levels were normalized [20, 33, 34] and platelet levels also normalized/increased [6, 19, 20, 22, 23, 29–31, 33, 34]. Treatment with eculizumab was generally associated with normalization (or near normalization) of levels of LDH [18, 22, 30, 31, 33, 34] and haptoglobin [18, 19, 21–23, 34]. Patients also experienced improved renal function [6, 18–20, 25–28, 32, 35], with stabilization or normalization of creatinine levels [21–24, 29–31, 33, 34].

Renal graft biopsies showed improvement of thrombotic microangiopathy in a male adolescent patient who had experienced two prior graft losses because of post-transplant aHUS, and who received ongoing treatment with eculizumab after his third transplant [30]. A biopsy performed 12 months after renal transplantation showed no evidence of thrombotic microangiopathy [30]. Similarly, after 7 weeks' treatment with eculizumab, no thrombotic microangiopathy and moderate residual interstitial fibrosis was seen on renal graft biopsy in a 34-year-old woman with aHUS following renal transplantation [23].

3 Pharmacokinetic Properties

In patients with aHUS, bodyweight-based dosage recommendations (see Sect. 6) were modelled on a target trough serum eculizumab concentration of 50–100 μg/mL [40]. This is higher than the target trough serum eculizumab concentration of 35 μg/mL used in patients with paroxysmal nocturnal haemoglobinuria, as incomplete terminal complement inhibition was sometimes seen using this lower target trough concentration; such breakthrough is considered clinically unacceptable in patients with aHUS [40]. The target maximum serum concentration (C_{max}) was set at <700 μg/mL [40].

Data regarding the pharmacokinetics of recommended dosages of intravenous eculizumab in adults aged >18 years with aHUS were obtained from two pivotal clinical trials ($n = 15$ and 16) [5] and from a subset of adult patients in a retrospective study ($n = 4$) [i.e. the pharmacokinetic analyses only included a proportion of patients from this trial] [40, 41]. Data regarding the pharmacokinetics of recommended dosages of intravenous eculizumab in adolescents aged 12–18 years with aHUS were also obtained from the two pivotal clinical trials ($n = 5$ and 1) [5] and from a subset of patients in the

retrospective study ($n = 2$) [40]; data from children aged 6 to <12 years ($n = 5$), 2 to <6 years ($n = 4$) and <2 years ($n = 5$) were also obtained from the retrospective study [40]. A population pharmacokinetic analysis using data from these studies was also conducted [14].

3.1 Absorption and Distribution

During administration of the induction eculizumab regimen in adult patients with aHUS, C_{max} ranged from 145 to 163 μg/mL across studies, the minimum serum concentration (C_{min}) ranged from 90 to 113 μg/mL across studies and the area under the serum concentration–time curve (AUC) ranged from 19,611 to 22,928 μg·h/mL across studies [5, 40]. During administration of the maintenance eculizumab regimen, ranges for C_{max}, C_{min} and AUC were 316–431 μg/mL, 100–214 μg/mL and 63,028–104,228 μg·h/mL, respectively [5, 40].

During administration of the induction eculizumab regimen in adolescent patients with aHUS, C_{max} ranged from 147 to 222 μg/mL across studies, C_{min} ranged from 104 to 130 μg/mL across studies and the AUC ranged from 20,905 to 28,908 μg·h/mL across studies [5, 40]. During administration of the maintenance eculizumab regimen, ranges for C_{max}, C_{min} and AUC were 392–457 μg/mL, 161–205 μg/mL and 95,117–99,956 μg·h/mL, respectively [5, 40].

Across the three age groups of children, ranges for C_{max}, C_{min} and AUC were 223–316 μg/mL, 154–171 μg/mL and 31,299–39,537 μg·h/mL, respectively, during the induction eculizumab regimen, and 278–473 μg/mL, 94–234 μg/mL and 56,583–113,954 μg·h/mL, respectively, during the maintenance eculizumab regimen [40].

Population pharmacokinetic analysis found that eculizumab had a volume of distribution of 6.14 L in a typical patient with aHUS who weighed 70 kg [14].

3.2 Metabolism and Elimination

Eculizumab contains only naturally occurring amino acids and has no known active metabolites [13]. Human antibodies undergo endocytotic digestion in cells of the reticuloendothelial system and are predominantly catabolized by lysosomal enzymes to small peptides and amino acids [13].

In a typical patient with aHUS who weighed 70 kg, the eculizumab clearance was 14.6 mL/h and it had an elimination half-life of ≈12.1 days, according to the results of population pharmacokinetic analysis [14].

3.3 Special Patient Populations

Although dedicated studies have not evaluated the pharmacokinetics of eculizumab in special patient populations (e.g. in patients with renal or hepatic impairment, or on the basis of age, race or gender), population pharmacokinetic analysis demonstrated that the pharmacokinetics of eculizumab were not affected by age, race, gender or renal impairment [14].

Plasma exchange markedly increased the systemic clearance of eculizumab to 3,660 mL/h and markedly reduced its elimination half-life to 1.26 h [14, 40]. Given this, supplemental dosing of eculizumab is needed in patients receiving concomitant plasmapheresis or plasma exchange, or fresh frozen plasma infusion [13, 14] (see also Sect. 6).

4 Therapeutic Efficacy

The focus of this section are the two noncomparative, prospective, pivotal trials on which the approval of eculizumab in patients with aHUS was based [5], supplemented with results of additional studies in adults [42] and paediatric patients [41, 43, 44] with aHUS. Numerous case reports also describe the efficacy of eculizumab in patients with aHUS [6, 11, 18–23, 25–35, 45–47]; however, these case reports are not discussed further.

4.1 In Patients with Progressing Thrombotic Microangiopathy Despite Plasma Exchange/Infusion

A noncomparative, multinational, 26-week, phase II trial examined the efficacy of eculizumab in 17 patients aged ≥12 years with aHUS who had clinical evidence of progressing thrombotic microangiopathy despite plasma exchange/infusion [5] (see Table 1 for trial inclusion and exclusion criteria). Patients in this trial had a median time from diagnosis to screening of 9.7 months, a median time from the current clinical presentation of aHUS to screening of 0.8 months and renal damage (e.g. 100 % of patients had an estimated glomerular filtration rate [eGFR] of <60 mL/min/1.73 m^2 for a median of 17 days) [5]. Additional baseline patient characteristics are shown in Table 1 [5].

Intravenous eculizumab was administered according to the recommended schedule (see Table 1), and patients were immunized with a meningococcal vaccine [5]. Fifteen patients completed 26 weeks' treatment with eculizumab [5]. After completion of the 26-week trial, 13 patients continued treatment with eculizumab in an ongoing extension study, with data available after a median treatment duration of 64 weeks [5] and 100 weeks (available as an abstract) [48].

The primary endpoints were the change in platelet count over 26 weeks and the proportion of patients with normalization of haematological values (see Table 1 for

Table 1 Trial design details and baseline patient characteristics in two noncomparative, multinational, phase II trials examining the efficacy of eculizumab in patients with atypical haemolytic uraemic syndrome [5]

	Pts with progressing TMA despite PE/PI ($n = 17$)	Pts with long disease duration and CKD receiving long-term PE/PI ($n = 20$)
Baseline characteristics		
Median pt age (range) (years)	28 (17–68)	28 (13–63)
No identified genetic mutation or autoantibody (% of pts)	24	30
Median time from diagnosis to screening (months)	9.7	48.3
Median time from current clinical TMA manifestation to screening (months)	0.8	8.6
Study design	Screening period of ≤3 days, then 26-week treatment period followed by a long-term extension	Screening period of ≤2 weeks, then 8-week observation period, then 26-week treatment period followed by a long-term extension
Key inclusion criteria	Aged ≥12 years; atypical haemolytic uraemic syndrome; progressing TMA measured by low platelet count (<150 × 10^9/L) at screening and a platelet count >25 % lower than the average of three platelet count measures before the most recent TMA complication; ≥4 PE/PI sessions in the week before screening; evidence of haemolysis[a]; impaired renal function[b]; no requirement for an identified genetic mutation	Aged ≥12 years; atypical haemolytic uraemic syndrome; no platelet count decrease of >25 % during the 8-week observation period; ≥1 PE/PI sessions every 2 weeks but ≤3 times per week for ≥8 weeks; evidence of haemolysis[a]; impaired renal function[b]; no requirement for an identified genetic mutation
Key exclusion criteria	ADAMTS13 activity ≤5 % in plasma; evidence of Shiga toxin-producing *Escherichia coli* infection; prior eculizumab exposure	
Eculizumab regimen	IV eculizumab 900 mg/week for 4 weeks, then 1,200 mg 1 week later and then a maintenance dosage of 1,200 mg every 2 weeks[c]	
Primary efficacy endpoints	Change in platelet count over 26 weeks	TMA event-free status[d]
	Normalization of haematological values[e]	Normalization of haematological values[e]

ADAMTS13 a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13, *CKD* chronic kidney disease, *IV* intravenous, *LDH* lactate dehydrogenase, *LLN* lower limit of normal, *PE* plasma exchange, *PI* plasma infusion, *pts* patients, *TMA* thrombotic microangiopathy, *ULN* upper limit of normal

[a] Defined as an LDH level of ≥ULN, a haptoglobin level of <LLN or the presence of schistocytes

[b] Defined as a creatinine level of ≥ULN

[c] Pts who received PE/PI during the eculizumab treatment period received a supplemental 600 mg dose of eculizumab before PI or within 1 h after the completion of each PE

[d] Defined as no decrease in platelet count of >25 %, no PE or PI and no initiation of dialysis for ≥12 weeks

[e] Defined as a normal platelet count and LDH level, sustained for ≥2 consecutive measurements over a period of ≥4 weeks

definition) [5]. Efficacy was assessed in the intent-to-treat (ITT) population [5, 48].

Eculizumab inhibited complement-mediated thrombotic microangiopathy and improved renal function in patients with aHUS and progressing thrombotic microangiopathy despite plasma exchange/infusion [5].

After 26 weeks' treatment with eculizumab, the platelet count had significantly increased from baseline by a mean of 73 × 10^9/L, 76 % of patients had normalization of haematological values and 82 % of patients had normalization of platelet counts (Table 2) [5]. The significant increase from baseline in platelet count was maintained in the extension phase, and 88 % of patients had normalization of haematological values and platelet counts after a median treatment duration of 64 [5] and 100 [48] weeks (Table 2).

Thrombotic microangiopathy event-free status was achieved by 15 of 17 eculizumab recipients (88 %) at week 26 and in the extension phase [5, 48] (Table 2) [5]. In addition, the median thrombotic microangiopathy intervention rate (defined as the number of plasma exchange/infusion interventions and/or new dialyses required per patient per day) significantly ($p < 0.001$) decreased from 0.88 events/patient/day at baseline to 0 events/patient/day at week 26 [5] and after a median treatment duration of 64 [5] and 100 [48] weeks in the extension phase. Plasma exchange/infusion was discontinued in 88 % of patients for the entire trial [5].

Table 2 Efficacy of eculizumab in patients with atypical haemolytic uraemic syndrome. Results of two noncomparative, multinational, phase II trials at week 26 [5] and after continued follow-up in the extension phase [5, 48, 50, 51]

Endpoint	Pts with progressing TMA despite PE/PI (n = 17)			Pts with long disease duration and CKD receiving long-term PE/PI (n = 20)		
	Week 26	Week 64[a]	Week 100[a]	Week 26	Week 62[a]	Week 114[a]
Mean change from baseline in platelet count[b] ($\times 10^9$/L)	73[c]***	91***	88****	5		
TMA event-free status[d] (% of pts)	88	88	88	80[c]	85	95
Normalization of haematological values[e] (% of pts)	76[c]	88	88	90[c]	90	90
Normalization of platelet count[f] (% of pts)	82	88	88			
Mean increase from baseline in eGFR (mL/min/1.73 m^2)	32***	32***	32***	6***	9**	7*
Increase in eGFR of ≥15 mL/min/1.73 m^2 (% of pts)	47	53	59	5	15	40
Improvement in CKD of ≥1 stage (% of pts)	59	65	71	35	45	60
≥25 % reduction from baseline in serum creatinine level (% of pts)	65	76	76	15	35	60
Decrease in proteinuria of ≥1 grade[g] (% of pts)	80	82	78	55	78	63
Mean increase from baseline in EQ-5D score[h]	0.32***	0.30***	0.33****	0.10***	0.13***	0.14****

CKD chronic kidney disease, *eGFR* estimated glomerular filtration rate, *EQ-5D* EuroQoL Group 5-Dimension Self-Report Questionnaire, *PE* plasma exchange, *PI* plasma infusion, *pts* patients, *TMA* thrombotic microangiopathy

* $p < 0.05$, ** $p < 0.01$, *** $p \leq 0.001$, **** $p \leq 0.0001$ vs. baseline

[a] Median treatment duration. The time of evaluation differed for some endpoints. For example, the change from baseline in platelet count was evaluated at weeks 60 [5] and 96 [48] in pts with progressing TMA despite PE/PI. In addition, the change from baseline in eGFR was evaluated at week 60 [5] in both trials, at week 96 in pts with progressing TMA despite PE/PI [48] and at week 104 in pts with long disease duration and CKD receiving long-term PE/PI [51], the reduction in proteinuria was evaluated at week 96 in pts with progressing TMA despite PE/PI [48] and the change in EQ-5D score was evaluated at week 96 in both trials [48, 50]

[b] The median baseline platelet count was 118 × 10^9/L in pts with progressing TMA despite PE/PI and 218 × 10^9/L in pts with long disease duration and CKD receiving long-term PE/PI

[c] Primary endpoint

[d] Defined as no decrease in platelet count of >25 %, no PE or PI and no initiation of dialysis for ≥12 weeks

[e] Defined as a normal platelet count and LDH level, sustained for ≥2 consecutive measurements over a period of ≥4 weeks

[f] Defined as a platelet count of ≥150× 10^9/L

[g] Evaluated in pts with proteinuria of at least grade 1 (15, 11 and 9 evaluable pts at weeks 26, 64 and 100, respectively, in pts with progressing TMA despite PE/PI, and 11, 9 and 16 evaluable pts at weeks 26, 62 and 114, respectively, in pts with long disease duration and CKD receiving long-term PE/PI)

[h] EQ-5D scores range from 0 to 1, with higher scores indicating better health-related quality of life

With eculizumab, mean eGFR significantly increased from baseline by 32 mL/min/1.73 m^2 at week 26 [5]; this increase was maintained in the extension phase [5, 48] (Table 2). In addition, an increase in eGFR of ≥15 mL/min/1.73 m^2 occurred in 47 % of eculizumab recipients at week 26, and in 53 and 59 % of eculizumab recipients after a median treatment duration of 64 and 100 weeks, respectively [5, 48] (Table 2). Earlier intervention with eculizumab was associated with greater improvement in eGFR ($p = 0.007$) [5]. Four of five patients (80 %) who required dialysis at the start of eculizumab therapy were able to discontinue dialysis during this trial [5].

In addition, an improvement from baseline of at least one chronic kidney disease stage occurred in 59 % of eculizumab recipients at week 26, and in 65 and 71 % of eculizumab recipients after a median treatment duration of 64 and 100 weeks, respectively [5, 48] (Table 2). At these time points, a ≥25 % reduction from baseline in serum creatinine levels occurred in 65, 76 and 76 % of eculizumab recipients, respectively, and a decrease in proteinuria of at least 1 grade (among patients with proteinuria of at least grade 1 severity) occurred in 80, 82 and 78 % of evaluable eculizumab recipients, respectively [5, 48] (Table 2).

In terms of health-related quality of life (HR-QOL), a significant increase from baseline in the mean EuroQoL Group 5-Dimension Self-Report Questionnaire (EQ-5D) score was reported in eculizumab recipients at week 26 and in the extension phase (Table 2) [5, 48]. A clinically meaningful EQ-5D score of 0.06 was exceeded by 12 of 15 (80 %) eculizumab recipients at week 26 and by 13 of 15 (87 %) eculizumab recipients after a median treatment duration of 64 weeks [5].

The efficacy of eculizumab therapy appeared similar in patients with or without identified genetic complement mutations or CFH autoantibodies [5, 48].

4.1.1 Subgroup Analyses

Subgroup analyses (available as posters) of this trial in patients with progressing thrombotic microangiopathy despite plasma exchange/infusion [5] were conducted in those receiving ($n = 5$) or not receiving ($n = 12$) dialysis at baseline [49] and those with ($n = 7$) or without ($n = 10$) prior renal transplantation [39].

Eculizumab inhibited complement-mediated thrombotic microangiopathy both in patients receiving and those not receiving dialysis at baseline [49] and in patients with or without prior renal transplantation [39].

Over 2 years of follow-up, the endpoints of haematological normalization and thrombotic microangiopathy event-free status were achieved and maintained by 100 % of patients receiving dialysis at baseline and by 83 % of patients not receiving dialysis at baseline [49]. By week 104, sustained, time-dependent increases from baseline in eGFR of 511 and 84 % were seen in patients receiving and not receiving dialysis at baseline, respectively. In addition, significant mean increases from baseline in the EQ-5D score were seen both in patients receiving (0.31; $p = 0.0004$) and not receiving (0.25; $p < 0.0001$) dialysis at baseline [49].

In patients with or without prior renal transplantation, the mean change in platelet count was 72.4 and 131.9 $\times$ 10^9/L, respectively, and the mean change in eGFR was 14.8 and 48.3 mL/min/1.73 m^2, respectively, at 104 weeks [39]. In both patient groups, earlier intervention with eculizumab was associated with greater increases in eGFR, and a time-dependent increase in eGFR was seen over 104 weeks of follow-up [39].

4.2 In Patients With Long Disease Duration and Chronic Kidney Disease Receiving Long-Term Plasma Exchange/Infusion

A noncomparative, multinational, 26-week, phase II trial examined the efficacy of eculizumab in 20 patients aged ≥12 years with aHUS who were receiving long-term plasma exchange/infusion (see Table 1 for trial inclusion and exclusion criteria) [5]. Patients in this trial had a longer duration of disease (median time from diagnosis to screening of 48.3 months; Table 1), compared with the trial in patients who had progressing thrombotic microangiopathy even with plasma exchange/infusion [5]. Patients had a median time from the current clinical presentation of aHUS to screening of 8.6 months, most of the patients had chronic kidney disease (e.g. 90 % of patients had an eGFR of <60 mL/min/1.73 m^2 for a median of 299 days), and patients had been receiving plasma exchange/infusion for a median 10.1 months. Additional baseline patient characteristics are also shown in Table 1 [5].

Patients whose platelet count did not decrease by more than 25 % during an 8-week observation period subsequently discontinued plasma exchange/infusion and received intravenous eculizumab according to the recommended schedule (Table 1) [5]. Patients were immunized with a meningococcal vaccine [5]. After completion of the 26-week trial, 19 patients continued treatment with eculizumab in an ongoing extension study, with data available after a median treatment duration of 62 weeks [5] and 114 weeks (available as an abstract [50] and poster [51]).

The primary endpoints were thrombotic microangiopathy event-free status and the proportion of patients with normalization of haematological values (see Table 1 for definitions) [5]. Efficacy was assessed in the ITT population [5, 50].

Eculizumab inhibited complement-mediated thrombotic microangiopathy in patients with aHUS who had been receiving long-term plasma exchange/infusion, permitting the discontinuation of plasma exchange/infusion in all patients [5].

Thrombotic microangiopathy event-free status was achieved in 80 % of eculizumab recipients at 26 weeks and in 85 % [5] and 95 % [50, 51] of eculizumab recipients after a median treatment duration of 62 [5] and 114 [50, 51] weeks, respectively (Table 2). The median thrombotic microangiopathy intervention rate significantly ($p < 0.001$) decreased from 0.23 events/patient/day at baseline to 0 events/patient/day at week 26 and in the extension phase [5].

Mean platelet counts were maintained with eculizumab at 26 weeks (mean increase from baseline of 5 $\times$ 10^9/L), without plasma exchange/infusion, and normalization of haematological values was achieved and maintained in 90 % of patients (Table 2) [5, 51].

Several measures of renal function showed increasing improvement over time with eculizumab therapy. For example, an increase in eGFR of ≥15 mL/min/1.73 m^2 occurred in 5 % of eculizumab recipients at week 26, and in 15 and 40 % of eculizumab recipients after a median treatment duration of 62 and 114 weeks, respectively [5, 50] (Table 2). In addition, at the corresponding time points, an improvement from baseline of at least one chronic kidney disease stage occurred in 35, 45 and 60 % of eculizumab recipients, respectively, and a ≥25 % reduction from baseline in serum creatinine levels occurred in 15, 35 and 60 % of eculizumab recipients, respectively [5, 50, 51] (Table 2). Among patients with proteinuria of at least grade 1 severity at baseline, a decrease in proteinuria of at least 1 grade occurred in 55 % of eculizumab recipients at week 26, and in 78 and 63 % of eculizumab recipients after a median treatment duration of 62 and 114 weeks, respectively [5, 51] (Table 2). With eculizumab, mean eGFR significantly increased from baseline at weeks 26, 60 and

104 (Table 2) [5, 51]. Earlier intervention with eculizumab was associated with greater improvements in eGFR ($p < 0.001$) [5].

In terms of HR-QOL, a significant increase from baseline in the mean EQ-5D score was reported in eculizumab recipients at week 26 [5] and was maintained in the extension phase [5, 50] (Table 2). The mean change in the EQ-5D score exceeded the clinically meaningful threshold of 0.06 over 104 weeks of follow-up [51]. A clinically meaningful EQ-5D score of 0.06 was exceeded by 8 of 11 (73 %) eculizumab recipients at both week 26 and after a median treatment duration of 62 weeks [5].

None of the patients receiving long-term eculizumab therapy required plasma exchange/infusion or new dialysis during either the 26-week study or the extension phase [5, 50]. In addition, the efficacy of eculizumab therapy appeared similar in patients with or without identified genetic complement mutations or CFH autoantibodies [5, 50].

4.2.1 Subgroup Analysis

A subgroup analysis (available as a poster) of this trial in patients with long disease duration and chronic kidney disease who had been receiving long-term plasma exchange/infusion [5] was conducted in those with ($n = 8$) or without ($n = 12$) prior renal transplantation [39].

In patients with or without prior renal transplantation, the mean change in platelet count was −39.1 and 21.0 × 10^9/L, respectively, the mean platelet count was 221.1 and 249.3 × 10^9/L, respectively, and the mean change in eGFR was 3.9 and 7.3 mL/min/1.73 m^2, respectively, at 104 weeks [39]. In both patient groups, earlier intervention with eculizumab was associated with greater increases in eGFR, and a time-dependent increase in eGFR was seen over 104 weeks of follow-up [39].

4.3 Additional Trials

Results are available from three additional trials examining the use of eculizumab in patients with aHUS, including prospective trials in adults [42] and paediatric patients [43], and a retrospective study in paediatric patients [41, 44]. All three studies are available as abstracts [41–44].

4.3.1 In Adults

An ongoing, noncomparative, phase II trial enrolled 41 adults aged ≥18 years (mean age 40.3 years) with aHUS and platelet levels below the lower limit of normal [42]. Thirty patients (73 %) had newly diagnosed aHUS, with a median time from diagnosis to the initiation of eculizumab of 2 weeks. Overall, the median time from the diagnosis of aHUS until screening was 0.8 months, and the median duration of the current clinical manifestation of aHUS was 0.5 months. Thirty-five patients (85 %) had received plasma exchange/infusion during their current clinical manifestation of aHUS (prior plasma exchange/infusion was not an inclusion criterion), and 41 % of patients had an eGFR of ≤60 mL/min/1.73 m^2 at baseline [42].

The primary endpoint was the proportion of patients with a complete thrombotic microangiopathy response at 26 weeks (defined as normalization of platelets and LDH and <25 % increase from baseline in serum creatinine levels on two consecutive measurements ≥4 weeks apart); 38 patients (93 %) received 26 weeks of eculizumab treatment [42].

Eculizumab inhibited complement-mediated thrombotic microangiopathy in adults with aHUS [42]. At week 26, a complete thrombotic microangiopathy response was seen in 30 eculizumab recipients (73 %). Haematological normalization (defined as platelets and LDH normalized for at least two consecutive measurements ≥4 weeks apart) was seen in 88 % of patients and platelet count normalization (defined as a platelet count of ≥150 × 10^9/L on at least two consecutive measurements ≥4 weeks apart) was seen in 98 % of patients. The mean platelet count was significantly ($p < 0.0001$) increased from baseline by 119 × 10^9/L [42].

With eculizumab, the mean eGFR was significantly ($p < 0.0001$) increased from baseline by 26.1 mL/min/1.73 m^2, and was increased from baseline by ≥15 mL/min/1.73 m^2 in 54 % of patients [42]. In addition, an improvement from baseline of at least one chronic kidney disease stage occurred in 63 % of patients [42].

By week 26, 20 of the 24 patients who were receiving dialysis at baseline had discontinued dialysis [42]. An additional two patients who were not receiving dialysis at baseline started dialysis during the treatment period [42].

4.3.2 In Paediatric Patients

4.3.2.1 Prospective Study An ongoing, noncomparative, phase II trial enrolled 22 paediatric patients aged 1 month to 17 years (mean age 6.6 years) with aHUS [43]. Sixteen patients (73 %) had newly diagnosed aHUS, with a median time from diagnosis to the initiation of eculizumab of 6 days. Overall, the median time from the diagnosis of aHUS until screening was 0.56 months, and the median duration of the current clinical manifestation of aHUS was 0.2 months. At baseline, ten patients (45 %) were receiving plasma exchange/infusion, and 82 % had an eGFR of ≤60 mL/min/1.73 m^2 [43].

The primary endpoint was the proportion of patients with a complete thrombotic microangiopathy response at 26 weeks (defined as normalization of platelets and LDH

and a ≥25 % improvement from baseline in serum creatinine levels on two consecutive measurements >4 weeks apart); 19 patients (86 %) completed 26 weeks of eculizumab treatment [43].

Early intervention with eculizumab was effective in paediatric patients with aHUS [43]. At week 26, a complete thrombotic microangiopathy response was seen in 14 eculizumab recipients (64 %). Haematological normalization (defined as platelets and LDH normalized for at least two consecutive measurements ≥4 weeks apart) was seen in 82 % of patients and platelet count normalization (defined as a platelet count of $\geq 150 \times 10^9$/L on at least two consecutive measurements ≥4 weeks apart) was seen in 95 % of patients [43].

With eculizumab, the mean eGFR was significantly ($p < 0.0001$) increased from baseline by 64 mL/min/1.73 m^2, and was increased from baseline by ≥15 mL/min/1.73 m^2 in 86 % of patients [43]. In addition, a reduction from baseline in serum creatinine levels of ≥25 % was seen in 73 % of eculizumab recipients [43].

By week 26, 9 of the 11 patients who were receiving dialysis at baseline had discontinued dialysis, and all of the 11 patients not receiving dialysis at baseline remained dialysis-free during the study period [43]. All ten patients receiving plasma exchange/infusion at baseline were able to discontinue plasma exchange/infusion [43].

4.3.2.2 Retrospective Study A retrospective study reported data from 19 male and female paediatric patients aged <18 years who had aHUS and who had received at least one dose of intravenous eculizumab between 2007 and 2009 outside of a controlled clinical trial setting [41, 44]. Five patients were aged <2 years, ten patients were aged 2–11 years and four patients were aged 12–17 years. The median duration of eculizumab therapy was 28 weeks (range 1–70 weeks). Data were collected retrospectively from medical records [44].

In terms of baseline characteristics, a platelet count of $<150 \times 10^9$/L was seen in 8 of 19 patients (42 %), an eGFR of <60 mL/min/1.73 m^2 was seen in 13 patients (68 %), eight patients (42 %) had received dialysis within 4 weeks of the first dose of eculizumab, and six patients (32 %) had received a kidney transplant [44]. A complement regulatory factor mutation or anti-complement regulatory factor antibodies were identified in ten patients (53 %) [41, 44].

Eculizumab was effective in the treatment of paediatric patients with aHUS [41, 44]. A normal platelet count was seen in 17 of 19 eculizumab recipients (89 %), including in seven of the eight patients (88 %) who had abnormal platelet counts at baseline [41, 44].

Thrombotic microangiopathy event-free status (defined as no decrease in platelet count of >25 %, no plasma exchange/infusion and no new dialysis for ≥12 weeks) was achieved by 13 of 19 eculizumab recipients (68 %), and the median thrombotic microangiopathy intervention rate (defined as the number of plasma exchange/infusion interventions and new dialyses required per patient per day) was 0 events/patient/day during eculizumab therapy, compared with 0.31 events/patient/day pretreatment [41, 44].

An improvement in eGFR of ≥15 mL/min/1.73 m^2 occurred in 9 of 19 eculizumab recipients (47 %) [41, 44]. Four of eight eculizumab recipients (50 %) were able to discontinue dialysis and no patient required new dialysis [41, 44].

The efficacy of eculizumab therapy appeared similar in patients with or without identified genetic mutations [41].

5 Tolerability

Data regarding the tolerability of intravenous eculizumab in patients with aHUS were obtained from the trials reported in Sect. 4 [5, 41–43], supplemented by data from the US prescribing information [14].

Intravenous eculizumab was generally well tolerated in patients with aHUS [5, 41–43].

Among eculizumab recipients with aHUS and progressing thrombotic microangiopathy despite plasma exchange/infusion, 12 of 17 patients (71 %) had adverse events considered possibly, probably or definitely related to eculizumab during the 26-week study or its extension phase (median treatment duration of 64 weeks) [5]. These treatment-related adverse events were all of mild to moderate severity and included nausea, vomiting and leukopenia (each reported in two patients), with all other adverse events (e.g. headache, asthenia, erythema, fatigue, impetigo, tremor) each reported in one eculizumab recipient [5]. Serious adverse events considered to be possibly related to eculizumab included accelerated hypertension of moderate severity (two events), severe hypertension (one event) and mild asymptomatic bacteriuria (one event). All four events resolved without interruption of treatment [5].

Among eculizumab recipients with aHUS who had a longer disease duration and who were receiving long-term plasma exchange/infusion, 7 of 20 patients (35 %) had adverse events of mild to moderate severity that were considered to be possibly, probably or definitely related to eculizumab during the 26-week study or its extension phase (median treatment duration of 62 weeks) [5]. These included headache, leukopenia or lymphopenia in two patients each, with all other adverse events (e.g. anaemia, hypotension, rhinorrhoea, alopecia, pyrexia, pruritus) each reported in one eculizumab recipient [5]. Three serious adverse events were considered to be possibly or probably

related to eculizumab (severe influenza, severe peritonitis and severe venous sclerosis at the infusion site). All three events resolved without interruption of treatment [5].

Results of extension studies with approximately 2 years of follow-up revealed that intravenous eculizumab was generally well tolerated in the longer term [48, 50]. In the study in patients with progressing thrombotic microangiopathy, one serious adverse event (hypertension) occurred that was considered possibly related to the study drug; however, this adverse event resolved without a change in eculizumab dosing [48]. In the study in patients receiving long-term plasma exchange/infusion, one death because of gastrointestinal bleeding occurred after 1.9 years of eculizumab treatment; however, this death was not considered to be related to the study drug [50].

The adverse event profile of eculizumab in paediatric patients in the retrospective study [41, 44] was similar to that seen in eculizumab recipients in the noncomparative, phase II studies [5].

Given that clearance of *Neisseria meningitidis* is highly dependent on the terminal complement pathway [1], eculizumab therapy is associated with an increased susceptibility to meningococcal infection. No cases of meningococcal infection and/or infection-related serious adverse events were reported in the pivotal phase II trials [5, 50] or the prospective trial in paediatric patients [43], although two patients had meningococcal infections in the trial in adults (one of whom continued treatment with eculizumab) [42]. One case of meningococcal sepsis was reported in a patient with aHUS who received eculizumab in a retrospective study [14]. Postmarketing surveillance across indications (i.e. in patients with paroxysmal nocturnal haemoglobinuria or aHUS) revealed cases of life-threatening or fatal meningococcal infection in eculizumab recipients [14].

In terms of immunogenicity, antibodies to eculizumab were detected in 1 of 37 (2.7 %) patients with aHUS (assessed using an electro-chemiluminescence bridging assay); no neutralizing activity was detected [14]. There was no apparent correlation between antibody development and clinical response [14].

6 Dosage and Administration

Eculizumab is approved for the treatment of aHUS in a number of countries worldwide, including the EU, the USA, Japan, Canada, Australia, Iceland, Norway, Israel, Switzerland, Colombia and Russia [13–16]. Specifically, eculizumab is approved for the treatment of aHUS in the EU [13], and for the treatment of patients with aHUS to inhibit complement-mediated thrombotic microangiopathy in the USA [14].

In patients with aHUS aged ≥18 years, the recommended regimen of intravenous eculizumab comprises 900 mg/week for the first 4 weeks, followed by 1,200 mg for the fifth week and then 1,200 mg every 2 weeks subsequently [13, 14]. The eculizumab dosage should be based on bodyweight in patients aged <18 years (Table 3) [13, 14]. In addition, supplemental dosing of eculizumab is needed in patients receiving concomitant plasmapheresis or plasma exchange, or fresh frozen plasma infusion [13, 14].

Eculizumab should be administered by intravenous infusion over 35 [14] or 25–45 [13] minutes. The EU summary of product characteristics (SPC) recommends that eculizumab therapy be continued for the patient's lifetime, unless discontinuation is clinically indicated [13].

The US prescribing information carries a black box warning stating that life-threatening and fatal meningococcal infections have occurred in eculizumab recipients and that recommendations from the US Advisory Committee on Immunization Practices for patients with complement deficiencies should be complied with [14]. Patients should be immunized with meningococcal vaccine ≥2 weeks prior to receiving the first dose of eculizumab [13, 14] (unless the risk of delaying treatment with eculizumab outweighs the risk of developing a meningococcal infection) [14]. The EU SPC states that patients who receive eculizumab <2 weeks after meningococcal vaccination must receive treatment with appropriate prophylactic antibacterials until 2 weeks after vaccination [13]. Some countries (e.g. France) recommend permanent antibacterial prophylaxis during eculizumab therapy in addition to vaccination [4]. Patients should be monitored for

Table 3 Bodyweight-based dosage recommendations for intravenous eculizumab in patients with atypical haemolytic uraemic syndrome aged <18 years [13, 14]

Patient bodyweight (kg)	Induction regimen	Maintenance regimen
≥40	900 mg q1w × 4 doses	1,200 mg at week 5, then 1,200 mg q2w
30 to <40	600 mg q1w × 2 doses	900 mg at week 3, then 900 mg q2w
20 to <30	600 mg q1w × 2 doses	600 mg at week 3, then 600 mg q2w
10 to < 20	600 mg q1w × 1 dose	300 mg at week 2, then 300 mg q2w
5 to <10	300 mg q1w × 1 dose	300 mg at week 2, then 300 mg q3w

qxw every x week/s

early signs of meningococcal infection, and evaluated immediately if infection is suspected [13, 14].

Eculizumab should be used in pregnancy only if clearly needed (according to the EU SPC) [13], and only if the potential benefit justifies the potential risk of the fetus (according to the US prescribing information) [14]. Case reports suggest that eculizumab can be used successfully in pregnant women with aHUS [52] or paroxysmal nocturnal haemoglobinuria [53].

Local prescribing information for eculizumab should be consulted for further information regarding contraindications, warnings and precautions and supplemental dosing recommendations in patients receiving concomitant plasmapheresis or plasma exchange, or fresh frozen plasma infusion.

7 Eculizumab in Atypical Haemolytic Uraemic Syndrome: Current Status

Prior to the approval of eculizumab, treatment options for aHUS were limited and inadequate [12]. Although plasma exchange/infusion has historically been considered the cornerstone of treatment in aHUS [4, 54], it is often poorly tolerated and outcomes (particularly in terms of renal prognosis) remain poor [4, 11, 12, 55]. Renal and/or liver transplantation may be suitable treatment options for some patients with aHUS, although outcomes are often poor [1, 4, 54]. Thus, the approval of eculizumab provides an important new option for use in aHUS.

A new algorithm was recently proposed for the treatment of aHUS in children and adults [11, 55]. First-line treatment with eculizumab is recommended for children with aHUS; eculizumab should be initiated as early as is feasible, in order to optimize the recovery of renal function [11, 55]. The first-line use of eculizumab also allows the use of central venous catheters and plasma exchange to be avoided in this patient group [11].

Compared with children, the number of alternative possible diagnoses is larger in adults with suspected aHUS (e.g. ADAMTS13 deficiency-related thrombotic microangiopathy and thrombotic microangiopathy associated with cancer, infection, pregnancy, malignant hypertension or systemic disease such as systemic lupus erythematosus), meaning that the initial work-up is more complex and takes longer [4, 11, 55]. It is suggested that patients be treated with plasma exchange initially [55]. If after 5 days alternative diagnoses have been excluded and patients are not improving with plasma exchange therapy, eculizumab should be started [55]. First-line treatment with eculizumab is also suggested in adults with an unequivocal diagnosis of aHUS, such as patients with familial aHUS, or patients with a history of aHUS who have native or transplanted kidneys and show clinical manifestations of aHUS [11, 55].

Although genetic studies provide valuable information that helps to individualize treatment in patients with aHUS [11, 54], treatment with eculizumab does not need to be delayed until results of such studies are available [11]. However, rapid screening for anti-CFH antibodies is advised, given that a positive result indicates the need for specific treatment with plasma exchange and immunosuppressants [11].

Intravenous eculizumab was effective in the treatment of patients aged ≥12 years with aHUS. Eculizumab inhibited complement-mediated thrombotic microangiopathy, as shown by the significant increase in platelet count in patients with progressing thrombotic microangiopathy despite plasma exchange/infusion (Sect. 4.1) and the absence of thrombotic microangiopathic events in patients with a long disease duration and chronic kidney disease who had been receiving long-term plasma exchange/infusion (Sect. 4.2). Outcomes were maintained throughout the 2 years of follow-up. Discontinuation of plasma exchange/infusion was achieved in 88 % of patients with progressing thrombotic microangiopathy despite plasma exchange/infusion and in 100 % of patients with a long disease duration and chronic kidney disease who had been receiving long-term plasma exchange/infusion. In this latter patient group, platelet counts and haematological normalization was maintained and plasma exchange/infusion was discontinued (Sect. 4.2).

Renal function was improved by eculizumab therapy in both studies (Sects. 4.1 and 4.2). In particular, in the trial in patients with progressing thrombotic microangiopathy despite plasma exchange/infusion, four of the five patients who required dialysis at baseline were able to discontinue dialysis during this trial (Sect. 4.1). In addition, among patients with chronic kidney disease receiving long-term plasma exchange/infusion, several measures of renal function showed increasing improvement over the 2 years of follow-up (Sect. 4.2). Earlier intervention with eculizumab was associated with greater improvements in eGFR in both studies. HR-QOL was also improved by eculizumab therapy in these studies (Sects. 4.1 and 4.2).

Up to 2 years of intravenous eculizumab was generally well tolerated in patients with aHUS (Sect. 5). Blockade of the terminal complement pathway by eculizumab increases the susceptibility of patients to meningococcal infection, meaning that patients must be immunized with meningococcal vaccine prior to starting treatment with eculizumab (Sects. 5 and 6). Permanent antibacterial prophylaxis during eculizumab therapy is also recommended in some countries [4].

The optimal duration of eculizumab therapy is currently unresolved [11, 55]. The EU SPC currently recommends

that treatment with eculizumab should be continued for the patient's lifetime, unless discontinuation is clinically indicated (Sect. 6). More data regarding the long-term use of eculizumab will be obtained from a prospective, observational, multinational study examining the long-term efficacy of eculizumab in patients with aHUS who previously participated in an eculizumab clinical trial [56].

There have been reports of successful prophylactic use of eculizumab in patients undergoing renal transplantation who are at high risk of thrombotic microangiopathy and graft loss [24, 57–61]. Trials to further examine the use of prophylactic eculizumab in candidates for renal transplantation who are at moderate to high risk of aHUS appear warranted [11]. Pharmacoeconomic studies examining the cost effectiveness of eculizumab in aHUS are also needed, given that it is an expensive drug [1].

A registry has also been initiated that is open to male and female patients of any age who have been diagnosed with aHUS [62]. The registry will collect safety and efficacy data specific to the use of eculizumab, as well as collecting outcomes data (including data on the long-term manifestations of thrombotic microangiopathy complications) in patients with aHUS, regardless of whether they are receiving eculizumab or other disease management approaches [62].

In conclusion, eculizumab is a valuable new agent for use in the treatment of aHUS.

Data selection sources: Relevant medical literature (including published and unpublished data) on eculizumab was identified by searching databases including MEDLINE (from 1946) and EMBASE (from 1996) [searches last updated 28 October 2013], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.
Search terms: Eculizumab, atypical haemolytic uraemic syndrome.
Study selection: Studies in patients with atypical haemolytic uraemic syndrome who received eculizumab. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

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