

Use of eculizumab for atypical haemolytic uraemic syndrome and C3 glomerulopathies

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Abstract | In the past decade, a large body of evidence has accumulated in support of the critical role of dysregulation of the alternative complement pathway in atypical haemolytic uraemic syndrome (aHUS) and C3 glomerulopathies. These findings have paved the way for innovative therapeutic strategies based on complement blockade, and eculizumab, a monoclonal antibody targeting the human complement component 5, is now widely used to treat aHUS. In this article, we review 28 case reports and preliminary data from 37 patients enrolled in prospective trials of eculizumab treatment for episodes of aHUS involving either native or transplanted kidneys. Eculizumab may be considered as an optimal first-line therapy when the diagnosis of aHUS is unequivocal and this treatment has the potential to rescue renal function when administered early after onset of the disease. However, a number of important issues require further study, including the appropriate duration of treatment according to an individual's genetic background and medical history, the optimal strategy to prevent post-transplantation recurrence of aHUS and a cost–efficacy analysis. Data regarding the efficacy of eculizumab in the control of C3 glomerulopathies are more limited and less clear, but several observations suggest that eculizumab may act on the most inflammatory forms of this disorder.

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Introduction

Atypical haemolytic uraemic syndrome (aHUS) and the C3 glomerulopathies are two ultra-rare kidney diseases that are recognized as complement-mediated conditions characterized by overactivation of the alternative complement pathway.^{1,2} During the past decade, an increasing number of mutations in genes coding for proteins involved in the formation or regulation of the alternative pathway C3 convertase complex have been reported to be associated with aHUS.^{2,3} aHUS is therefore emerging as a paradigm of disease caused by the inefficient protection of the endothelium from complement attack. C3 convertase dysregulation induces excessive cleavage of C3, and subsequent excessive cleavage of C5, leading to endothelial cell damage, which triggers platelet recruitment and thrombus formation in the kidney microvasculature.⁴ Although uncontrolled complement activation is involved in the pathogenesis of both C3 glomerulopathies and of aHUS, the complement dysregulation in C3 glomerulopathies takes place in the fluid phase, rather than on the surface of the endothelium, and leads to C3 being released into the bloodstream and deposited in the kidney.^{5,6} To date, genetic abnormalities identified in patients with aHUS and C3 glomerulopathies have involved components of

the alternative pathway, including complement factor H (CFH), complement factor I (CFI), membrane cofactor protein (MCP), complement factor B (CFB) and complement component 3 (C3). Although both diseases involve overactivation of the alternative complement pathway and although both lack an effective therapy, substantial differences have been noted between the mechanism of aHUS, which primarily involves the terminal activation of C5b–9, and that of C3 glomerulopathies, in which C3 split products have been shown to have a pathogenic role.⁷ Breakthroughs in our understanding of the pathogenesis of aHUS have coincided with the availability of an innovative drug, eculizumab, which is an inhibitor of the terminal complement pathway.^{8,9} Eculizumab can be considered the standard of care for the treatment of paroxysmal nocturnal haemoglobinuria (PNH) and its use has so far been associated with only one major adverse effect, an increased risk of meningococcal infection.^{10–13}

During 2012, eculizumab has begun to emerge as the new targeted disease-modifying treatment for aHUS and in the near future it might also be used for the treatment of some types of C3 glomerulopathy.

Functional effects of eculizumab

Eculizumab is a recombinant, fully humanized hybrid IgG2/IgG4 monoclonal antibody directed against human complement component C5. The drug has been engineered to minimize immunogenicity and Fc-mediated functions, including recruitment of inflammatory cells and complement activation (Figure 1a). Normal C5

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Competing interests

J. Zuber, F. Fakhouri, C. Loirat and V. Frémeaux-Bacchi declare associations with the following company: Alexion Pharmaceuticals. See the article online for full details of the relationships. L. T. Roumenina declares no competing interests.

Key points

- Eculizumab has shown greater efficacy than plasma therapy in the prevention and treatment of episodes of atypical haemolytic uraemic syndrome (aHUS)
- Eculizumab may be considered as a first-line therapy in children with a first episode of aHUS as it avoids the complications associated with apheresis and central venous catheters
- In adults, eculizumab can be used as a first-line therapy when aHUS diagnosis is undisputable, although plasma therapy should be used as a first-line therapy if uncertainty in diagnosis warrants further investigation
- Evidence of plasma resistance or dependence should lead to a prompt switch to eculizumab; the sooner eculizumab is initiated, the better the recovery of renal function
- Renal transplant candidates with a genetically determined risk of post-transplantation aHUS recurrence should be given a prophylactic protocol based on eculizumab if at high risk, and plasma exchange or eculizumab if at moderate risk
- Eculizumab may be effective in curbing part of the inflammatory process involved in a subset of C3 glomerulopathies

concentration in plasma is approximately 70 µg/ml. *In vivo*, eculizumab achieves complete complement blockade when its serum concentration reaches 35 µg/ml,¹⁴ a finding in line with the idea that any IgG binds bivalently to its cognate antigen. Following its intravenous administration, eculizumab has a half-life of approximately 11 ± 3 days and is distributed in the vascular space.^{13–15} The poor transplacental transfer of IgG²⁶ may account for the low, if any, detection of eculizumab in cord blood samples harvested in pregnant women with PNH who are receiving eculizumab at the time of delivery.^{17,18}

Although the C5 epitope bound by eculizumab is located far from the C5a portion of C5 (Figure 1b), eculizumab can block C5 cleavage effectively.¹³ Using crystallographic data on the molecular structures of the C3 convertase C3bBb^{19,20} and a C5 convertase analogue,²¹ we have modelled the well-characterized part of the alternative pathway of C3/C5 convertase, C3bBb, as being in a complex with C5. Mapping the eculizumab epitope on this molecular model indicates that eculizumab binds to an area involved in the contact interface between C5 and C5 convertase (Figure 1b). We propose that eculizumab prevents the entry of the substrate molecule C5 into the C5 convertase (Figure 1b), which means that C5 cleavage and the formation of C5a and C5b-9 are inhibited, resulting in blockade of the pro-inflammatory, pro-thrombotic and lytic functions of complement (Figure 1c). The inhibition of complement activation at the level of C5 creates a functional C5 deficiency. Patients with genetically determined C5 deficiency suffer from recurrent infection episodes, particularly meningitis caused by *Neisseria* species.^{22,23} In clinical trials and extension studies of eculizumab in PNH, the *Neisseria* infection rate was 4.2 cases per 1,000 patient-years: two cases of meningococcal sepsis occurred over 474.1 patient-years of eculizumab exposure.²⁴ Prophylactic measures for coping with this increased risk of infection are described (Box 1). However, blockade of the complement cascade at the C5 level does preserve the early components of complement that are essential for the opsonization of microorganisms and the clearance of immune complexes.

Atypical HUS and eculizumab

Remarkable insights into the complement-mediated pathogenesis of aHUS have been gained over the past decade (Table 1).^{2,25,26} Since 2009, a growing number of patients with aHUS have been treated with eculizumab and data from these patients have demonstrated the effectiveness of eculizumab in treating this disease. Eculizumab has become the first breakthrough in the treatment of aHUS since the introduction of plasma therapy as the gold-standard first-line therapy several decades ago. However, drawing clear and useful recommendations from heterogeneous sporadic case reports might be an uphill task for non-expert readers, and it seems an opportune time to take a stock of what this preliminary experience has taught us. It is important to acknowledge that most of the data presented here come from single case reports, which are susceptible to publication bias. For a number of these cases, updated outcome data have been provided by the authors and are cited with permission.^{8,9,27–43} We have also included preliminary results of the prospective trials, which have been communicated in congresses but have not yet been published in peer-reviewed journals. Given these methodological limitations, the opinions and proposals expressed herein must be interpreted with some caution while awaiting the publication of results from the prospective trials and the extended follow-up of treated patients.

Treating overt aHUS: data from case reports

To date, 24 patients (Table 2), including 11 children, have reportedly been given eculizumab as a curative therapy for overt aHUS episodes involving either native kidneys ($n = 14$)^{8,29,32,34,35,37,39–41,44–48} or transplanted kidneys ($n = 10$).^{9,27,28,30,31,33,36,49–52} Complement mutations were found in 15 of these patients (62.5%), mostly in *CFH* (10/24, 42%); no mutations were identified in nine patients (37.5%). Of the 22 patients who received plasma therapy prior to eculizumab, 19 had shown a partial or null response to plasma therapy (that is, they were plasma resistant); the other three patients were considered to be fully sensitive to plasma, yet dependent on it, and were switched to eculizumab as a result of an allergic reaction to plasma or for personal convenience. The other two patients were given eculizumab as first-line treatment for an overt aHUS episode. Strikingly, eculizumab therapy consistently succeeded in achieving complete remission in the 21 patients with active aHUS who received eculizumab as either a first-line therapy or as a rescue therapy for plasma-resistant aHUS: these patients showed a prompt and full recovery from aHUS-related haematological disturbances and severe extrarenal manifestations, including gangrene of the fingers and toes in two patients^{29,37} and brain involvement in one patient.³⁹

Complete follow-up data are available for 20 of the 21 patients with active aHUS who had been given eculizumab following an overt aHUS episode, following a nonresponse to plasma therapy or following no previous treatment. Among these patients, four out of six on

dialysis at the time of eculizumab treatment have been weaned from dialysis, 10 patients have shown complete recovery of renal function and eight patients have shown partial recovery of renal function, after a median treatment period of 6.8 months (range 2–22 months).^{8,9,27–29,32–37,39,40,44,45,47,48,50–52} The mean (\pm SD) creatinine level at last follow-up (a median interval of 16 months [range 2.5–42 months] after treatment) was 97.8 μ mol/l (\pm 75.8 μ mol/l) in the 15 patients maintained on eculizumab and off dialysis.^{8,27–29,32–35,39,40,44,50–52} Importantly, the extent of renal function recovery correlated inversely with the time interval between the onset of an episode of aHUS and the initiation of eculizumab (Figure 2).

In addition, eculizumab enabled the complete and safe withdrawal of plasma therapy in the three patients in whom long-term plasma therapy was required for the maintenance of remission from aHUS.^{30,41,49} Interestingly, these patients all experienced a mild yet clinically significant improvement in renal function after switching to eculizumab.

In addition to the data from 11 paediatric case reports compiled from the literature (Table 2), a retrospective study of 15 young children treated with off-label eculizumab has been reported by the FDA¹⁵ and the European Medicines Agency⁵³ and the findings have been communicated in international congresses.⁵⁴ The retrospective study included five children aged <2 years, three children aged 2–4 years and seven children aged 5–11 years; reported outcomes were excellent, similar to those seen in the prospective trials in adults and adolescents. Among these children, 93% achieved a normal platelet count and 80% showed thrombotic microangiopathy (TMA) event-free status (defined as no decrease in platelet count of >25% from baseline, no need for plasma therapy and no new dialysis for 12 consecutive weeks). In addition, 57% showed an increase in estimated glomerular filtration rate of \geq 15 ml/min/1.73 m², and the safety profile was similar to that reported in older individuals.^{14,15,53,54}

Prevention of post-transplant aHUS recurrence

Eculizumab has also successfully been used as a prophylactic treatment to prevent post-transplantation recurrence of aHUS in four children in whom a genetic abnormality in the SCR20 (short consensus repeat) of the *CFH* gene predicted a risk of recurrence of >90%.^{38,42,43,55} Two of these children harboured the *CFH/CFHR1* hybrid gene, resulting from a non-allelic homologous recombination between the *CFH* and *CFHR1* genes;^{38,55} one of these two patients had already lost a graft from recurrence.³⁸ All four patients experienced an event-free post-transplantation course and all had a normal serum creatinine level, ranging from 44 μ mol/l to 70 μ mol/l, after a median follow-up of 19.5 months (range 15–39 months). The initial reports proposed that eculizumab be started prior to transplantation ($n = 2$), in the context of scheduled living-donation or urgent-status listing for deceased-donor renal transplantation,^{38,42} or with the replacement of daily prophylactic plasma exchange during the early post-transplantation

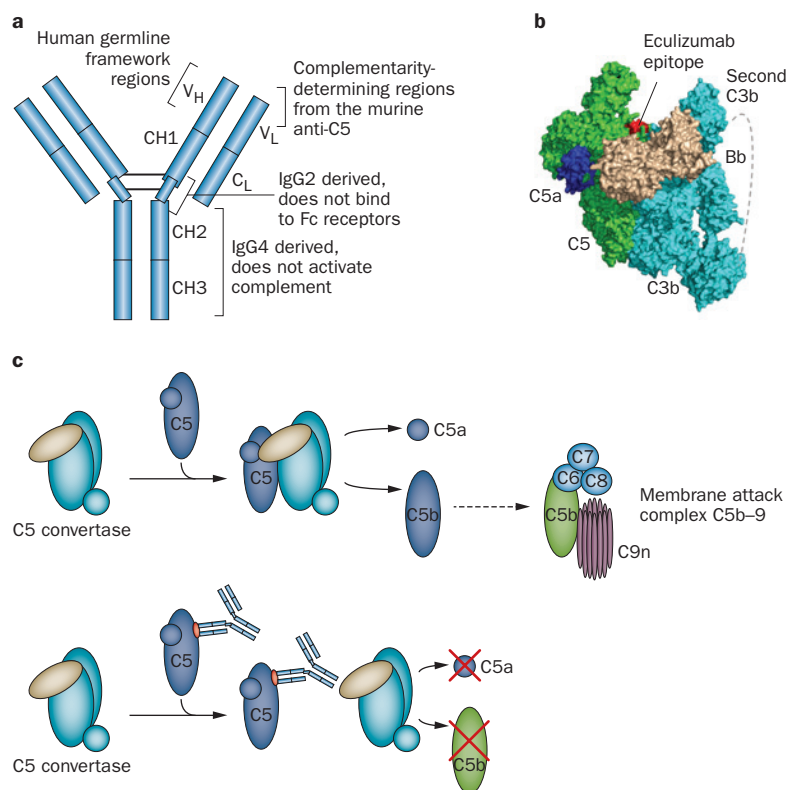


Figure 1 | Eculizumab: molecular structure and mode of action. **a** | A schematic representation of the structure of eculizumab. Eculizumab is a humanized monoclonal antibody that was derived from the murine antihuman C5 antibody m5G1.1. Eculizumab carries the complementary-determining regions of the mouse anti-human C5 IgG, inserted into a germline framework region, including the hinge region from human IgG2, which does not bind Fc receptors, and the CH2–CH3 domains from human IgG4, which are unable to activate complement. These modifications minimize immunogenicity and prevent pro-inflammatory responses mediated by the IgG Fc portion. **b** | A molecular model of the C5 convertase portion C3bBb (in cyan and beige, respectively) in a complex with a substrate molecule C5 (green). The second C3b molecule of the C3bBbC3b complex is depicted as a dashed line because its location is still unknown. Mapping the 21-residue-long peptide, in the middle of which is the m5G1.1 epitope KSSKC (red), on this structure reveals the molecular mechanism of action of eculizumab. Because the C5 convertases of the classical and the alternative pathway are very similar, we suggest that eculizumab prevents the entry of the substrate molecule C5 into the C5 convertases. **c** | A schematic representation of the molecular mechanism of action of eculizumab. Upper part: in the absence of the drug, the substrate C5 enters into the C5 convertase and is cleaved to C5a and C5b. C5b binds C6, C7, C8 and several molecules of C9 to form the membrane attack complex C5b–9. Lower part: eculizumab binds to C5 with a very high affinity, preventing its entry into the C5 convertase. This effect prevents C5 cleavage and the formation of C5a and C5b–9.

course ($n = 1$).⁴³ A report of a 7-year-old boy with a known hybrid *CFH/CFHR1* gene has shown that eculizumab therapy started just before transplantation was also effective in preventing aHUS recurrence.⁵⁵ Evidence that complement products are released in large amounts following reperfusion^{43,56} has raised the issue that an additional dose of anti-C5 would be needed on day 1 to fully antagonize circulating C5 in the days after transplantation, as proposed in the protocols designed to prevent catastrophic antiphospholipid syndrome (CAPS)^{57,58} or early antibody-mediated rejection^{59,60} in sensitized patients.

Box 1 | Measures for reducing the risk of *Neisseria meningitidis* infections

All patients with atypical haemolytic uraemic syndrome should be vaccinated against *Neisseria meningitidis*. Vaccination should be administered as early as possible in the course of the disease, to optimize the efficacy of meningococcal vaccine, and should be mandatory before the administration of eculizumab. Tetravalent vaccines (A, C, Y, W135), preferably conjugated ones, should be used. Current recommendations state that patients treated with eculizumab <2 weeks after vaccination should be given daily prophylactic antibiotics (for example, oral penicillin) for 2 weeks after vaccination. A macrolide can be given to patients allergic to penicillin. However, currently available vaccines do not cover all *N. meningitidis* strains, including the most prevalent serogroup in Europe and America—serogroup B.¹²⁴ In addition, a great deal of uncertainty surrounds the effectiveness of vaccines in immunocompromised patients (for example, those with end-stage renal disease and renal transplant recipients). These concerns have prompted a few countries, including France, to require continuous antibiotic prophylaxis throughout eculizumab treatment. We are not aware of any case of *Neisseria* infection occurring in patients given antibiotic prophylaxis. As soon as the first vaccine providing protection against serogroup B is approved by the medicine regulatory agencies, it will be included in the anti-meningococcal vaccination schedule. Patients must be revaccinated according to current medical guidelines. Patients must be educated regarding the early signs and symptoms of meningococcal infection and the need for prompt medical evaluation and treatment. A treatment information card providing information and recommendations about the risk of infection should be given to every patient treated with eculizumab. Of note, vaccination against *Streptococcus pneumoniae* and *Haemophilus influenzae* type B infections is also required in children treated with eculizumab.^{14,15}

Prospective trials: preliminary results

Prospective trials, for which preliminary results have so far only been released in congresses, were conducted in adults^{61,62} and adolescents^{63,64} with aHUS resistant to plasma exchange or plasma infusions (C08-002 study, 17 patients)^{15,53,54,65–67} or on chronic plasma exchange or plasma infusion therapy (C08-003 study, 20 patients).^{15,53,54,68–70} Although the results of these trials have not yet been peer-reviewed, we feel that they should be mentioned in this Review because they were judged to have been convincing enough to support the approval of eculizumab for aHUS treatment by both the US and European health agencies.^{14,15,53} The Highlights of Prescribing Information from the FDA¹⁵ and the Summary of Product Characteristics from the European Medicines Agency⁵³ both include the preliminary results of the two trials. In both trials, approximately 85% of patients had achieved TMA event-free status, as defined above, at 26 weeks^{14,15,65,70} and at data cut-off (58 weeks in one trial and 60 weeks in the other trial).^{66–69} Improvement in renal function was significant not only in the resistant plasma exchange/plasma infusion trial but also in the chronic plasma exchange/plasma infusion trial, despite the long duration of chronic kidney disease in these patients prior to eculizumab treatment. Health-related quality of life significantly improved in both trials, and eculizumab was well tolerated.

Eculizumab in clinical practice

The FDA¹⁵ and the European Medicines Agency⁵³ have extended the therapeutic indication of eculizumab to include the treatment of paediatric and adult patients with aHUS. The opinions and therapeutic proposals presented in the present manuscript were established

by a 24-member study group of French adult and paediatric nephrologists, coordinated by authors J. Zuber, F. Fakhouri, C. Loirat and V. Frémeaux-Bacchi, with the aim of providing patients in France with a homogeneous therapeutic approach. Subgroups were tasked with critically reviewing the literature and providing useful proposals for the treatment of adults and children with aHUS. Final recommendations were approved by the whole study group after thorough discussions at a meeting held in Paris on 19 March 2011, and communicated to a broader French nephrologist audience on 8 April 2011. These opinions (Box 2) are not intended to be definitive guidelines because knowledge about aHUS and the indications of eculizumab in other forms of TMA is rapidly evolving. In addition, access to eculizumab differs between countries, partly due to the high cost of the drug.

Who should be treated with eculizumab?

All patients with aHUS that involves either native or transplanted kidneys (post-transplantation recurrence) should be eligible for eculizumab therapy. Medical history, a thorough physical examination, and rapid laboratory tests may be sufficient to eliminate most secondary causes of HUS in children (Figure 3). However, the aetiological diagnosis of HUS and its distinction from TTP can be more difficult in adults (Figure 3). The challenge of establishing a diagnosis may require further investigations to exclude other causes of TMA, including Shiga-toxin (Stx)-producing *Escherichia coli* (STEC), systemic lupus erythematosus, antiphospholipid syndrome, infections, malignancies, endothelial-insulting chemotherapies, and thrombotic thrombocytopenic purpura (TTP).^{71,72} In some institutions, the result of ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) assays can be provided within a couple of days, whereas in other cases, the diagnosis of ADAMTS13-deficiency-related TMA can be presumed based on simple clinical features. In this respect, four studies have shown that a serum creatinine level >150–200 µmol/l or a platelet count >30,000/mm³ almost eliminates a diagnosis of severe ADAMTS13 deficiency.^{73–76}

Incomplete forms of aHUS, with mild or no hallmark haematological features (for example, no haemolytic anaemia or normal platelet count), account for approximately 20% of cases of aHUS^{77,78} and patients with such forms should be considered for eculizumab therapy in the same manner as those with full-blown aHUS.³² In addition, in patients on plasma therapy and in those who have undergone kidney transplantation, special attention should be paid to poorly explained anaemia, even in the absence of obvious mechanical haemolysis, increased need for antihypertensive drugs or a slight decrease in renal function.⁴¹ In these puzzling settings, a renal biopsy might be useful. If examination of the biopsy sample discloses fresh TMA lesions, which may progress towards irreversible damage,^{77,78} the initiation of eculizumab or a switch from plasma therapy to eculizumab should be considered.³² A small number

Table 1 | Evidence supporting the role of complement dysregulation and the benefit of C5 blockade in aHUS and C3G

Evidence type	aHUS	C3G
Evidence supporting role of complement-mediated disease		
Mice	Spontaneous aHUS occurs in mice deficient in endothelial surface recognition domains in CFH (<i>Cfh</i> ^{-/-} .FHD16–20) ²⁶	<i>Cfh</i> deficiency in mice leads to the occurrence of glomerulonephritis similar to human MPGN ¹¹⁴ In <i>Cfh</i> -deficient mice, the restoration of the regulation of the CAP through the administration of human purified CFH leads to the clearance from glomeruli of C3 fragments ¹¹⁶ The pathogenic role of C3 split products has been demonstrated in mice with C3G related to CFH deficiency ⁷
Humans	~60–70% of patients with aHUS have mutations in genes encoding regulatory factors of the complement system (<i>CFH</i> , <i>CFI</i> , <i>MCP</i> , <i>THBD</i> , <i>CFB</i> , <i>C3</i>) or anti-CFH antibodies ²	C3 nephritic factor, an IgG that stabilizes the alternative C3 convertase, has been documented in 50–80% of patients with C3G ^{5,6} Mutations in <i>CFH</i> , <i>CFI</i> , <i>MCP</i> , and <i>C3</i> , and <i>CFHR5</i> duplications, are found in ~20% of patients with C3G ^{5,6}
Evidence supporting anti-C5 efficacy		
Mice	Spontaneous aHUS does not develop in C5-deficient mice (unlike in C5-sufficient mice) that also lack the endothelial surface recognition domains of CFH (<i>Cfh</i> ^{-/-} .FHD16–20) ²⁵	Inactivation of the C5 gene in <i>Cfh</i> ^{-/-} mice does not prevent C3 deposition and capillary wall changes or reduce proteinuria, but significantly decreases glomerular inflammation ¹¹⁷
Humans	Data from 37 patients in phase II trials and 27 patients treated in off-label studies have demonstrated the effectiveness of eculizumab in preventing and treating aHUS episodes ^{14,15}	Data from 10 patients treated in off-label studies suggest that eculizumab can curb glomerular inflammation in a subset of patients with the most inflammatory forms of C3G and circulating MAC (see Table 3)
Abbreviations: aHUS, atypical haemolytic uraemic syndrome; CAP, complement alternative pathway; C3, complement component 3, C3G, C3 glomerulopathy; CFB, complement factor B; CFH, complement factor H; FHD16–20, factor H lacking the terminal five SCR domains; CFHR5, complement factor-H-related protein 5; CFI, complement factor I; MAC, membrane attack complex; MCP, membrane cofactor protein; MPGN, membranoproliferative glomerulonephritis; THBD, thrombomodulin.		

of reports have also suggested that eculizumab might reverse extra-renal aHUS-related organ failure, including neurological involvement³⁹ and digital ischaemia.^{29,37} These initial findings highlight the fact that patients with active aHUS-related extra-renal manifestations may benefit from eculizumab even if they don't have renal impairment.

During the course of an acute flare-up, late initiation of eculizumab has been shown to result in a partial recovery of renal function in one patient on dialysis³³ and a complete recovery of renal function in another patient on dialysis,³⁴ for a period as long as 120 days.³⁴ By contrast, two other patients who had been on dialysis for 90 days and 150 days at the onset of eculizumab failed to achieve independence from dialysis.^{37,45} Therefore, the beneficial effects of late-introduced eculizumab therapy to recover renal function in patients with aHUS who have been maintained on dialysis for a prolonged period following an acute flare seem to be inconsistent. This issue deserves further exploration. Renal biopsy might be useful to determine the extent of irreversible lesions in such situations.

In addition to its use in the field of aHUS, eculizumab may be efficient in controlling severe STEC HUS with neurologic involvement,⁷⁹ CAPS^{80,81} and even TTP.^{82,83} The potential for a short-term eculizumab regimen to be used as treatment for STEC HUS is beyond the scope of our manuscript and is covered by another Review in this issue of *Nature Reviews Nephrology*.⁸⁴ In addition, evidence showing genetically determined complement dysregulation in patients with post-partum HUS⁸⁵ and *de novo* post-transplantation HUS⁸⁶ indicate that eculizumab could be an attractive therapeutic option in

these settings as well. Notably, eculizumab has shown success in treating graft-threatening *de novo* aHUS that had been nonresponsive to conventional therapies (that is, plasma exchange and withdrawal of calcineurin inhibitors).^{87,88} It remains to be established as to whether HELLP (haemolysis, elevated liver enzymes and low platelet count) syndrome^{89,90} and preeclampsia,⁹¹ which are also shown to be associated with genetic complement dysregulation, will become indications for eculizumab.

Impact of complement investigations

Whether or not the results of complement investigations impact therapeutic decisions relates to two different issues. The first issue is whether eculizumab should be used only in patients in whom a mutation in a complement gene or an anti-CFH antibody has been identified. Although up to half of patients with aHUS have no identified mutations,⁷⁷ such patients have been shown to respond to eculizumab in both case reports^{8,29,32,36,39,47,48,50,51} and prospective trials.^{15,53} We therefore feel that there is no reason to postpone eculizumab initiation at the acute phase of the disease while awaiting results of complement investigations. However, rapid screening for anti-CFH antibodies should be conducted because positive results would indicate the need for specific therapies based on plasma exchange and immunosuppressive drugs.^{92–95} Patients harbouring both a mutation associated with aHUS and anti-CFH antibodies should be managed with eculizumab in the same way as mutation carriers.⁹⁶ Blood samples for complement assessment should be collected before the initiation of any treatment, without delaying treatment.³

Table 2 | Clinical and genetic characteristics of 24 off-trial patients treated with eculizumab for overt aHUS

Patient characteristics	Children (n = 11)	Adults (n = 13)
Epidemiological data		
Median age at aHUS onset	0.9 years (range 0.02–8 years)	22.5 years (range 3–50 years)
Familial aHUS	2/10 (20%)	2/11 (18.2%)
Complement mutation identified	8/11 (72.7%)	7/13 (53.8%)
<i>CFH</i>	6/11 (54.5%)	4/13 (30.8)
–C-terminal mutation and NAHR in <i>CFH</i>	3/4 (75.0%)*	3/4 (75%)
<i>CFI</i>	0/11 (0%)	1/12 (8.3%)
<i>C3</i>	2/11 (18.2%)	1/12 (8.3%)
<i>CFB</i>	0/11 (0%)	0/12 (0%)
<i>MCP</i>	0/11 (0%)	1/12 (8.3%)
Mutation not identified/not specified	3/11 (27.3%)	6/13 (46.2%)
At the time of the current aHUS episode		
aHUS in native kidneys	9/11 (81.8%)	5/13 (38.5%)
First episode of aHUS in native kidneys	4/9 (44.4%)	4/5 (80.0%)
aHUS in transplant kidneys	2/11 (18.2%)	8/13 (61.5%)
RTx with recurrence in previous graft	1/1 (100%)	5/5 (100%)
At the time of anti-C5 therapy		
First-line therapy for overt aHUS episode	0/11 (0%)	2/13 (15.4%)
Null or incomplete response to plasma therapy	10/11 (90.9%)	9/13 (69.2%)
Plasma dependence	1/11 (9.1%)	2/13 (15.4%)
Median age	4 years (range 0.1–15 years)	34 years (range 18–50 years)
Patients on dialysis	3/10 (30%)	3/12 (25%)
Mean ± SD day 0 creatinine level in off-dialysis patients	231 ± 158 µmol/l	366 ± 249 µmol/l
Median interval between aHUS and anti-C5	21 days (range 2–225 days)	30 days (range 1–420 days)
Response to anti-C5 therapy		
Normalization of aHUS-related haematological features	11/11 (100%)	13/13 (100)
Full recovery of baseline renal function	8/10 (80%)	4/13 (30.7%)
Decrease in creatinine level greater than 25%	9/10 (90%)	9/13 (69.2%)
Percentage reduction in creatinine level	63.3 ± 28.8	41.9 ± 29.5
Median follow-up†	22 months (range 2.5–42 months)	15 months (range 2–49 months)
Mean ± SD creatinine level at last follow-up‡	53.9 ± 34.5 µmol/l	163.2 ± 96.2 µmol/l
*Information regarding the location of the mutation in <i>CFH</i> was lacking for two children. †Extended follow-up data provided by the authors, with permission. Abbreviations: aHUS, atypical haemolytic uraemic syndrome; anti-C5, anti-component 5 of the complement (eculizumab); NAHR, nonallelic homologous recombination; RTx, renal transplantation.		

The second issue is whether genetic investigations should be conducted for the long-term management of patients with aHUS. In our opinion, genetic investigations are useful for firmly establishing whether the disease is complement-mediated. Genetic findings may further influence decisions, including assessment for the risk of post-transplantation recurrence, eligibility for liver transplantation, genetic counselling, and the selection of the best candidates for protocols for eculizumab withdrawal.

First-line therapies for aHUS

Previous guidelines for the management of aHUS were published in 2009, before the era of eculizumab, and highlighted the need for plasma therapy to be started as early as possible (that is, within 24 h of disease onset).^{97,98} The same recommendation should apply to eculizumab if it is used as a first-line therapy. The earlier eculizumab is started, the greater the recovery of renal function seems to be (Figure 2).

Despite the lack of evidence from controlled and randomized studies, a number of arguments suggest that eculizumab achieves better control of aHUS than does plasma therapy. In series in which the majority of patients with aHUS were treated with plasma therapy, patient outcomes were reported as being poor.^{77,78} Moreover, the switch from plasma therapy to eculizumab has been shown to improve renal function even in patients with long-lasting and stable chronic kidney disease (Table 2).^{14,15,30,41,49,53,68–70} Regarding the issue of tolerability, the balance is also tipped in favour of eculizumab. Complications related to plasma exchange have been reported to occur in up to 55% of plasma exchange sessions in children^{99,100} and in 15% of sessions in adults.¹⁰¹ Tolerable eculizumab doses have now been established in patients with aHUS, including in children, for whom doses and intervals should be adapted to their weight.^{14,15} We are aware of only nine children aged less than 2 years old who have been treated with

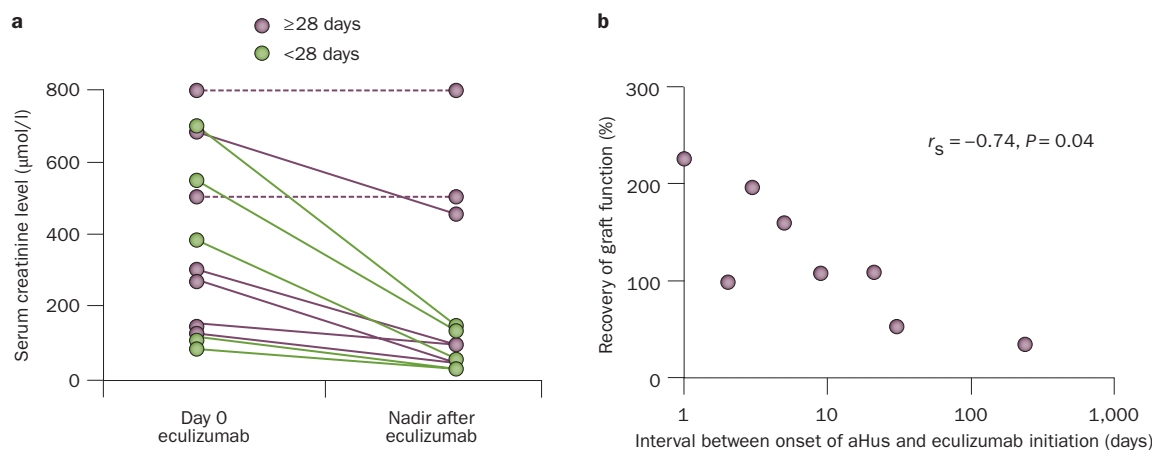


Figure 2 | Recovery of renal function is better with a shorter interval between onset of aHUS and initiation of eculizumab. **a** | The longitudinal follow-up of serum creatinine level in patients with aHUS involving native kidneys. Creatinine level before and after eculizumab indicates the values at day 0 of the treatment and the nadir creatinine level achieved within the 6 months following, respectively. Green dots represent patients in whom treatment was administered <28 days after onset of aHUS and purple dots indicate patients in whom treatment was administered ≥28 days after the onset of aHUS. Dashed lines show patients who could not be weaned off dialysis. **b** | The correlation of graft function recovery with the interval between the onset of an aHUS episode and the initiation of eculizumab treatment in eight renal transplant recipients for whom a baseline creatinine level before the onset of the current aHUS episode was available. The following formula was used to calculate the recovery of renal function after anti-C5 therapy: Graft function recovery = (Day 0 creatinine level – post-anti-C5 creatinine level)/(Day 0 creatinine level – pre-aHUS creatinine level) × 100. Abbreviation: aHUS, atypical haemolytic uraemic syndrome.

eculizumab,^{8,14,15,29,34,37,53,54} three of whom were aged younger than 1 year.^{29,34,37}

In practice, in children, the desire to avoid plasma exchange and central venous catheters owing to the high risk of complications and the improved efficacy of eculizumab compared with plasma exchange or plasma infusions support the use of eculizumab as the first-line therapy for all episodes of aHUS (Figure 3). The same recommendation may apply to adults with clinically definitive diagnoses of aHUS (for example, familial aHUS, relapsing aHUS and post-transplantation recurrent forms of aHUS). However, a first episode of HUS in native kidneys in adults may justify first-line plasma exchange while investigations (for example, for cancer or TTP) are completed (Figure 3). Subsequently, if a series of five daily plasma exchanges fails to normalize platelet count and LDH level or to reduce serum creatinine level by 25% (plasma resistance), or if a relapse occurs during plasma weaning (plasma dependence), in a patient with detectable ADAMTS13 activity, the patient should be switched to eculizumab without delay (Figure 3). A switch to eculizumab requires the concurrent discontinuation of plasma therapy, which would otherwise hasten the clearance of eculizumab.

Duration of eculizumab treatment in aHUS

Four patients who received a single injection of eculizumab experienced a relapse after a remission of aHUS lasting 1 month, 2 months, 11 months and 21 months after eculizumab and progressed to end-stage renal disease (ESRD) (J. Nürnberger and M. Lozano, personal communication).^{9,36,47,48} Further treatment with eculizumab failed to prevent progression towards ESRD in two of the three patients in whom treatment was resumed.^{9,36,48}

The FDA and European Medicines Agency approval letters mentioned that five out of the 18 patients (mostly treated outside of protocols), who missed a dose or discontinued eculizumab, experienced TMA-related clinical complications.^{14,15,53} The risk of relapse in patients with aHUS is influenced by the genetic background,⁷⁷ and the interval between flares is extremely difficult to predict. Influenza vaccination induced aHUS relapse in one patient 3 months after discontinuation of eculizumab.⁵⁰

The issue of the optimal duration of eculizumab treatment has not yet been properly addressed. The European Medicines Agency has approved life-long eculizumab treatment for patients with aHUS.⁵³ Given the broad exposure to endothelial-insulting factors, including immunosuppressive drugs, ischaemia, rejection episodes and viruses in post-transplantation settings,⁵² we suggest that this recommendation is applied to all renal transplant recipients treated with eculizumab either to prevent recurrence in the subset of patients at high risk of recurrence, or to treat post-transplantation recurrence of aHUS. However, the high cost of the drug and the uncertainties surrounding the natural history of aHUS in patients for whom eculizumab prevented the progression to ESRD, raise the question of whether life-long treatment is warranted for all patients with aHUS. Eculizumab therapy can be stopped if patients do not recover from ESRD but remain free from any clinically overt extra-renal signs of aHUS. Thus far, the number of cases with silent aHUS-related extra-renal damage, such as ischaemic dilated cardiomyopathy^{102,103} or stenoses of the large cerebral arteries,^{49,104,105} is too limited to recommend the use of eculizumab in patients on chronic dialysis. In this respect, a study assessing the progression of extra-renal vascular lesions and cardiac

Box 2 | Authors' opinions on use of eculizumab in clinical practice**Who should be treated with eculizumab?**

- Any patient with a clinical presentation of aHUS should be considered as a candidate
- The spectrum of indications encompasses aHUS involving either native or transplanted kidneys as well as aHUS with incomplete clinical presentation

Do complement investigations impact therapeutic decisions?

- Eculizumab should be considered for all patients with aHUS without waiting for results from complement investigations, although screening for anti-CFH antibodies should be done rapidly as positive results would indicate a switch to plasma exchange and immunosuppressive drugs
- Screening for genetic complement abnormalities is needed for individualized management

When and what first-line therapies should be initiated for aHUS?

- Test results for detection of Shiga-toxin-producing *Escherichia coli* and ADAMTS13 assay should be attained rapidly (within <24 h)
- Evidence of plasma resistance or dependence should lead to the prompt initiation of eculizumab
- First-line eculizumab therapy might be the best strategy, whatever the age of the individual, for treatment of familial aHUS, aHUS relapse or post-transplantation recurrence of aHUS
- In children, eculizumab may be considered as a first-line therapy for a first episode of aHUS in native kidneys

For how long should patients with aHUS be given eculizumab?

- A single dose of eculizumab is inappropriate
- The key issue of optimal treatment duration should be urgently addressed
- In our opinion, a strategy for planned eculizumab discontinuation should be guided by complement genetics

How should intercurrent events be managed and treatment efficacy be monitored in patients on eculizumab therapy?

- Complement blockade should be monitored if eculizumab fails to control the aHUS episode
- Vaccination against seasonal influenza is recommended
- Given the apparent fair safety profile of eculizumab during pregnancy, we believe that pregnancy should no longer be a formal contraindication for eculizumab in highly motivated women with aHUS, as long as the pros and cons are thoroughly discussed, ideally with both parents

Does eculizumab change renal transplant options for patients with aHUS?

- In the absence of other contraindications, all patients with aHUS-related end-stage renal disease should be considered as eligible for renal transplantation after a thorough genetic-based assessment of their risk of recurrence
- Kidney transplantation from a living-related donor can be considered with extreme caution in rare situations but remains inadvisable if the donor shares a genetic susceptibility factor with the recipient or if no mutations have been identified in complement genes
- Prophylactic eculizumab therapy should be recommended in patients with a high risk of post-transplantation aHUS recurrence and should be initiated prior to surgery at day 0 and include an additional dose at day 1
- CLKT can be considered on a case-by-case basis for well-informed and highly motivated patients with aHUS who have mutations in *CFH*, *C3* or *CFB*
- The CLKT perioperative period must be covered by plasma exchange or eculizumab

Abbreviations: aHUS, atypical haemolytic uraemic syndrome; CFH, complement factor H; CLKT, combined liver and kidney transplantation.

impairment in patients with aHUS would provide meaningful information.

Given that the natural history of aHUS differs depending on the underlying genetic abnormalities,^{77,78} treatments could be tailored on the basis of an individual's complement genetics. To date, life-long treatment may be appropriate in patients with aHUS who have mutations associated with poor outcomes (for example, *CFH*

or *C3/CFB* gain-of-function mutations). By contrast, eculizumab therapy may reasonably be withdrawn in the subgroup of children with an isolated *MCP* mutation who have fully recovered from aHUS. These patients may have a single episode of aHUS (especially when triggered, for example, by influenza or varicella) or may have relapses with several years of event-free intervals between them.^{77,78} One unexplored issue is whether other patients (for example, those with aHUS caused by isolated *CFI* mutations,¹⁰⁶ those with a mutation of unknown functional consequence, and those with no identified genetic abnormalities despite thorough investigations) would be able to stop eculizumab therapy after, for example, 12 months of continuous treatment. After eculizumab withdrawal, any relapse should lead to the prompt re-initiation of treatment. The development of a valid endothelial biomarker that can accurately indicate endothelial damage early on and can predict aHUS relapse is critically needed, particularly for eculizumab withdrawal protocols. The issues of optimal treatment duration and ways to taper off eculizumab clearly warrant further prospective studies.

Monitoring complement blockade

Recommended eculizumab doses and intervals^{15,53} have been designed to maintain permanent complement blockade during the whole inter-dose interval. However, we feel that assessing complement blockade using a CH50 assay (haemolytic assay of complement using sensitized sheep erythrocytes) or assessing eculizumab trough level (which is only available from the Alexion laboratory) may be helpful in evaluating possible underdosing when interdose intervals have been spaced out,^{30,31} or when clinical or histological features suggest an incomplete response to eculizumab. In our opinion, careful monitoring of C5 blockade should also be undertaken at the beginning of the treatment, especially in the youngest patients,²⁹ and in those with hastened clearance of proteins (for example, those with nephrotic syndrome or exudative enteropathy).

In addition, some intercurrent events, including infections,^{38,42} pregnancy or post-partum events,⁸⁵ surgery and trauma,^{107,108} and ischaemia-reperfusion,^{43,56} may augment the activation or production of complement factors, including C5. Indeed, a transient increase in serum levels of C5b-9 (sC5b-9) membrane attack complex was observed in two patients with concomitant infections who received eculizumab.^{38,42} Notably, in one patient, the detection of functional C5 coincided with a slight decrease in platelet count, indicative of a mild reactivation of the aHUS process.³⁸ In order to prevent infection-triggered relapse of aHUS, vaccination against influenza and early treatment of any overt infections is mandatory.

Similarly, women with aHUS should be informed about the increased risk of an aHUS flare during pregnancy, and the even greater risk in the post-partum period.⁸⁵ However, although the precautionary principle discourages the administration of any new drugs in pregnant women, the preliminary experience gained from pregnant

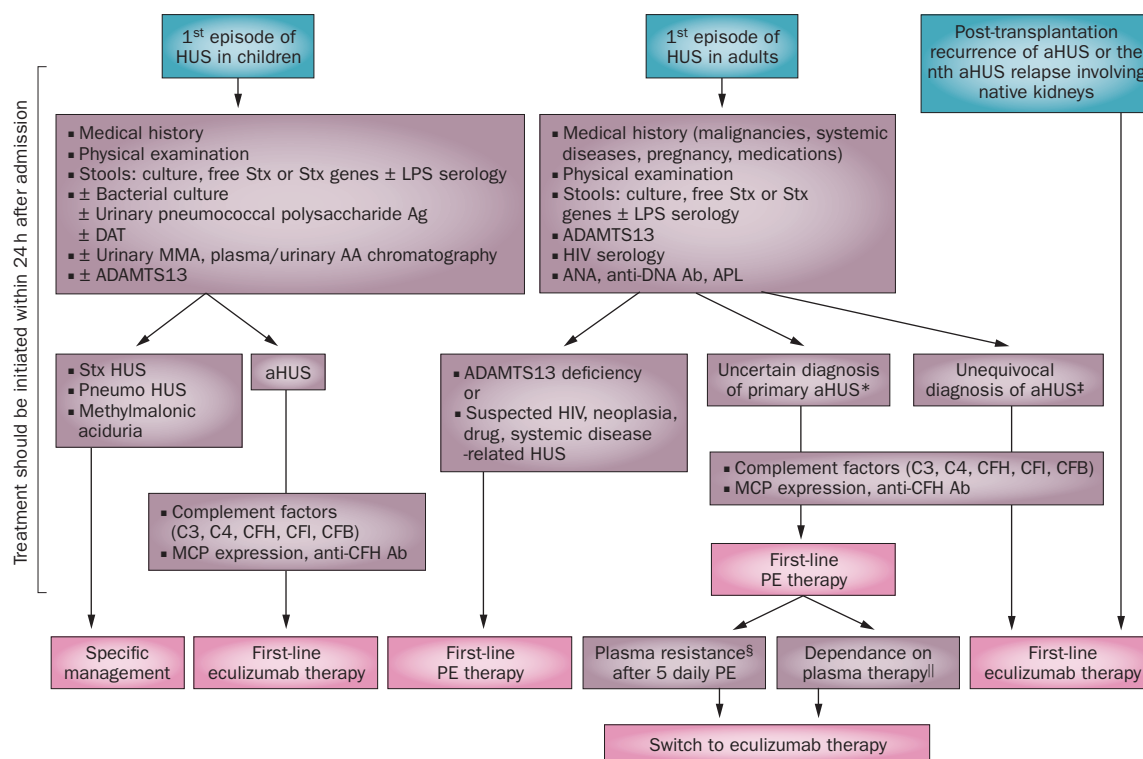


Figure 3 | Diagnostic algorithm and therapeutic options for aHUS. The main indications of eculizumab in patients with aHUS are depicted here. The treatment of a first aHUS episode is the most difficult situation, because several alternative diagnoses should be considered, especially in adults. However, the initiation of the treatment should not be delayed but should be based on rapid clinical judgement. The initial therapeutic option should later be re-evaluated in light of a complete aetiological work-up and the response to the treatment. *A firm diagnosis of primary aHUS requires awaiting the results of investigations for secondary causes, especially malignant and systemic diseases, or ADAMTS13 deficiency. †In particular, familial aHUS but also certain primary aHUS diagnoses based on physician judgement; first-line plasma exchange therapy remains, however, a suitable strategy as an alternative to eculizumab in these patients, depending on multiple factors including individual vascular access for plasma exchange, local accessibility to the immediate delivery of eculizumab, and the local availability of diagnostic assays. §The failure of five daily plasma exchanges to normalize platelet count or LDH level or to reduce creatinine level by at least 25%. ¶The relapse of aHUS during the weaning of plasma treatment. Abbreviations: AA, amino acid; Ab, antibodies; ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; aHUS, atypical haemolytic uraemic syndrome; ANA, antinuclear antibody; APL, antiphospholipid antibodies; C3, complement component 3, C4, complement component 4, CFH, complement factor H; CFI, complement factor I; DAT, direct antiglobulin test; MCP, membrane cofactor protein; MMA, methylmalonic acid; Pneumo, pneumococcal-related; LPS, lipopolysaccharides; PE, plasma exchange; Stx, Shiga-like toxin; U, urinary.

women with PNH who had been treated with eculizumab suggests a risk–benefit balance leaning towards the use of eculizumab.^{17,18,109} In women with a medical history of an episode of aHUS, the late administration of eculizumab in the near-term and during post-partum periods would theoretically offer two advantages: reducing the risk of adverse effects in the fetus and covering the period with the greatest risk of aHUS relapse.

Eculizumab and renal transplant in aHUS

The effectiveness of eculizumab has revolutionized the management and outcomes of aHUS and has opened up the possibility of renal transplantation in patients with aHUS (Figure 4). Although deceased-donor transplantation is the preferred option in patients with aHUS, living-non-related transplantation can be considered on a case-by-case basis. The issue of living-related donor transplantation in this setting is more complex because

the donor, in whom a genetic susceptibility factor to aHUS might have been unrecognized, could develop aHUS after the nephrectomy.¹¹⁰ Thus, living-related donation should be considered very rarely (Figure 4). The risk of post-transplantation recurrence of aHUS strongly depends on the underlying complement genetic abnormality.^{52,77,110} In this respect, screening for non-allelic homologous recombination using multiplex ligation-dependent probe amplification in the CFH region, including the hybrid gene *CFH/CFHR1*, should be performed.³ Previous studies in which the researchers did not perform this investigation may have overestimated the risk of recurrence in the subset of patients classified as having no identified mutation. Individual assessments of the recurrence risk based on complement investigations and recurrence in previous grafts may be used to tailor the therapeutic strategy to particular renal transplant candidates (Figure 4).¹¹¹

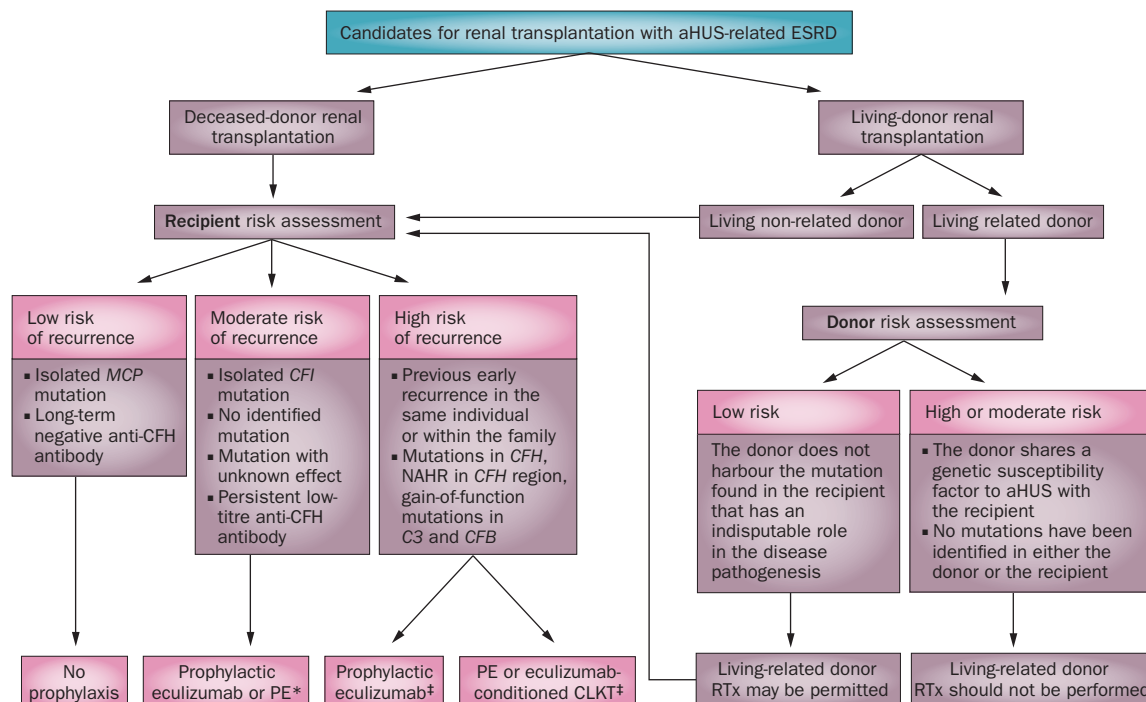


Figure 4 | Risk assessment for patients with aHUS who are candidates for renal transplantation. A kidney transplant from a deceased or living non-related donor is far preferable to a kidney transplant from a living related donor. The risk of post-transplantation recurrence of aHUS is assessed based on medical history (previous recurrence) and complement investigations. Regarding anti-CFH antibodies, the first-line strategy based on immunosuppressive drugs and plasma exchanges is dictated by the attempt to clear circulating antibodies before the transplantation. The different options presented here depend on whether anti-CFH antibodies are still detectable at the time of transplantation. Prophylactic therapy is mandatory for patients with a moderate or high risk of recurrence. Eculizumab, if available for prophylaxis, is preferable over plasma therapy. *The choice between prophylaxis with plasma therapy or eculizumab can depend on whether the patient has vascular access and on the local availability of eculizumab for prophylaxis. ‡The choice between life-long eculizumab therapy and preconditioned CLKT in patients with high-risk mutations should be determined on a case-by-case basis based on their individual ability to undergo liver transplantation, local skills in the surgical procedure, quality-of-life issues, and the society’s ability to afford the cost of life-long eculizumab treatment. Abbreviations: C3, complement component 3, CFB, complement factor B; CFH, complement factor H; CFI, complement factor I; CLKT, combined liver and kidney transplantation; MCP, membrane cofactor protein; NAHR, non-allelic homologous recombination; PE, plasma exchange; RTx, renal transplantation.

As mentioned earlier, we propose that patients with a high risk of recurrence should be given prophylactic eculizumab therapy, including a first dose prior to surgery and an additional dose within the 24 h following reperfusion (Figure 4).¹¹¹ The subset of patients at moderate risk can be given a prophylactic therapy based on plasma or on eculizumab, depending on vascular access and the local availability of eculizumab for prophylaxis. An important question is the optimal duration of prophylactic eculizumab therapy after transplantation. Life-long treatment seems to be the most suitable strategy in renal transplant recipients with a high risk of recurrence (Figure 4). However, prophylactic treatment may be discontinued in the subgroup of patients at moderate risk following a 12-month post-transplantation period free from any recurrence of aHUS. These issues warrant further study, and our proposals could provide a basis for the design of future clinical trials.¹¹¹

Combined liver and kidney transplantation (CLKT) has been shown to be effective in curing aHUS caused by mutations in *CFH* and *CFB* genes, which encode for liver-produced complement factors.¹¹² Although the procedure

has become safer following the introduction of plasma preconditioning,^{52,71,112} it remains risky; two out of 14 patients enrolled in a protocol that specified pre-conditioning died from surgical complications.⁷¹ Therefore, CLKT should be performed in well-informed patients with aHUS who have mutations in *CFH*, *C3* or *CFB*, and who are well-informed of the risks and make a clear request for this procedure to improve their quality of life (Figure 4). We acknowledge that the financial issue of whether health-care systems in different countries can afford expensive life-long eculizumab treatment could interfere with the benefit–risk assessment for some patients.

Cost of eculizumab for treatment of aHUS

Eculizumab was developed for an orphan disease, namely PNH. This positioning was used to justify the initial very high cost of the drug, which has remained unchanged even with the extension of indications to aHUS. Based on the price of a 300 mg vial of eculizumab of approximately €4,600 (US\$5,830), the cost per year of treatment ranges from roughly €82,800 (\$104,940) in a child weighing <10 kg, to €460,000 (\$583,001) in

Table 3 | Characteristics and outcomes of 10 patients with C3 glomerulopathy treated with eculizumab

Reference/s	Sex/age (years)/disease location	Pathology and complement abnormality	Time since diagnosis	Baseline parameters*	Duration of Ecu treatment	Outcome	Repeat KB
Bomback <i>et al.</i> (2012) ¹¹⁸ Herlitz <i>et al.</i> (2012) ¹²³	M/22/N	DDD CFH mutation	25 months	SCr 177 µmol/l UPCR 0.32 g/g sMAC increased	>53 weeks (follow-up 53 weeks)	↓ in SCr to 115–144 µmol/l Slight ↑ in UPCR (0.58 g/g)	↓ in activity with no evidence of EP
Bomback <i>et al.</i> (2012) ¹¹⁸ Herlitz <i>et al.</i> (2012) ¹²³	M/32/N	DDD C3Nef	322 months	SCr 168 µmol/l UPCR 2.4 g/g sMAC normal	40 weeks (follow-up 40 weeks)	↑ in SCr (256 µmol/l) and ↑ in UPCR (4.7 g/g)	ND
Bomback <i>et al.</i> (2012) ¹¹⁸ Herlitz <i>et al.</i> (2012) ¹²³	M/42/T	DDD No abnormality found	20 months	SCr 106 µmol/l UPCR 5.9 g/g	53 weeks (follow-up 52 weeks)	↓ in UPCR (1.7 g/g)	↓ in MP and less extensive deposits on EM
Bomback <i>et al.</i> (2012) ¹¹⁸ Herlitz <i>et al.</i> (2012) ¹²³	M/25/N	C3GN No abnormality found	162 months	SCr 141 µmol/l UPCR 2.2 g/g sMAC normal	52 weeks (follow-up 52 weeks)	↑ in SCr (203 µmol/l) following discontinuation of Cs/MMF	↑ in chronicity (85% sclerotic glomeruli) and persistent active C3GN
Bomback <i>et al.</i> (2012) ¹¹⁸ Herlitz <i>et al.</i> (2012) ¹²³	M/22/T	C3GN C3Nef	8 months	SCr 150 µmol/l UPCR 4.4 g/g sMAC increased	52 weeks (follow-up 69 weeks)	Slight ↑ in SCr (203 µmol/l) at week 52 ↑ in SCr (743 µmol/l) 7 weeks after Ecu completion (crescentic C3G on KB) PE, Cs and Ecu resumption led to ↓ in SCr (336 µmol/l)	↓ in MP and EP and ↓ in inflammatory cells at week 53
Bomback <i>et al.</i> (2012) ¹¹⁸ Herlitz <i>et al.</i> (2012) ¹²³	M/20/T	C3GN C3Nef MCP mutation	2 months	SCr 159 µmol/l UPCR 0.07 g/g sMAC mildly increased	53 weeks (follow-up 53 weeks)	Slight ↓ in SCr (124 µmol/l) Pr remained undetectable	Mild MP unchanged compared with initial biopsy
Daina <i>et al.</i> (2012) ¹¹⁹	F/22/N	DDD C3Nef	11 years	SCr 194 µmol/l Pr 6 g/day sMAC increased	48 weeks (follow-up 48 weeks)	↓ in Pr (~2.5 g/day) ↓ in SCr (~133 µmol/l) ↑ in SAlb from <20 g/l to >30 g/l	ND
Radhakrishnan <i>et al.</i> (2012) ¹²⁰	F/16/N	MPGN I C3Nef Complete CFHR1 deficiency	50 days	Anuric and on HD NS sMAC increased	>6 weeks (follow-up >6 weeks)	Normalization of SCr and resolution of NS Recovery of thrombocytopenia, anaemia, seizures associated with MPGN	ND
Vivarelli <i>et al.</i> (2012) ¹²¹	M/17/N	DDD C3Nef	7 years	SCr 106 µmol/l Pr 3.5–5.5 g/day	>27 weeks (follow-up >30 weeks)	↓ in Pr (0.9 g/day) and normalization of SAlb ↓ in SCr (~88 µmol/l) ↑ in Pr (2–5 g/day) following Ecu discontinuation, but ↓ to 0.96 g/day after Ecu was resumed Persistently low serum C3 levels	↓ in thickness of GC walls and in C3 and C5b–9 glomerular deposits at repeat KBs at 6 months and 18 months ↑ in GS (50%)
McCaughan <i>et al.</i> (2012) ¹²²	F/29/T	Crescentic DDD C3Nef	13 weeks	SCr 433 µmol/l UPCR 858 mg/mmol	>9 weeks (follow-up 9 weeks)	↓ in SCr (168 µmol/l) ↓ in UPCR (229 mg/mmol)	ND

Abbreviations: ↑, increase; ↓, decrease; C3G, C3 glomerulopathy; C3GN, C3 glomerulonephritis; C3Nef, C3 nephritic factor; Cs, corticosteroids; DDD, dense deposit disease; Ecu, eculizumab; EM, electron microscopy; EP, endocapillary proliferation; F, female; GC, glomerular capillary; GS, glomerular sclerosis; HD, haemodialysis; IVIg, intravenous immunoglobulin; KB, kidney biopsy; M, male; MP, mesangial proliferation; MPA, mycophenolic acid; MPGN 1, membranoproliferative glomerulonephritis type I; MMF, mycophenolate mofetil; N, in native kidney; ND, not done; NS, nephrotic syndrome; PE, plasma exchange; Pr, proteinuria; RTx, renal transplantation; SAlb, serum albumin; SCr, serum creatinine; sMAC, serum membrane attack complex (C5b–9); T, in transplant; Tac, tacrolimus; UPCR, urinary protein-to-creatinine ratio.

an adult. In this context, and despite the rarity of the disease, a medicoeconomic evaluation of the overall cost associated with the use of eculizumab for the treatment of aHUS could be useful.¹¹¹ Such an analysis should not only compare the cost of eculizumab with that of plasma therapy but should also integrate the money saved by any increased efficacy and decreased iatrogenic morbidity associated with eculizumab. Other factors that would

need to be taken into consideration in an analysis of the cost-effectiveness of eculizumab versus plasma therapies include the following: the avoidance of central-line-related complications, reductions in length of hospital stay and duration of dialysis period, improved renal survival, avoidance of chronic dialysis and of kidney transplantation failure due to recurrence, reduced cardiovascular risk in off-dialysis patients, improved

Box 3 | Authors' opinions on use of eculizumab in C3 glomerulopathy

- Treatment with eculizumab warrants further assessment in patients with C3 glomerulopathies, ideally in the setting of prospective studies
- Optimal candidates for eculizumab therapy are most likely patients with C3 glomerulopathy who have had a relatively short duration of disease, have shown active inflammatory renal lesions (extensive endocapillary proliferation and crescents) and limited glomerular and interstitial fibrosis in a recent kidney biopsy, and have demonstrated a recent increase in serum creatinine level and/or proteinuria and increased circulating serum C5b-9 level

health-related quality of life and preserved education and ability to work.

C3 glomerulopathy and eculizumab

The term 'C3 glomerulopathy' encompasses a heterogeneous spectrum of immune-mediated nephropathies that share a common pathological feature, glomerular deposition of C3. Accumulating experimental and clinical data (Table 3) indicate that dysregulation of the alternative complement pathway and the subsequent glomerular deposition of C3 degradation products, particularly C3d, are the primary events leading to the development of C3 glomerulopathies.^{1,6,7,113,114} However, the necrotic and inflammatory glomerular lesions (mesangial expansion and endocapillary and extracapillary proliferation), most likely triggered by C5a release, have a major role in the progression towards renal fibrosis and renal function impairment. For instance, in a large survey of cases of C3 glomerulopathy, the presence of crescents, and to a lesser extent, of mesangial proliferation in the initial biopsy, but not the type of C3 glomerulopathy, determined the risk of ESRD and, most interestingly, the risk of C3 glomerulopathy recurrence in the renal graft.¹¹⁵

Treatments for C3 glomerulopathies can target one or both of the initial glomerular deposition of C3 degradation products and/or the subsequent glomerular inflammatory changes. The clearance of C3 fragments from glomeruli in CFH-deficient mice through the restoration of complement regulation suggests that the initial process leading to C3 glomerulopathy is dynamic and reversible, at least in the early phase of the disease.^{114,116} In the same mouse model of C3 glomerulopathy, the inhibition of the complement common final pathway through C5 blockade ameliorated glomerular inflammatory changes but did not alter C3 deposition or the development of changes in the capillary walls.¹¹⁷ However, complete deficiency in CFH is an extreme condition of alternative pathway dysregulation and animal data do not necessarily translate into clinical practice.

To date, no drug that specifically inhibits the alternative C3 convertase is clinically available. By contrast, blockade of the complement common final pathway using the clinically available anti-C5 antibody, eculizumab, may be a potential therapy for C3 glomerulopathies. Available data concerning the use of eculizumab in patients with C3 glomerulopathy remain relatively scarce and are mostly in the form of case reports, which are susceptible to publication bias (Table 3). Therefore, we believe that formal prospective studies are warranted

to assess the effect of eculizumab on the evolution of C3 glomerulopathy. Reports of 10 cases of C3 glomerulopathies treated with eculizumab are available, including six cases of C3 glomerulopathy affecting the native kidneys¹¹⁸⁻¹²¹ and four cases of C3 glomerulopathy recurring in the renal graft.^{118,122} The results from these studies are rather disparate, especially compared with results of eculizumab in patients with aHUS. Nevertheless, the use of eculizumab led to an improvement in renal parameters in six out of ten treated patients.¹¹⁸⁻¹²² An increased level of circulating sC5b-9 and the presence of endocapillary or extracapillary proliferation in the initial kidney biopsy tended to correlate with a beneficial effect of eculizumab on the course of C3 glomerulopathy.¹¹⁸⁻¹²² The limited available pathological data indicate that eculizumab decreased endocapillary proliferation and inflammatory cell infiltration in three out of five patients who underwent repeat kidney biopsy.^{118,121,123} These findings are in accordance with animal data which showed that anti-C5 therapy effectively targeted the inflammatory component of C3 glomerulopathy.¹¹⁷ By contrast, staining for C3 and—more surprisingly—for C5b-9, remained unchanged in the post-eculizumab biopsy samples. This finding indicates that eculizumab could not hasten the clearance of C5b-9 that was deposited in renal tissue before the initiation of treatment. Moreover, glomerular inflammation and structural changes may prolong the half-life of C5b-9 in the renal tissue. Another unexpected histological finding consisted of the post-treatment pattern of monoclonal Ig (IgGk) deposits co-localizing with C3 and C5b, a pattern that suggests an accumulation of eculizumab in the kidney. Although eculizumab was engineered not to induce any complement activation, the long-term impact of IgG accumulation in the kidney needs further assessment.¹²³

Finally, all forms of C3 glomerulopathy carry a high risk of recurrence in the renal graft, ranging from 40% to 60%.⁵ Close monitoring of renal function and proteinuria remains mandatory following renal transplantation, to enable the early detection and prompt treatment of C3 glomerulopathy. Limited available data suggest that eculizumab is efficient in treating rapidly progressive and/or crescentic forms of C3 glomerulopathy recurring in the renal graft.¹²² Whether preventive treatment with eculizumab is warranted after renal transplantation in patients with a history of rapidly progressive C3 glomerulopathy in their native kidneys remains unclear. Our opinions on eculizumab in C3 glomerulopathy are summarized in Box 3.

Conclusions

Since 2009, eculizumab has become the new breakthrough treatment in patients with primary aHUS, providing improved control of the disease over plasma exchange, with a good safety profile. In our opinion, eculizumab seems to be on the way to becoming the new standard of care for aHUS. In the era of eculizumab, aHUS is poised to evolve from one of the most severe and disabling kidney diseases to being a curable disease with a specific treatment. However, the optimal treatment duration remains

unclear and should be prospectively addressed. The lack of an answer to this question increases the risk that financial considerations will take precedence over medical considerations. The overwhelming financial burden of prolonged treatment might lead to the inappropriate interruption of treatment in some patients, when, in fact, life-long treatment may be needed in a subset of these patients. In addition to the use of eculizumab in aHUS, more disparate data suggest that some forms of C3 glomerulopathy, especially the most inflammatory types, may also be responsive to eculizumab.

Review criteria

We searched PubMed for articles published up to 30 April 2012 using the following terms: “atypical hemolytic uremic syndrome”, “eculizumab”, “membranoproliferative glomerulonephritis”, and “C3 glomerulopathy”. The reference lists of publications were also reviewed to identify additional relevant articles. We focused on English-language, primarily full-text papers, although some abstracts and reports of congresses were also analyzed, and late outcome data on some case study patients were obtained from authors.

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Author contributions

The authors contributed equally to all aspects of the manuscript.