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A national specialised service in England for atypical haemolytic uraemic syndrome – the first year’s experience

Neil Sheerin, David Kavanagh, Timothy H J Goodship, Sally Johnson

Institutes of Genetic Medicine and Cellular Medicine, Newcastle University and The Newcastle upon Tyne Hospitals NHS Foundation Trust

All authors contributed equally to this manuscript.

Address for correspondence: Professor Tim Goodship  
Institute of Genetic Medicine  
Newcastle University  
Central Parkway  
Newcastle upon Tyne  
NE3 1BZ

[t.h.j.goodship@ncl.ac.uk](mailto:t.h.j.goodship@ncl.ac.uk)

## **Abstract**

In 2013 NHS England commissioned the use of eculizumab for both new patients with aHUS and those undergoing transplantation. This national service is delivered locally but coordinated by an expert centre at the Newcastle upon Tyne Hospitals NHS Foundation Trust. In the first year of the service 43 aHUS patients received eculizumab, 15 children and 28 adults. 23 were new patients and 20 prevalent. 15 of the 23 new patients required dialysis before eculizumab was started, 8 of these recovered renal function. 12 of the 20 prevalent patients who received eculizumab were transplant patients, 8 with prophylactic use and 4 for recurrent disease; the outcome in all was good. Eculizumab was withdrawn in 14 patients, 5 were patients who had not recovered renal function. In 3 of the 14 patients it was necessary to reintroduce eculizumab because of recurrent disease. There were 2 deaths in the 43 patients, neither was associated with use of eculizumab. There were no episodes of meningococcal disease. The establishment of this national service has enabled aHUS patients in England to receive eculizumab when they need it for as long as they need it.

**Key words:** aHUS, complement, eculizumab.

## Introduction

Atypical haemolytic uraemic syndrome (aHUS) is an ultra-rare disease characterised by acute kidney injury, thrombocytopenia and microangiopathic haemolytic anaemia<sup>1</sup>. aHUS is distinguished from typical (also known as shiga toxin-producing *E.coli* [STEC]) HUS, which is associated with a preceding enterohaemorrhagic *E.coli* (EHEC) infection, by appropriate bacteriological, molecular and serological investigations. The phenotypic triad can, however, be seen in other conditions where there is a co-existent renal thrombotic microangiopathy. Criteria have been established in the UK by the aHUS rare disease group (<http://rarerenal.org/rare-disease-groups/atypical-haemolytic-uraemic-syndrome-rdg/>) for the diagnosis of the disease (Table 1).

Approximately 50% of patients with aHUS have either an inherited and/or acquired abnormality of complement regulation<sup>1</sup>. Mutations have been described in genes encoding both complement regulators (factor H [*CFH*], *CD46*, factor I [*CFI*] and thrombomodulin [*THBD*]) and activators (*C3* and factor B [*CFB*]). Autoantibodies against factor H and factor I have also been described. That mutations have been described in aHUS in the gene (*DGKE*) encoding diacyl-glycerol kinase epsilon, a component of the protein kinase C pathway<sup>2</sup>, suggests that not all cases of aHUS will have a primary underlying complement abnormality.

Until recently the prognosis for patients presenting with aHUS was poor with the majority developing end-stage renal failure despite treatment with plasma exchange<sup>3</sup>. Renal transplantation in those on dialysis is also associated with a poor prognosis with a high risk of recurrent disease leading to allograft failure<sup>4</sup>.

Because the majority of patients with aHUS have an underlying complement abnormality it was logical that complement inhibitors would be an appropriate

therapy. Initial anecdotal reports suggested that the anti-C5 humanised monoclonal antibody eculizumab was highly effective and this was confirmed in subsequent open-label studies<sup>5</sup>. The results of these studies led to approval by both the FDA and EMA in 2011 for the use of eculizumab in aHUS. In England high-cost therapies (such as eculizumab) for very rare diseases (such as aHUS), are usually delivered through a national specialised service. An application to establish such a service for aHUS was first submitted to the Advisory Group for Nationalised Specialised Services (AGNSS) in 2011. Following evaluation of the application AGNSS submitted a report to the Department of Health. Based on this a statement was issued in January 2013 that “Ministers agreed with AGNSS that there is evidence for the clinical effectiveness of Eculizumab for the treatment of atypical haemolytic uraemic syndrome but wanted further advice on the affordability of the drug”. The National Institute for Health and Care Excellence (NICE) was therefore asked to undertake an evaluation of eculizumab. This process will culminate with the publication of a Final Evaluation Document (FED) in January 2015. The draft FED published in December 2014 recommends that “Eculizumab, within its marketing authorisation, is recommended for funding for treating atypical haemolytic uraemic syndrome, only if all the following arrangements are in place: coordination of eculizumab use through an expert centre, monitoring systems to record the number of people with a diagnosis of atypical haemolytic uraemic syndrome and the number who have eculizumab, and the dose and duration of treatment, a national protocol for starting and stopping eculizumab for clinical reasons and a research programme with robust methods to evaluate when stopping treatment or dose adjustment might occur

<https://www.nice.org.uk/guidance/indevelopment/gid-atypicalhaemolyticuraemicsyndromeahuseculizumab>.

In the meantime NHS England in 2013 resolved to commission eculizumab for both patients with newly diagnosed aHUS and also for those patients on dialysis who needed eculizumab to prevent the recurrence of aHUS in the transplanted kidney (<http://www.england.nhs.uk/wp-content/uploads/2013/09/e03-hss-a.pdf>). This service is delivered locally but co-ordinated by an expert centre (interim national specialised service) provided by the Newcastle upon Tyne Hospitals NHS Foundation Trust. We here report the activity and outcomes for the first year of this service.

### **Patients treated with eculizumab**

From the 1<sup>st</sup> April 2013 to 31<sup>st</sup> March 2014 43 patients received eculizumab under the NHS England commissioning policy. Of these 15 were children (aged < 18 years, 11 male and 4 female) and 28 were adults (9 male and 19 female). Of the 43 patients 23 were incident (3 familial) and 20 prevalent. 31/43 patients are still receiving eculizumab, treatment has been withdrawn in the remaining 12. Of the 31 patients still receiving eculizumab one has moved to Scotland and funding for eculizumab has been provided by the appropriate Health Board following submission of an individual patient treatment request (IPTR).

### **Dose of eculizumab**

All adult patients received an initial dose of 900 mg via 35 minute IV infusion then 900 mg every 7 days for the first 4 doses, followed by 1200 mg for the fifth dose 7 days later. The maintenance dose was 1200 mg every 14 days. The paediatric dosing schedule was according to weight and is shown at <http://rarerenal.org/clinician-information/haemolytic-uraemic-syndrome-atypical-ahus-clinician-information/#Eculizumab> dosage. One adult patient suffered severe migraine

immediately after treatment on the maintenance dose of 1200 mg every two weeks. The dose was therefore decreased to 900 mg every ten days with an improvement in the symptoms. In another adult patient receiving eculizumab prophylactically for a renal transplant trough haemolytic assays showed incomplete complement blockade on 1200mg every two weeks with some evidence on biopsy of the transplant kidney of a low grade thrombotic microangiopathy. The dose of eculizumab in this patient was increased to 1500 mg every two weeks.

### **Treatment of incident patients**

Clinicians in England who suspect a diagnosis of aHUS in a patient presenting for the first time are requested to complete an aHUS diagnostic checklist (supplementary information). This form requests clinical information and provides a list of investigations required to exclude other causes of a renal thrombotic microangiopathy. Clinicians are asked to submit the form electronically via nhs.net as soon as the result for the ADAMTS13 activity (to exclude thrombotic thrombocytopenic purpura – TTP) is available. This is because plasma therapy is the treatment of choice for TTP and should not be stopped before the diagnosis is excluded. Each submission is evaluated independently by the four clinicians (three adult nephrologists; THJG, NS, DK and one paediatric nephrologist; SJ) who oversee the interim national service to determine if the clinical presentation is compatible with a diagnosis of aHUS and if so whether treatment with eculizumab would be beneficial. In the majority of cases there was unanimous consensus. If this was for a diagnosis of aHUS and that eculizumab should be given then approval for funding was sought electronically from NHS England. In all cases this was obtained within 24 hours. The local clinician was then

informed immediately. All the information necessary for local physicians to initiate eculizumab and subsequently monitor patients is provided at [www.rarerrenal.org](http://www.rarerrenal.org).

The outcome of the incident patients is shown in Figure 1. Of the 23 incident patients 14 were adults and 9 children. All 14 adult patients and 2 of the 9 paediatric patients underwent at least one session of plasma exchange or plasma infusion before eculizumab was given. 15 of the 23 required dialysis before starting eculizumab. 8/15 patients requiring dialysis recovered renal function (Table 2). Eculizumab was continued in all except one. The longest time that any of these patients remained on dialysis before recovery of renal function was 30 weeks. The level of renal function (eGFR) that was recovered ranged from 28 to 126 ml/min/1.73m<sup>2</sup>. 5/15 requiring dialysis did not recover renal function despite at least 4 months treatment with eculizumab. In all these patients eculizumab was withdrawn. In all there was evidence (either from renal biopsy and/or renal imaging) at the time of withdrawal of eculizumab that there was no potential for recovery of renal function. In two patients it was subsequently necessary to reintroduce eculizumab because of recurrent haemolysis associated with hyperkalaemia. In both this resolved with reintroduction of eculizumab. There were two patients on dialysis in whom eculizumab was withdrawn earlier. One was non-compliant with all forms of therapy including dialysis and in the other, a child, both dialysis and eculizumab were withdrawn because of the diagnosis of a co-existent condition (ponto cerebellar hypoplasia type I) which was managed conservatively. 8/23 incident patients did not require dialysis. Eculizumab has been withdrawn in 5. One was found to have a *CD46* mutation, one was found to have typical HUS and three were not found to have any mutations. Three have continued on eculizumab.



Assuming a population for England of ~53 million the incidence of presumed aHUS in the first year of the service was 0.43 per million population but the true incidence was 0.42 once the patient with typical HUS was removed.

### **Treatment of prevalent patients on dialysis**

As of 1<sup>st</sup> April 2013 there were 45 patients (43 adults and 2 children) on dialysis in England with a primary renal diagnosis of aHUS. 19 of these individuals had lost a previous renal transplant to recurrent disease. Mutation screening of *CFH*, *CFI*, *CD46*, *C3* and *CFB* had been undertaken in all. In 32/45 a mutation was identified (*CFH* 13, *CFI* 5, *C3* 8, *CFB* 2, *CFH/CFHRI* hybrid 2, *CFHRI/CFH* hybrid 1, combined *CFHRI/CFH* hybrid and *CFI* 1). Of the 13 patients without an identified mutation 5 had lost a previous transplant to recurrent diseases. This suggests that in these individuals there is an, as of yet, unidentified inherited or acquired factor that has resulted in recurrent disease. All patients were also screened for factor H autoantibodies. One patient who also had a *CFI* mutation was positive. The majority of these 45 patients were not listed for a transplant because of the risk of recurrent disease. The introduction of the NHS England commissioning policy for aHUS allowed these patients to be listed for a transplant. NHS Blood and Transplant approved a proposal that retrospective weighting on the transplant list be given to those aHUS patients who had not been listed for a kidney transplant because of the risk of recurrent disease. The longest period of retrospective weighting that was given was 25 years. From 1<sup>st</sup> April 2013 – 31<sup>st</sup> March 2014 9/45 were transplanted. 8/9 were given prophylactic eculizumab using a standard protocol ([http://rarerenal.org/clinician-information/haemolytic-uraemic-syndrome-atypical-ahus-clinician-information/#Transplantation of aHUS patients using eculizumab](http://rarerenal.org/clinician-information/haemolytic-uraemic-syndrome-atypical-ahus-clinician-information/#Transplantation%20of%20aHUS%20patients%20using%20eculizumab)) and

1 patient received eculizumab for recurrence of the disease in the early post operative period. All 9 patients have continued to receive eculizumab and have good transplant function.

### **Treatment of prevalent patients not on dialysis**

8 of the 11 prevalent patients who were not on dialysis were given eculizumab to prevent further relapses. The remaining three were transplant patients. One who was known to have a C3 mutation started eculizumab 29 months after transplant when a biopsy undertaken for progressive decline in transplant function showed evidence of a chronic thrombotic microangiopathy. With introduction of eculizumab there was an improvement in transplant function which has been maintained. The two other transplant patients had primary diagnoses of typical HUS and hypertensive end-stage renal disease respectively. Both developed a thrombotic microangiopathy in the transplant kidney early after transplantation leading to a revised primary renal diagnosis of aHUS. In both there was a good response to treatment with eculizumab and transplant function remains stable. One was subsequently found to carry a pathogenic *CFH* mutation.

### **Investigation of incident and prevalent patients**

**Mutation screening.** 22 of the 23 incident patients underwent screening for mutations in *CFH*, *CFI*, *CD46*, *C3*, *CFB* and *DKGE*. The one patient who did not undergo screening was diagnosed as having typical HUS within the first week of presentation and received only one dose of eculizumab. No mutations were identified in 11/22

patients. In the other 11 patients there were 6 *CFH*, 2 *CD46*, 3 *C3* and 1 *CFI* mutation. One patient carried both a *CFH* and a *C3* mutation. Of the 15 incident patients who required dialysis before eculizumab was started 8 carried a mutation and 7 did not. Of the 9 patients who recovered renal function 4 carried a mutation and 5 did not.

All of the 20 prevalent patients had been screened for mutations in *CFH*, *CFI*, *CD46*, *C3*, *CFB* and *DGKE*. 18/20 carried a mutation (8 *CFH*, 6 *C3*, 3 *CFI*, 1 *CD46*).

Table 3 shows the mutations found in both the incident and prevalent patients.

**Factor H autoantibodies.** Screening for factor H autoantibodies was undertaken as described previously<sup>6 7</sup>. Six patients were found to have factor H autoantibodies (Table 4). Three were prevalent and three incident. Two patients, one incident and one prevalent, had borderline titres. The remaining 4 patients, 2 prevalent and 2 incident, had high titres. In all 4 multiplex ligation-dependent probe amplification (MLPA) analysis<sup>8</sup> showed zero copies of *CFHR1*. Three of the 4 patients were also found to carry a complement gene mutation – 3 *CFI* (one homozygous) and 1 *C3*.

### **Meningococcal disease**

Prevention of meningococcal disease was managed according to guidelines for both adults and children (available at <http://rarerenal.org/clinician-information/haemolytic-uraemic-syndrome-atypical-ahus-clinician-information/>). The guidelines recommend that all patients receive a tetravalent A,C,W, Y conjugated vaccine and the multi component serogroup B vaccine Bexsero. We recommend that antibody titres be tested at 4-6 weeks post-vaccination. In addition we recommend that all patients as soon as they start eculizumab receive prophylactic antibiotics which they should

remain on as long as they are on eculizumab. There have been no episodes of meningococcal disease in any of the aHUS patients treated with eculizumab in the first year of the national service. Antibody titre results for the A, C, Y and W serogroups are available for 10 patients. Seroprotection (serum bactericidal activity [SBA] titre > 8) for all 4 serogroups was seen in 6/10 patients. In the remaining 4 patients two had titres of < 8 for the Y serogroup, one had titres of < 8 for the C and Y serogroups, and one had titres of < 8 for the C and W serogroups. Revaccination was recommended for these 4 patients.

### **Withdrawal of eculizumab**

Eculizumab was withdrawn in 14 patients (9 adults and 5 children) (Table 5). In 5 patients the drug was withdrawn after the patients had been on dialysis for at least 4 months without any evidence of recovery of renal function. In 2 of these patients it was necessary to restart eculizumab because of the development of significant haemolysis with associated hyperkalaemia. In both reintroduction of eculizumab led to resolution of the haemolysis. Eculizumab was withdrawn in one patient on dialysis because of non-compliance with all forms of treatment including dialysis. In one patient eculizumab was withdrawn after only one dose because of the diagnosis of typical HUS. In two patients who presented with acute kidney injury not needing dialysis with subsequent complete recovery of renal function no mutations were found and eculizumab was withdrawn. There has been no recurrence of the disease in either of these patients. In one patient who recovered renal function after needing dialysis no mutations were found and eculizumab was withdrawn. Again there has been no recurrence of the disease in this patient. In two patients with a *CD46* mutation eculizumab was withdrawn. In one of these patients there was a relapse 36 weeks after eculizumab was withdrawn. Eculizumab was reintroduced with complete

recovery of renal function and has been maintained since. In one patient eculizumab was withdrawn after the diagnosis of a complex neurological disorder (ponto cerebellar hypoplasia type I) which was treated conservatively.

### **Monitoring the response to eculizumab**

In the clinician information at [www.rarerrenal.org](http://www.rarerrenal.org) we recommend that in addition to routine biochemistry and haematology investigations that all patients under go measurement of a pre-dose (trough) alternative pathway and classical pathway haemolytic assay at least twice once the patient is taking the routine long-term dose of eculizumab (for instance 1200mg every two weeks in adults). We recommend that both assays should show no detectable haemolytic activity. In addition we suggest that measurement of platelet count, LDH, haptoglobins and urine protein/creatinine ratio is undertaken monthly. The aim of this surveillance is to ensure that complement blockade is complete and that there is no evidence to suggest an ongoing TMA. In one adult patient (known to have a pathogenic *CFH* mutation) receiving eculizumab prophylactically to enable a renal transplant there was evidence of incomplete complement blockade (detectable lysis on both the alternative pathway and classical pathway assays) and ongoing low grade TMA on renal biopsy with deteriorating transplant function. This patient was receiving 1200 mg of eculizumab every two weeks. The dose of eculizumab was increased to 1500 mg with a subsequent improvement in transplant function. Another patient (paediatric) showed biopsy evidence of ongoing TMA despite complete complement blockade. No mutations (including *DGKE*) were found in this patient. We also routinely screen all

patients for the *C5* polymorphism (c.2654G>A; p.Arg885His, rs56040400) that is associated with resistance to eculizumab<sup>9</sup>. None of the patients in this cohort were found to carry this variant.

## **Discussion**

The introduction of eculizumab represents a step-change in the management of patients with aHUS<sup>5</sup>. The recognition in the past two decades that most patients with aHUS will have either an inherited and/or acquired abnormality of complement leading to excessive activation of the alternative pathway has paved the way for the use of complement inhibitors in this disease. Eculizumab can profoundly affect the prognosis both for patients presenting for the first time and also those patients on dialysis who are unable to be transplanted because of the risk of recurrent disease. However, eculizumab is extremely expensive costing ~£360,000 per year for an adult patient. Because of this Health Ministers in England decided after an initial assessment by the Advisory Group for National Specialised Service in 2013 to refer the drug to the National Institute for Health and Care Excellence. The Final Evaluation Document produced by the Highly Specialised Evaluation Technology Committee affirms the clinical efficacy of eculizumab in aHUS and recommends funding for the use of the drug in England provided that there is coordination of its use through an expert centre and monitoring systems to record the number of people with a diagnosis of atypical haemolytic uraemic syndrome and the number who have eculizumab, and the dose and duration of treatment. We report here the experience of an interim national specialised service commissioned by NHS England which was established in 2013 and fulfils these conditions.

In the first year of this national service 23 patients were diagnosed for the first time as having aHUS and treated with eculizumab. One of these was subsequently shown to have typical HUS and correcting for this gives an incidence of 0.42 per million population. Little information is available from other countries as to either the incidence or prevalence of aHUS. Data from France for the period 2000 – 2008 based on the number of patients referred for screening gives an incidence of 0.23 per million population per year<sup>10</sup>. We believe that the incidence may be higher than observed in the first year of this national service in England. To date in the second year of the service the incidence is projected to be 0.68 per million population.

The service that we have established is locally-delivered with the local clinician taking primary responsibility for the patient. The clinician decides if he/she wishes to approach the national service for funding for eculizumab and does this by completing the aHUS diagnostic checklist (supplementary information). In most cases advice has already been sought from one of the four clinicians responsible for the national service. We are usually able to provide confirmation of funding for eculizumab, including approval by NHS England, within 24 hours of receiving the completed aHUS diagnostic checklist. On this we provide a list of tests that we suggest are undertaken to rule out other forms of a renal thrombotic microangiopathy. The only test that we require there to be a result of prior to authorisation of eculizumab is the ADAMTS13 activity. Most adult patients and some children have received plasma therapy by the time that the first dose of eculizumab is given.

Of the 23 incident patients 16 had started dialysis by the time that eculizumab was started. 5 of these individuals did not recover renal function including two patients with a known pathogenic complement mutation (one *C3* and the other a *CFH/CFHR1* hybrid gene). Both of these individuals had at least one other family member who

had been affected by the disease. Despite remission of the TMA in these 5 individuals all showed evidence (either from biopsy or serial ultrasound) of irreversible stage 5 CKD at the time of withdrawal of eculizumab. All received eculizumab for at least 4 months. The importance of early recognition of potential aHUS in unaffected at-risk family members is something that both we and the national patient-family support group aHUSUK ([www.ahusuk.org](http://www.ahusuk.org)) emphasise. We provide for such individuals information in a credit card sized format which can be shown to healthcare professionals.

In those patients who recovered renal function the time spent on dialysis after the start of eculizumab ranged from 2 to 30 weeks. In the latter case there was evidence during this period of increasing urine output suggesting that there was potential for recovery of renal function.

Mutation screening showed that 50% of the incident patients carried a mutation in a known aHUS complement gene. This is similar to the prevalence of 46% reported for the USA<sup>11</sup> but lower than that reported in other cross-sectional cohorts of aHUS patients where up to 70% of patients<sup>3 10</sup> carry a mutation. We have, however, not included in this figure disease predisposing *CFH* and *CD46* haplotypes or the *CFHR3/1* deletion. The presence/absence of a mutation was not related to either the need for dialysis in incident patients or the outcome with regard to recovery of renal function. In contrast 90% of prevalent patients who received eculizumab carried a mutation. The outcome in the prevalent patients was good. Prophylactic use of eculizumab to enable transplantation was associated with excellent transplant outcomes. Three patients received eculizumab post transplant. One was known to have aHUS as the primary disease but in the other two the primary diagnosis was respectively typical HUS and malignant hypertension. We now recommend that all



patients on dialysis with a primary renal diagnosis of typical HUS undergo mutation screening. Even in the absence of a mutation we recommend that typical HUS patients are counselled that there may still be a risk of developing a transplant TMA which would redefine the diagnosis and require treatment with eculizumab.

Withdrawal of eculizumab in aHUS is an area where there is no clear consensus. We are of the opinion that the evidence for lifelong treatment with eculizumab in aHUS is not robust. There is some evidence from small single cohort studies that eculizumab can be withdrawn in some patients without significant risk of relapse. We think that this would be best addressed in a rigorous randomised controlled trial of long-term versus disease driven intermittent treatment. Until such a study is established we recommend that the decision to withdraw treatment is taken on a case by case basis with input from the local physician, the national service, the patient and his/her carers/family. Guidelines for the withdrawal of treatment and subsequent monitoring are at [www.rarerrenal.org](http://www.rarerrenal.org). Of the 43 patients treated in the first year of the service eculizumab has been withdrawn in 14 patients. In three there has been evidence of recurrent disease requiring reintroduction of eculizumab. Two are dialysis patients who developed haemolysis and hyperkalaemia. The other was a child with a *CD46* who relapsed 36 weeks after treatment was withdrawn. All three responded quickly to reintroduction of treatment.

Another area where there is no clear consensus is what level of complement blockade is necessary to induce and maintain remission. The dosing regimen advocated is based on that used in the open label trials and was designed to completely block terminal pathway activity between doses. Drug levels can be used to monitor this with a recommended trough level of greater than 50 µg/l. Because of the logistics of undertaking this assay which is currently only available in the USA we do not

routinely undertake this. We do, however, recommend that alternative and classical pathway haemolytic assays are undertaken at least twice once a patient is on the maintenance dose of eculizumab. We have found the information provided for these assays useful in two patients. Once was a transplant patient with deteriorating renal function who on biopsy showed evidence of low grade TMA. Haemolytic assays in this patient showed incomplete blockade immediately pre-dose and we, therefore, increased the dose of eculizumab to 1500 mg every two weeks. This was associated with an improvement in transplant function. The other was a child who relapsed on treatment. Haemolytic assays in this individual show complete blockade and we are suspicious there is a non-complement mediated mechanism underlying the TMA. This is under further investigation.

In conclusion; we report here the first year's experience of a devolved national specialised service in England for the investigation and treatment of patients with aHUS. We believe that the activity and outcomes that we report here justify retention of this service on a long-term basis. We are of the opinion that locally-delivered national specialised services such as the one that we have established provides an ideal infrastructure for the management of very rare disease such as aHUS.

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## Legends to figures

**Figure 1.** Outcome in the incident patients. \* Eculizumab was withdrawn early in two of the patients needing dialysis. Both later deceased.

**Table 1.** Diagnostic criteria for aHUS

*Exclusion*

Thrombotic thrombocytopenic purpura

Shiga toxin associated HUS

Drug mediated TMA

Infection (HIV, Streptococcus pneumonia)

Ttransplantation (bone marrow, liver, lung, cardiac)

Cobalamin deficiency

Systemic lupus erythematosus

Antiphospholipid antibody syndrome

Scleroderma

*Inclusion*

Renal biopsy showing a thrombotic microangiopathy

and/or

Triad of microangiopathic haemolytic anaemia, thrombocytopenia and renal failure

**Table 2.** Patients who required dialysis before eculizumab was started and subsequently recovered renal function

Age at start of treatment with eculizumab (years)	Gender	Length of time on dialysis	Renal function (eGFR ml/min/1.73m <sup>2</sup> )	Mutations and/or factor H autoantibodies	Eculizumab
36	Male	19 weeks	33	<i>CD46</i> (c.286+2T>G )	Continues
25	Female	2 weeks	85	<i>CFH</i> (c.c.694C>T; p.Arg232*) and <i>C3</i> (c.193A>C; p.Lys65Gln)	Continues
69	Female	9	38	Nil	Continues
33	Male	30 weeks	28	<i>C3</i> (c.493G>T; p.Val165Phe)	Continues
53	Male	6 weeks	52	Nil	Continues
11 months*	Male	2 weeks	126	Nil	Withdrawn after 34 weeks
3 months	Male			<i>CFH</i> (c.1825G>A; p.Val609Ile)	Continues
3	Male			Factor H autoantibody positive	Continues

\*same patient as in Table 5

**Table 3.** Mutations found in incident and prevalent patients

Prevalent or Incident	Gene	Variant
Incident	<i>CFH</i>	c.213G>A; p.Trp71*
Incident*	<i>CFH</i>	c.694C>T; p.Arg232*
Prevalent	<i>CFH</i>	c.942G>A; p.Trp314*
Incident	<i>CFH</i>	c.1825G>A; p.Val609Ile
Prevalent	<i>CFH</i>	c.1933delA; p.Thr645fs
Prevalent	<i>CFH</i>	c.2850G>T; p.Gln950His
Incident	<i>CFH</i>	c.2850G>T; p.Gln950His
Prevalent	<i>CFH</i>	c.2867C>T; p.Thr956Met
Prevalent	<i>CFH</i>	c.3572C>T; p.Ser1191Leu
Prevalent	<i>CFH</i>	c.3643C>G; p.Arg1215Gly
Prevalent	<i>CFH</i>	c.3643C>G; p.Arg1215Gly
Prevalent	<i>CFH</i>	c.3643C>G; p.Arg1215Gly
Incident	<i>CFH</i>	c.3643C>G; p.Arg1215Gly
Incident	<i>CFH</i>	<i>CFH/CFHR1</i> hybrid
Prevalent	<i>C3</i>	c.193A>C; p.Lys65Gln
Prevalent	<i>C3</i>	c.193A>C; p.Lys65Gln
Incident*	<i>C3</i>	c.193A>C; p.Lys65Gln
Prevalent	<i>C3</i>	c.481C>T; p.Arg161Trp
Incident	<i>C3</i>	c.485C>G; p.Thr162Arg
Prevalent	<i>C3</i>	c.485C>G; p.Thr162Arg
Incident	<i>C3</i>	c.493G>T; p.Val165Phe
Prevalent	<i>C3</i>	c.3142C>G;p.Arg1042Gly
Prevalent	<i>C3</i>	c.3343G>A; p.Asp1115Asn
Incident	<i>CD46</i>	c.286+2T>G
Incident	<i>CD46</i>	c.286+2T>G
Prevalent	<i>CD46</i>	c.646T>G; p.Trp216Gly
Prevalent	<i>CFI</i>	c.859G>A; p.Gly287Arg
Incident	<i>CFI</i>	c.1456T>C; p.Trp486Arg (homozygous)
Prevalent	<i>CFI</i>	c.1733T>C; p.Ile578Thr

\*One patient carried both a *CFH* and a *C3* mutation

**Table 4.** Factor H autoantibody positive patients

Age at start of treatment with eculizumab (years)	Gender	Prevalent/incident	Autoantibody titre	CFHR3 copy number	CFR1 copy number	Mutations
11	Female	Prevalent	+++	0	0	<i>CFI</i> (c.859G>A; p.Gly287Arg)
11 months	Male	Incident	Borderline	2	2	Nil
9	Female	Prevalent	+++	1	0	<i>CFI</i> (c.1216C>T; Arg406Cys)
17	Male	Prevalent	Borderline	2	2	<i>C3</i> (c.3142C>G;p.Arg1042Gly)
11 months	Male	Incident	+++	0	0	<i>CFI</i> homozygous (c.1456T>C; p.Trp486Arg)
3	Male	Incident	+++	0	0	Nil

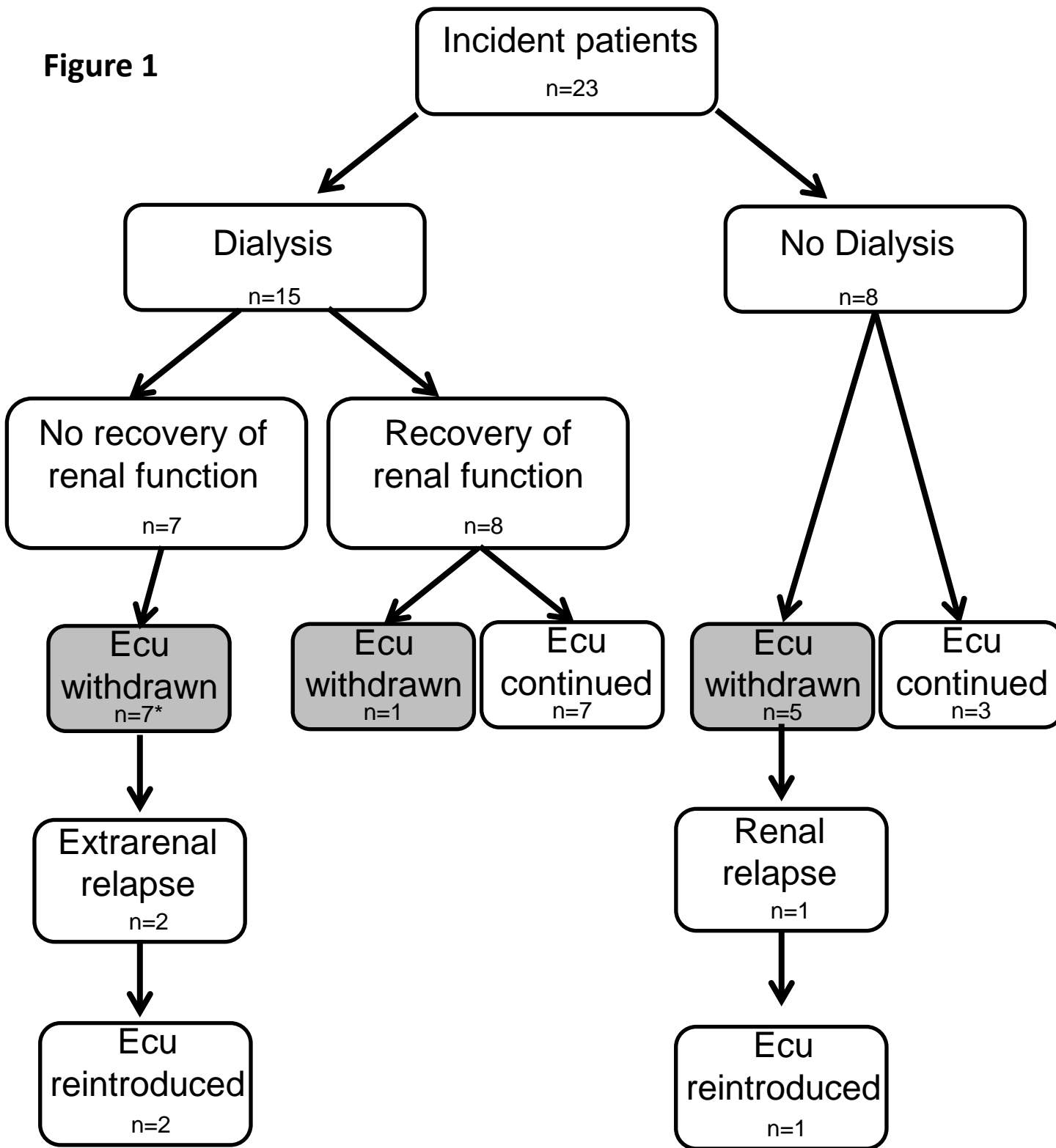


**Table 5.** Patients in whom eculizumab was withdrawn

Age at start of treatment with eculizumab (years)	Gender	Duration of treatment with eculizumab	Dialysis	Mutations	Outcome
51	Female	27 weeks	Yes	<i>C3</i> (c.485C>G; p.Thr162Arg)	Dialysis
48	Female	24 weeks	Yes	Nil	Dialysis. Eculizumab reintroduced after six weeks because of haemolysis.
21	Male	33 weeks	Yes	Nil	Dialysis
38	Female	19 weeks	Yes	Nil	Dialysis
23	Female	4 weeks	Yes	<i>CFH</i> (c.213G>A; p.Trp71*)	Deceased. Non-compliant with all therapy.
66	Female	16 weeks	Yes	Nil	CKD
31	Male	24 weeks	Yes	<i>CFH/CFHR1</i> hybrid	Dialysis. Eculizumab reintroduced after ten weeks because of haemolysis
48	Female	26 weeks	No Creatinine 350 µmol/l	Nil	Creatinine 77 µmol/l
21	Female	15 weeks	No	<i>CD46</i> (c.646T>G; p.Trp216Gly)	No relapses.
5	Male	27 weeks	No	<i>CD46</i> (c.286+2T>G)	Relapsed after 36 weeks and eculizumab reintroduced.
10 months	Female	1 week	No	N/A	Typical HUS. Complete recovery
11 months*	Male	34 weeks	Yes	Nil	Complete recovery
2	Female	26 weeks	No	Nil	Complete recovery
6 months	Male	4 weeks	Yes	<i>CFH</i> (c.2850G>T; p. Gln950His)	Deceased. Co-existing ponto-cerebellar hypoplasia type I.

\*same patient as in Table 2.

**Figure 1**



Dialysis dependent  
n=7

Dialysis independent  
n=16