Long-term safety and effectiveness of eculizumab for patients with atypical haemolytic uraemic syndrome: outcomes from a prospective observational clinical trial

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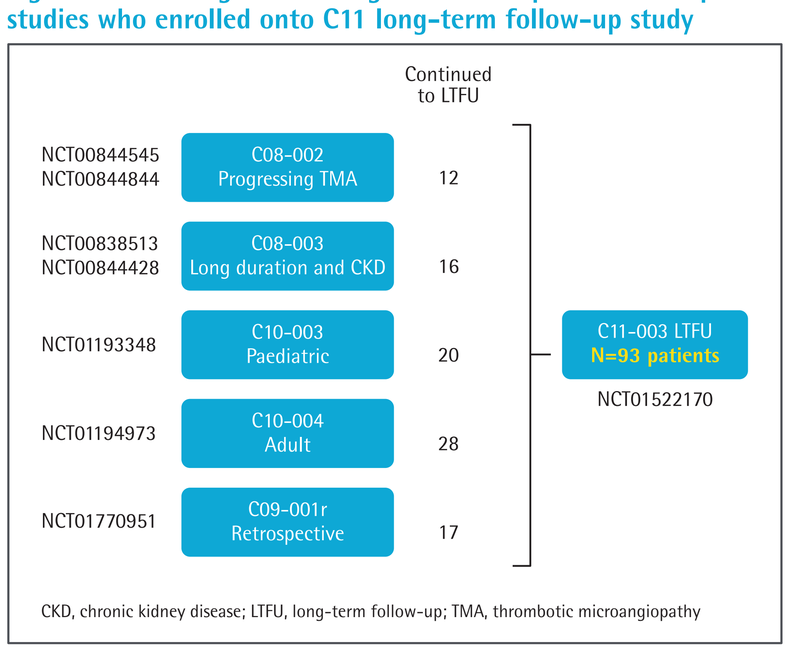
INTRODUCTION

- Atypical haemolytic uraemic syndrome (aHUS) is a rare, life-threatening disease caused by genetic or acquired dysregulation of the complement system, leading to systemic thrombotic microangiopathy (TMA).[1]
- Clinical presentation of aHUS is typically nonimmune haemolytic anaemia, thrombocytopenia and acute renal failure, with underlying TMA lesions of the kidneys, and often other systems.[2]
- Eculizumab, a complement protein C5-inhibitor, is the only approved treatment for aHUS.[3]
- The safety and efficacy of eculizumab has been demonstrated in four prospective, multicentre studies, and one retrospective study.[4–8]
- Here we investigate long-term safety and the risk of TMA in patients with aHUS who received ongoing eculizumab treatment and those who discontinued eculizumab.

METHODS

- Patients with aHUS who participated in any of the five previous eculizumab studies (parent study) could enrol in this observational, long-term follow-up study – C11 (NCT01522170, Figure 1).
  - Patients were eligible regardless of whether they continued eculizumab treatment after parent study completion.
  - Data for the C11 study were collected after parent study completion.
- The primary endpoint was TMA manifestation rate for on-treatment (i.e., receiving eculizumab regardless of dosing regimen) and off-treatment (i.e., discontinued from eculizumab) periods (Table 1).
  - Patients could have both on- and off-treatment periods.
- Time to first TMA manifestation was analysed using a Cox proportional hazards model with treatment status as a time-dependent explanatory variable and complement gene abnormality status as a covariate.
- Targeted serious adverse events (serious infections, meningococcal infection, sepsis, leukopenia, infusion reactions, renal or hepatic impairment and malignancy) were also assessed.
- Data cut-off was March 2016.

Figure 1. Flow diagram showing numbers of patients from parent studies who enrolled onto C11 long-term follow-up study



CKD, chronic kidney disease; LTFU, long-term follow-up; TMA, thrombotic microangiopathy

Table 1. Definitions of TMA used in study

Per-protocol definition of TMA

The occurrence of a change in ≥1 of the following:

- ≥1 laboratory value change
  - platelet count decrease ≥25% compared with baseline and <LLN
  - increase in SCr or LDH level ≥25% compared with baseline and >ULN
- Clinical sign or symptom of TMA considered definitely related to aHUS
  - thrombosis
  - seizure
  - reduction in renal function
  - proteinuria (new or worse compared to baseline and >1+ or >30 mg/dL)
  - haematuria (new or worse compared to baseline and >50 RBC/HPF)
  - increase in haemolytic anaemia
  - biopsy-proven TMA
  - other (e.g. extrarenal TMA manifestations)
- Intervention
  - requirement for PE/PI, dialysis, blood transfusion, or renal transplant due to a TMA manifestation

Post-hoc definition of TMA

To give a more stringent definition of TMA, patients who had a change in **only one laboratory value** without meeting another criterion above were excluded.

aHUS, atypical haemolytic uraemic syndrome; HPF, high-powered field; LDH, lactate dehydrogenase; LLN, lower limit of normal; PE/PI, plasma exchange/plasma infusion; RBC, red blood cells; SCr, serum creatinine; TMA, thrombotic microangiopathy; ULN, upper limit of normal.

RESULTS

- Fifty-four adults and 39 children at a median follow-up of 61.5 months (>5 years), across the parent and current studies, were included in this analysis. Clinical characteristics are shown in Table 2.
- A total of 82 patients had on-treatment periods, and 42 patients had periods off-treatment (Figure 2). Some patients had several on- and off-treatment periods during the study.
- TMA manifestation data for per-protocol and post-hoc TMA definitions are presented in Table 3. TMAs during on-treatment periods were less frequently associated with hospitalisation than off-treatment, as shown previously.[9]
- When patients were treated with the labelled dosing regimen, the TMA rate decreased 3.7-fold (per-protocol analysis) and 13.7-fold (post-hoc analysis) compared to off-treatment.
- Table 4 compares TMA manifestation rates for patients treated on labelled and non-labelled dosing regimens.

Table 2. Clinical and demographic data

	All patients (n=93)
Median age at first eculizumab dose, years (range)	21.0 (0.0–80.0)
Female, n (%)	57 (61)
Complement abnormality, n (%)[a]	55 (59)
Number of aHUS manifestations prior to first eculizumab dose, n (%)	
1[b]	59 (63)
≥2	34 (37)
Median time from most recent aHUS manifestation to first eculizumab dose, months (range)	0.9 (0.0–47.4)
Median time from aHUS diagnosis to first eculizumab dose, months (range)	4.0 (0.0–313.3)
Patients with dialysis at baseline of parent study, n (%)	38 (41)
Patients with kidney transplant prior to first eculizumab dose, n (%)	23 (25)
Median duration of follow-up, months (range)	
Parent and current study	61.5 (9.9–98.7)
Current study only	40.6 (3.1–92.3)

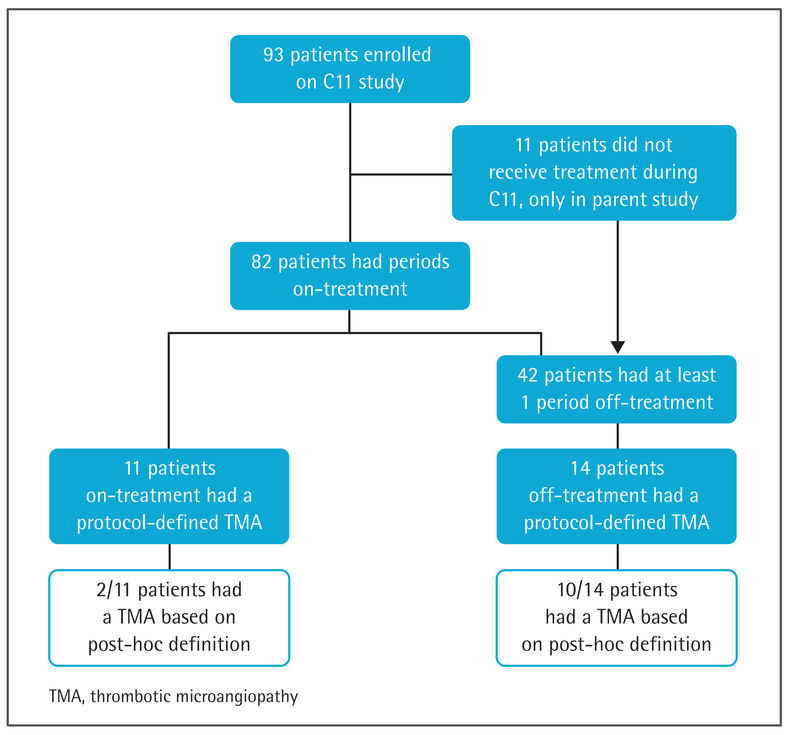
[a]Identified mutations in complement factor (CF) H, CFI, CFB, membrane cofactor protein, C3, anti-CFH antibodies, and CFHR1-3 polymorphisms. [b]This was the first TMA manifestation experienced by these patients.

Table 3. Rate of TMA manifestations for on- and off-treatment periods

TMA manifestations	On-treatment[a] period (n=82)	Off-treatment period (n=42)
Per protocol TMA definition		
Patients, n (%)	11 (13)	14 (33)
Manifestations, n	17	18
Total patient years	267.4	95.0
Rate per 100 patient-years	**6.4**	**19.0**
Fold change in rate versus patients on-treatment	**–**	**3.0**
Hazard Ratio (p-value)	**–**	**4.6 (p=0.0002)**
Excluding TMA manifestation only meeting a single laboratory criterion		
Patients, n (%)	2 (2)	10 (24)
Manifestations, n	3	13
Total patient years	267.4	95.0
Rate per 100 patient-years	**1.1**	**13.7**
Fold change in rate versus patients on-treatment	**–**	**12.5**
Hazard Ratio (p-value)	**–**	**14.8 (p=0.0005)**

TMA, thrombotic microangiopathy. [a]Includes patients on labelled and non-labelled dosing regimens.

Figure 2. Patient flow diagram detailing treatment periods during C11 only



TMA, thrombotic microangiopathy

- Table 5 shows the TMA rate during on- and off-treatment periods stratified based on confirmation of complement abnormalities. Regardless of the presence of a confirmed complement abnormality, the TMA rate was lower during on-treatment vs. off-treatment periods.
- Targeted serious adverse event data are shown in Table 6.
- During the C11 study, two patients experienced meningococcal infection:
  - One 16-year-old male with C3 mutation and renal transplant. Patient received prophylactic antibiotics.
  - One 17-year-old female with CFH mutation and renal transplant. This patient did not receive prophylactic antibiotics.
  - Each case occurred on-treatment and was considered potentially related to eculizumab. Both patients were vaccinated, recovered with antibiotics and continued treatment.
- During follow-up, three patients died:
  - One adult patient on non-labelled dosing with C3 mutation who discontinued eculizumab. Patient died due to severe intensive care complications and multi-organ dysfunction secondary to a gastrointestinal haemorrhage, lithiasic cholecystitis and severe sepsis.
  - One child, male, 2 years of age with no complement abnormality. Patient had infection, fatigue, hypotension, pulmonary haemorrhage, dialysis and blood transfusion. Patient suffered a seizure and died after nearly 10 months of eculizumab on labelled eculizumab dosing.
  - One child, female, <1 year of age with no complement abnormality. Patient had been on dialysis and had been treated with eculizumab for 2 months but discontinued due to lack of efficacy. Patient suffered a TMA manifestation with multiorgan failure and died of sepsis after being off-treatment for 7 months.
  - No death was considered related to eculizumab.

Table 4. Rate of TMA manifestations for on-treatment period, stratified by dosing regimen

TMA manifestations	Labelled dosing (n=73)	Non-labelled dosing (n=35)
Per protocol TMA definition		
Patients, n (%)	9 (12)	4 (11)
Manifestations, n	10	7
Total patient years	196.4	70.5
Rate per 100 patient-years	**5.1**	**9.9**
Fold change in rate versus patients on labelled dosing	**–**	**1.9**
Excluding TMA manifestation only meeting a single laboratory criterion		
Patients, n (%)	2 (3)	1 (3)
Manifestations, n	2	1
Total patient years	196.4	70.5
Rate per 100 patient-years	**1.0**	**1.4**
Fold change in rate versus patients on labelled dosing	**–**	**1.4**

TMA, thrombotic microangiopathy.

Table 5. Rate of TMA manifestations for on- and off-treatment periods, stratified by presence of a complement abnormality

TMA manifestations	Confirmed complement abnormality		No confirmed complement abnormality	
	On-treatment period (n=51)	Off-treatment period (n=24)	On-treatment period (n=31)	Off-treatment period (n=18)
Per protocol TMA definition				
Patients, n (%)	8 (16)	11 (46)	3 (10)	3 (17)
Manifestations, n	14	13	3	5
Total patient years	171.1	44.5	96.3	50.4
Rate per 100 patient-years	**8.2**	**29.2**	**3.1**	**9.9**
Fold change in rate versus patients on-treatment	**–**	**3.6**	**–**	**3.2**
Excluding TMA manifestation only meeting a single laboratory criterion				
Patients, n (%)	1 (2)	7 (29)	1 (3)	3 (17)
Manifestations, n	2	9	1	4
Total patient years	171.1	44.5	96.3	50.4
Rate per 100 patient-years	**1.2**	**20.2**	**1.0**	**7.9**
Fold change in rate versus patients on-treatment	**–**	**16.8**	**–**	**7.9**

TMA, thrombotic microangiopathy.

Table 6. Targeted serious adverse events

TMA manifestations	On-treatment	Off-treatment
Paediatric patients	*n=35*	*n=17*
Total number of patients with at least one event, n (%)	9 (26)	4 (24)
Total patient years	128.3	30.7
Any serious targeted adverse event, rate per 100 patient years	11.7	26.0
Adult patients	*n=47*	*n=25*
Total number of patients with at least one event, n (%)	10 (21)	10 (40)
Total patient years	139.1	64.2
Any serious targeted adverse event, rate per 100 patient years	15.1	18.7

Targeted serious adverse events included: aspergillus infection, bacteraemia, bacterial infection, candida infection, enterococcal infection, escherichia infection, escherichia urinary tract infection, escherichia pyelonephritis, leukopenia, lung infection, meningitis, meningococcal infection, malignant neoplasm, acute otitis media, pneumococcal infection, renal impairment, viral respiratory tract infection, sepsis.

DISCUSSION

- This is the largest prospective observational study of patients with aHUS receiving eculizumab to date.
- There was a significant difference in TMA rate between on- and off-treatment periods for both per-protocol and post-hoc defined TMAs, but the latter showed greater differences.
  - The post-hoc definition of TMA manifestations, excluding TMAs meeting only a single laboratory criterion, aimed to minimise false positives and allow more precise detection of clinically-relevant TMAs.
- Stratification of TMA manifestations based on presence of complement abnormalities showed that patients with a confirmed complement abnormality had a higher rate of TMAs than patients with no identified abnormalities during both on- and off-treatment periods.
- Patients discontinuing treatment experienced a greater rate of targeted serious adverse events, potentially because of an increase in disease-specific events.
  - Meningococcal infections only presented in patients on-treatment.
- Overall, discontinuing eculizumab or altering treatment regimens may lead to worse outcomes than continuing treatment.

CONCLUSIONS

- Patients with aHUS have a significantly greater risk of TMA during off-treatment periods.
- TMA rate was greater in treated patients that were not dosed per the labelled regimen.
- The rate of targeted serious adverse events was greater in patients discontinuing treatment.
- Eculizumab continues to be effective and well-tolerated after >5 years of treatment, with no unexpected safety concerns reported.

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ACKNOWLEDGEMENTS

Medical writing support (funded by Alexion Pharma) was provided by Dr Ciaran Wright of Bioscript Medical.

Presented at the 54th European Renal Association & European Dialysis and Transplant Association congress, June 03–06, 2017, Madrid, Spain