Atypical Haemolytic Uraemic Syndrome (aHUS) in Children and Adults: Data from the Global aHUS Registry

Sally Johnson,[1] Christoph Licht,[2] Gianluigi Ardissino,[3] Gema Ariceta,[4] David J. Cohen,[5] Christoph Gasteyger,[6] Larry A. Greenbaum,[7] Masayo Ogawa,[8] Varant Kupelian,[8] Franz Schaefer,[9] Johan Vande Walle,[10] Véronique Frémeaux-Bacchi[11]

[1]Great North Children's Hospital, Newcastle upon Tyne, UK; [2]The Hospital for Sick Children, Toronto, Canada; [3]Fondazzione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [4]Hospital Universitari Vall d'Hebron, Barcelona, Spain; [5]Columbia University Medical Center, New York, NY, USA; [6]Alexion Pharma GmbH, Zurich, Switzerland; [7]Emory University, Atlanta, GA, USA; [8]Alexion Pharmaceuticals, Inc., Cheshire, CT, USA; [9]Heidelberg University Hospital, Heidelberg, Germany; [10]University Hospital Ghent, Ghent, Belgium; [11]Assistance Publique - Hopitaux de Paris, Hopital Europeen Georges Pompidou, Paris, France.

INTRODUCTION

- Atypical haemolytic uraemic syndrome (aHUS) is a rare, genetic, life-threatening disease predominantly caused by chronic, uncontrolled complement activation that leads to thrombotic microangiopathy (TMA) and renal and other end-organ damage.
- Historically, disease outcomes have been dire – over 50% of patients with aHUS die, have required dialysis, or have developed permanent kidney damage within 1 year, despite the use of plasma exchange or plasma infusion.[1]
- Eculizumab, a humanised monoclonal antibody that inhibits alternative pathway activation by blocking the generation of C5b-9 (membrane attack complex),[2] has been shown to be effective in treating patients with aHUS.[3-5]
- Patient registries can lead to improved knowledge of the natural history of a disease and, dependent on the data collected, can be analysed to evaluate the effectiveness of clinical therapies, monitor drug safety and measure the quality of care in a real life setting.[6,7]
- The global aHUS Registry was initiated in April 2012 to:
  - Record information on the natural history of aHUS patients, irrespective of treatment.
  - Prospectively collect safety and effectiveness data on patients treated with eculizumab.
  - Fulfil Alexion's post-marketing regulatory requirements by providing long-term follow-up on the aHUS indication for eculizumab.[8]

OBJECTIVE

- To report baseline paediatric and adult demographics, genotype and phenotype from the global aHUS Registry specifically for patients enrolled in the UK.

METHODS

Inclusion / exclusion criteria

- All patients who have been clinically diagnosed with aHUS are eligible for enrolment:
  - With or without identified complement abnormalities or anti-complement factor H antibody (if tested).
- Patients with cases of Shiga toxin *Escherichia coli*-positive HUS, or ADAMTS13 activity <5% are excluded.

Data collection

Data that are collected at enrolment and every 6 months thereafter include:

- Demographics, medical and disease history.
- Symptomology and laboratory results.
- TMA complications and safety of eculizumab treatment and other aHUS management strategies.
- Clinical and patient reported outcomes.

Data analysis

- Baseline is defined as date of enrolment or immediately before eculizumab treatment, whichever occurred earlier.
- Patients with all of the following data were included:
  - Date of birth, gender, Registry enrolment date.
  - Knowledge of treatment with eculizumab or no previous eculizumab treatment.
  - For eculizumab-treated patients, date of first eculizumab dose.
- Patients were stratified by age at enrolment into the Registry.

Registry support

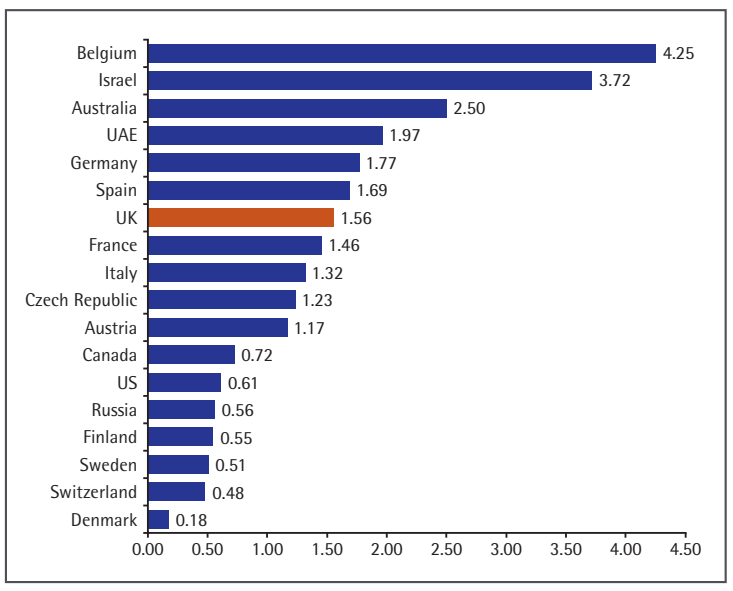
- The Registry is supported by Alexion Pharmaceuticals, Inc., with governance by an independent scientific advisory board and national coordinators representing each participating country.

RESULTS

Baseline characteristics

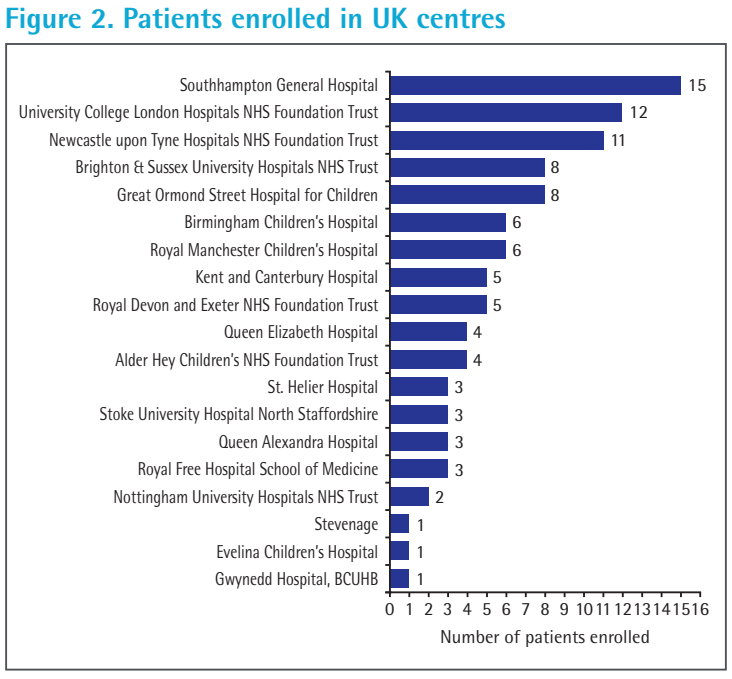
- Worldwide, as of 30 November 2015, 964 patients were enrolled from 18 countries (Figure 1).

Figure 1. Patients enrolled per million by country population



- Enrolment per million inhabitants was 1.56 in UK compared with a median of 1.28 (range, 0.18–4.25) for the 18 countries.
- To date, 101 patients have enrolled in 19 centres across the UK (Figure 2).

Figure 2. Patients enrolled in UK centres



- Demographic characteristics for the overall global Registry and UK patients were generally similar (Table 1).

Table 1. Demographic characteristics

	Global (N=964)		UK (N=99)	
	Paediatric (n=367)	Adult (n=597)	Paediatric (n=45)	Adult (n=54)
Gender, n (%)				
Male	197 (54)	227 (38)	23 (51)	20 (37)
Female	170 (46)	370 (62)	22 (49)	34 (63)
Age at enrolment, years, median (range)	8.0 (0.0–17.9)	39.9 (18.0–90.6)	7.4 (0.6–17.9)	39.5 (19.2–80.8)
Age at initial aHUS symptoms, years median (range)	3.41 (0.0–17.3)	32.62 (0.1–90.6)	2.54 (0.3–16.9)	28.25 (0.3–74.7)
Age (years) at initial symptoms of aHUS, n (%)				
<2	137 (38)	20 (4)	19 (44)	2 (4)
≥2 to <5	82 (23)	13 (2)	10 (23)	2 (4)
≥5 to <12	109 (30)	17 (3)	10 (23)	0 (0)
≥12 to <18	30 (8)	18 (3)	4 (9)	1 (2)
≥18	–	484 (81)	–	46 (85)
Family history of aHUS, n (%)	56 (15)	83 (14)	6 (13)	8 (15)

- Just over one third (37%) of the overall Registry population were aged <18 years compared to 43% in the UK registry at initial symptoms.
- Across the two paediatric and adult populations, gender and age at enrolment were similar.
- A family history of aHUS was similar between both populations.

Eculizumab treatment

- Approximately two thirds of global Registry patients, compared with half of patients enrolled in the UK, have received eculizumab treatment (Table 2).
- Within each population, the proportion of paediatric and adult patients ever receiving eculizumab treatment were similar.
- The proportion of adults receiving eculizumab prior to enrolment is lower in the UK (60%) compared with the overall global population (84.7%), though time on treatment was similar.
- Initiation of eculizumab treatment after diagnosis of aHUS appeared to be quicker in UK paediatric patients (median time 0.02 years vs 0.06 years) but slower in UK adult patients (median time 7.14 years vs 0.06 years), compared to the overall population.

Table 2. Eculizumab treatment

	Global		UK	
	Paediatric (n=367)	Adult (n=597)	Paediatric (n=45)	Adult (n=54)
Received eculizumab, n (%)	230 (67)	352 (64)	21 (50)	25 (51)
Of whom received eculizumab prior to enrolment, n (%)	205 (89)	298 (85)	19 (90)	15 (60)
Time from aHUS diagnosis to initiation of eculizumab, years, median (range)	0.06 (0–17.0)	0.06 (0–36.3)	0.02 (0–5.5)	7.14 (0–28.4)
Time on eculizumab, years, median (range)	1.44 (0–5.7)	0.89 (0–6.9)	2.04 (0.1–4.6)	0.83 (0–3.6)

Clinical characteristics at baseline and prior management in the UK population

- Within the enrolled UK aHUS patient population, the proportion of paediatric and adult patients receiving PE/PI prior to baseline were similar, regardless of eculizumab treatment.
- Paediatric patients who went on to be treated with eculizumab tended to have had less prior dialysis and transplants, while the opposite was true for the adult population (Table 3).
- Organ manifestations were rarely reported in the patient group that had never been treated with eculizumab while the proportion of extrarenal manifestations ranged from 12-28% in adults and 20-50% in paediatric patients that were subsequently treated with eculizumab.

Table 3. Clinical characteristics at baseline of UK aHUS patients who did or did not subsequently receive eculizumab treatment.

	Ever treated with eculizumab		Never treated with eculizumab	
	Paediatric (n=20)	Adult (n=25)	Paediatric (n=21)	Adult (n=24)
Prior kidney transplantation, n (%)	1 (5)	8 (32)	5 (24)	5 (21)
Prior dialysis, n (%)	7 (35)	20 (80)	13 (62)	14 (58)
Prior PE/PI, n (%)	8 (40)	15 (60)	9 (43)	19 (79)
Symptoms experienced 6 months prior to baseline				
Renal, n (%)	18 (90)	16 (64)	0 (0)	1 (4)
GI, n (%)	10 (50)	5 (20)	0 (0)	1 (4)
CV, n (%)	7 (35)	7 (28)	1 (5)	0 (0)
Pulmonary, n (%)	5 (25)	3 (12)	0 (0)	1 (4)
CNS, n (%)	4 (20)	6 (24)	0 (0)	0 (0)

Genetic analysis and extrarenal manifestations

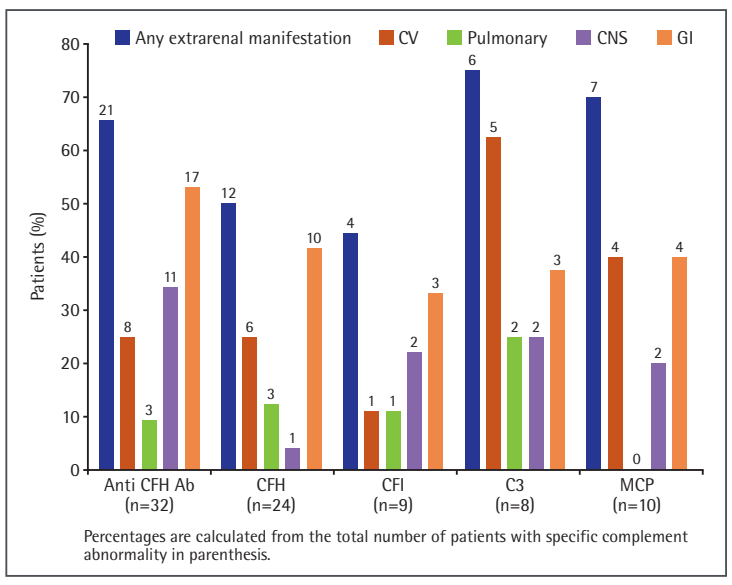
- Within the global Registry, complement abnormality was identified in 46% of patients tested (Table 4).
- In patients from the global Registry with an identified complement abnormality, extrarenal manifestations were common (44–75%), figure 3.
- Extrarenal manifestations appear to be most common in patients with C3 mutations and least common in patients with CFI mutations.

Table 4. Complement abnormalities identified in patients enrolled in the global aHUS Registry

	Paediatric n (%)[a]	Adult n (%)[a]
CFH	74 (32)	87 (35)
MCP	39 (20)	22 (11)
C3	21 (13)	21 (13)
CFI	8 (4)	26 (12)
CFB	3 (2)	2 (2)
Anti-CFH Ab	47 (24)	39 (19)

Data presented from n=851. [a]Percentage of patients tested for that particular abnormality.

Figure 3. Extrarenal manifestations associated with complement abnormalities in patients with baseline data ≤6 months from disease onset (overall global population).



Percentages are calculated from the total number of patients with specific complement abnormality in parenthesis.

CONCLUSION

- This is the first comparison of UK and global baseline data of the aHUS Registry and shows that characteristics are generally comparable.
- A significant proportion of UK patients had received supportive care or eculizumab prior to study enrolment.
- Initiation of eculizumab treatment after aHUS diagnosis is slower for UK adult patients.
- A significant proportion of patients showed extrarenal manifestations.
- Patients subsequently treated with eculizumab had more extra-renal manifestations, suggesting that a more severe disease presentation with multiple organ system complications increases the likelihood for these patients to be treated with eculizumab.
- Emerging data aim to link genetic mutations to outcomes or treatment strategies.
- By maintaining quality assurance of data collection, data from the global aHUS Registry will improve understanding of the natural history of aHUS and may help optimise patient care while also allowing analysis of country- or region-specific data.
- Enhancing enrolment in the UK will allow for more detailed analyses, including linking genetic mutations with extrarenal manifestations, to occur at the local level.

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ACKNOWLEDGEMENTS

Medical writing support (funded by Alexion) was provided by Dr Jonathan Plumb of Bioscript Medical.