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 infusions.1

- Eculizumab, a humanized monoclonal antibody that inhibits alternative pathway activation by blocking the generation of C3b (membrane attack complex)2,3 has been shown to be effective in the treatment of aHUS.4

- 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.5

- 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.

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-
  - Factor H antibodies.

- 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 treatment.

- 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
  - Independent governance by an independent scientific advisory board and
  - Bioscript Medical.

RESULTS

Baseline characteristics

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

- 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, 110 patients have been enrolled in 19 centres across the UK (Figure 2).

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

Table 1. Demographic characteristics

<table>
<thead>
<tr>
<th>Global (N=964)</th>
<th>UK (N=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at enrolment, years (median)</td>
<td>8.0 (0.0–17.0)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td>464 (85)</td>
</tr>
<tr>
<td>Female</td>
<td>219 (45)</td>
</tr>
<tr>
<td>Genotype known, n (%)</td>
<td>868 (90)</td>
</tr>
<tr>
<td>Anti-CFH Ab</td>
<td>24 (5)</td>
</tr>
<tr>
<td>Anti-C1q</td>
<td>62 (13)</td>
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- 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 was 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 appears 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 year), compared to the overall population.

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/P during baseline was comparable, 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 2. Eculizumab treatment

<table>
<thead>
<tr>
<th>Paediatric</th>
<th>Adult</th>
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<tr>
<td>ever treated with eculizumab</td>
<td>584 (85)</td>
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<tr>
<td>median time to first eculizumab treatment, years</td>
<td>1.9</td>
</tr>
</tbody>
</table>

- 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 at baseline.

- 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 extrarenal manifestations, including a more severe disease presentation with multiple organ system complications increases the likelihood for these patients to be treated with eculizumab.

CONCLUSION

- 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.

- Enhancing enrolment in the UK will allow for more detailed analysis of country- or region-specific data.

- Within the global Registry, complement abnormality was identified in 48% of patients tested (Table 4).

- In patients from the global Registry with an identified complement abnormality, extramembrane 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. Extramembrane abnormalities identified in patients enrolled in the global aHUS Registry

- Post-treatment eculizumab

- Paediatric | Adult |
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</tbody>
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GENETIC ANALYSIS AND EXTRAMEMBRANE MANIFESTATIONS

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

- Prior dialysis, n (%) | 1 (2) | 0 (0) |
| CL(n) | 10 (50) | 2 (2) |
| CFH(n) | 7 (35) | 2 (2) |
| C1q(n) | 2 (10) | 0 (0) |
| Anti-CFH Ab | 4 (20) | 3 (6) |

REFERENCES

5. Licht et al. BMC Nephrol. 2015;16:207

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- Enhancing enrolment in the UK will allow for more detailed analyses, including linking genetic mutations with extrarenal manifestations, to occur at the local level.

ACKNOWLEDGEMENTS

- Medical writing support (funded by Alexion) was provided by Jonathan Plunk of Bioscript Medical.