An Observational, Non-interventional, Multicenter, Multinational Registry of Patients With Atypical Hemolytic Uremic Syndrome: Methodology

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

[1]The Hospital for Sick Children, Toronto, ON, Canada; [2]Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico, Milano, Italy; [3]Hospital Vall d'Hebron, Barcelona, Spain; [4]Alexion Pharmaceuticals, Lausanne, Switzerland; [5]Columbia University, New York, NY, USA; [6]Emory University, Atlanta, GA, USA; [7]Newcastle Upon Tyne Hospital, Newcastle Upon Tyne, UK; [8]Alexion Pharmaceuticals, Inc., Cheshire, CT, USA; [9]Heidelberg University Clinic Pediatric Nephrology, Heidelberg, Germany; [10]UZ Gent Dienst nefrologie, Ghent, Belgium; [11]Assistance Publique-Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Paris, France

INTRODUCTION

Atypical Hemolytic Uremic Syndrome: Background

- Atypical hemolytic uremic syndrome (aHUS) is a genetic, progressive, life-threatening disease mostly resulting from chronic, uncontrolled complement activation. It is characterized by systemic thrombotic microangiopathy (TMA) leading to renal and other end-organ damage
- Plasma exchange and infusion (PE/PI) has historically been used to manage aHUS[1]; however, evidence suggests that PE/PI offers no significant benefit over simple supportive therapy[2,3]
- Eculizumab (Soliris®; Alexion Pharmaceuticals, Inc., Cheshire, CT), a terminal complement inhibitor, is a humanized monoclonal antibody that binds with high affinity to the human C5 complement protein, blocking the generation of pro-inflammatory C5a and C5b-9[4]
- Eculizumab is the first approved treatment for aHUS in pediatric and adult patients[4–7]
- A single, global aHUS patient registry can maximize both physician and patient participation to best capture information on disease, safety, and efficacy data in a population with a very rare disease
- The global aHUS patient registry (ClinicalTrials.gov identifier: NCT01522183) was initiated in April 2012 to prospectively capture postmarketing effectiveness and safety data on patients treated with eculizumab; the registry will record information on the progression of disease in all aHUS patients (whether treated with eculizumab or with other disease management strategies)
- Furthermore, the registry fulfills postmarketing regulatory requirements by providing follow-up on the aHUS indication for eculizumab, and exemplifies the need for and benefit of successful partnering between sponsors and academia

OBJECTIVE

- To report patient characteristics and describe important milestones achieved by patients enrolled in the aHUS registry from its inception (April 2012) through 1 year (April 1, 2013)

METHODS

Patient Eligibility Criteria

- Inclusion criteria
  - Male or female patients of any age who have been diagnosed clinically with aHUS
    - With or without an identified complement regulatory factor genetic abnormality or anti-complement factor antibody (if tested)
    - ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif; C-terminal carboxy-terminal) >5%, if performed
  - Written informed consent from a patient or parent/legal guardian (if applicable as determined by the central Institutional Review Boards/Independent Ethics Committees)
- Exclusion criteria
  - HUS due only to Shiga toxin-producing *Escherichia coli*

Primary Outcome Measures

- Proportion of patients who experience pre-specified events
- Collection and evaluation of safety and efficacy data specific to the use of eculizumab in patients with aHUS
- Time to first and subsequent occurrence of pre-specified events
- Assessment of the long-term manifestations of TMA complications of aHUS; other clinical outcomes, including morbidity and mortality in patients with aHUS receiving eculizumab treatment or treated with other disease-management approaches

Data Collection

- Data are collected at study enrollment and every 6 months thereafter and include the following:
  - Demographics
  - Medical and disease history
  - Symptomology
  - Targeted laboratory results (including genetic results)
  - TMA complications
  - Associated treatments and concomitant medications
  - Clinical and patient-reported outcomes
  - Safety of eculizumab and other aHUS treatments
- To follow each patient and assess long-term outcomes for a minimum of 5 years, information from patient medical records is entered via a secure web portal and maintained anonymously

Registry Support

- The registry is supported by Alexion Pharmaceuticals, Inc., with governance by an independent scientific advisory board (SAB) and national coordinators representing each participating country
- Some key responsibilities of the SAB are to:
  - Provide scientific advice on aHUS registry-related matters
  - Propose, discuss, and evaluate program objectives with Alexion
  - Review and provide guidance on future amendments to the protocol, data variables to be collected, and case report refinements (all as appropriate)
  - Advise on analyses and scientific questions of interest
  - Review and provide feedback on publication goals and logistics
  - Contribute to the development of the publication plan
  - Establish and follow protocols for the review and approval of external requests for analyses and publications from individual investigators or national coordinators
  - Advise, counsel, and guide individuals on publications that utilize aHUS registry data and resources and/or use the aHUS registry name
  - Review publication drafts before submission to journals or public release

Inclusion for the Current Analysis

- All enrolled patients with the following data were included in this analysis:
  - Ever treated with eculizumab or never treated with eculizumab
  - Registry enrollment date, date of birth, and sex must be available
  - For treated patients, date of first eculizumab treatment (if treated) must also be available

RESULTS

Patient Characteristics in Global aHUS Patient Registry

- **Tables 1–4** provide information on demographics, aHUS diagnosis, baseline clinical characteristics, and eculizumab treatment characteristics

Countries Enrolling Patients Into aHUS Patient Registry (as of April 1, 2013)

- Australia (n=7)
- Austria (n=4)
- Denmark (n=1)
- Germany (n=2)
- Israel (n=1)
- Spain (n=8)
- United Kingdom (n=5)
- United States (n=25)

Breakdown of Enrolling Sites: Specialist Type

- Nephrologists (84%)
- Hematologists (16%)

Breakdown of Enrolling Sites: Adult– Versus Pediatric–centric

- Pediatric–centric sites (52%)
- Adult–centric sites (47%)

Table 1. Patient Demographics in Global aHUS Patient Registry (as of April 1, 2013)

	Ever Treated With Eculizumab (n=32)	Never Treated With Eculizumab (n=21)	Total (N=53)
Mean age at registry enrollment (SD), years	38.1 (18.38)	33.0 (15.62)	36.1 (17.36)
Age at registry enrollment, n (%)			
≥2 to <5 years	2 (6.3)	2 (9.5)	4 (7.5)
≥5 to <12 years	1 (3.1)	0 (0.0)	1 (1.9)
≥12 to <18 years	0 (0.0)	1 (4.8)	1 (1.9)
≥18 years	29 (90.6)	18 (85.7)	47 (88.7)
Sex, n (%)			
Female	22 (68.8)	7 (33.3)	29 (54.7)
Male	10 (31.3)	14 (66.7)	24 (45.3)
Race, n (%)			
Black	2 (6.3)	0 (0.0)	2 (3.8)
Caucasian	29 (90.6)	21 (100.0)	50 (94.3)
Latino	1 (3.1)	0 (0.0)	1 (1.9)
Year of registry enrollment, n (%)			
2012	17 (53.1)	4 (19.0)	21 (39.6)
2013	15 (46.9)	17 (81.0)	32 (60.4)

aHUS, atypical hemolytic uremic syndrome; SD, standard deviation.

Table 2. aHUS Diagnosis Characteristics at Registry Entry (as of April 1, 2013)

	Ever Treated With Eculizumab (n=32)	Never Treated With Eculizumab (n=21)	Total (N=53)
Mean age at initial symptoms (SD), years	37.7 (19.84) (n=29)	24.2 (13.63) (n=15)	33.1 (18.94) (n=44)
Mean age at diagnosis (SD), years	39.2 (19.00) (n=28)	25.8 (15.97) (n=15)	34.5 (18.95) (n=43)
Family history of aHUS, n (%)			
N/A	28 (87.5)	15 (71.4)	43 (81.1)
Yes	4 (12.5)	6 (28.6)	10 (18.9)
Any identified complement genetic mutation or auto-antibody, n (%)			
N/A	3 (9.4)	7 (33.3)	10 (18.9)
No	20 (62.5)	7 (33.3)	27 (50.9)
Yes	9 (28.1)	7 (33.3)	16 (30.2)

aHUS, atypical hemolytic uremic syndrome; N/A, not available; SD, standard deviation.

Table 3. Baseline Clinical Characteristics of Patients at Registry Entry (as of April 1, 2013)

	Ever Treated With Eculizumab (n=32)	Never Treated With Eculizumab (n=21)	Total (N=53)
Any prior kidney transplant, n (%)			
Yes	4 (12.5)	1 (4.8)	5 (9.4)
Any prior dialysis, n (%)			
Yes	15 (46.9)	4 (19.0)	19 (35.8)
Any prior plasma exchange/infusion, n (%)			
Yes	17 (53.1)	4 (19.0)	21 (39.6)
Mean baseline eGFR (SD), mL/min/1.73 m^2	10.6 (7.29) (n=7)	86.8 (116.73) (n=2)	27.6 (53.58) (n=9)

eGFR, estimated glomerular filtration rate; SD, standard deviation.

Table 4. Characteristics of Patients Treated With Eculizumab at Registry Entry (as of April 1, 2013)

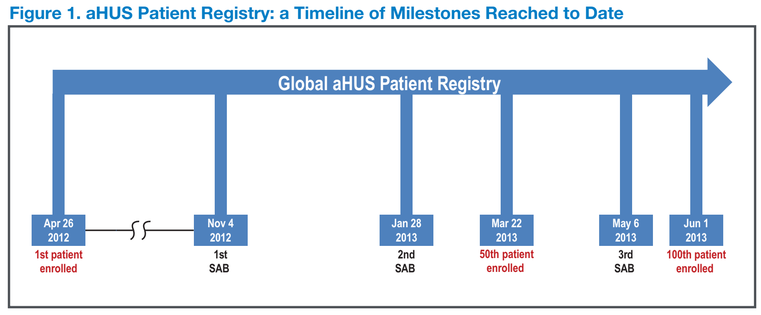
	Ever Treated With Eculizumab (N=32)
Mean age at eculizumab treatment initiation (SD), years	38.1 (18.38) (n=47)
Median dose at initiation of eculizumab (range), mg	900.0 (600–1200)
Mean time on eculizumab (SD), years	0.9 (0.85) (n=31)
Any discontinuation of eculizumab, n (%)	
No	30 (93.8)
Yes	2 (6.3)
Restarted eculizumab (among those who discontinued), n (%)	
No	1 (50.0)
Yes	1 (50.0)

SD, standard deviation.

Milestones Achieved for the Global aHUS Patient Registry

- **Figure 1** shows the milestones that have been reached to date since enrollment of the first patient on April 26, 2012

Figure 1. aHUS Patient Registry: a Timeline of Milestones Reached to Date



aHUS, atypical hemolytic uremic syndrome; SAB, scientific advisory board

CONCLUSIONS

- Based on the limited enrollment at this time, reflecting the early stage of the registry, it would be premature to draw scientific conclusions from the data presented in this poster
- The global aHUS patient registry is dedicated to increasing the understanding and awareness of aHUS disease history and progression
- The results of analyses from collected data and outcomes provide an opportunity to optimize care and improve quality of life for aHUS patients
- A single, global aHUS patient registry can maximize both physician and patient participation to best capture information on disease, safety, and efficacy data in a population with a very rare disease
- New clinical sites are encouraged to participate

REFERENCES

1. Campistol JM, *et al*. *Nefrologia* 2013;33:27–45.
2. Michael M, *et al*. *Am J Kidney Dis* 2009;53:259–272.
3. Noris M, *et al*. *Nat Rev Nephrol* 2009;186–188.
4. Soliris (eculizumab) [prescribing information]. Cheshire, CT: Alexion Pharmaceuticals, Inc.; 2011.
5. Soliris (eculizumab) [summary of product characteristics]. Paris, France: Alexion Europe SAS; 2011.
6. Schmidtko J, *et al*. *Am J Kidney Dis* 2013;61:289–299.
7. Rother RP, *et al*. *Nature Biotech* 2007;25:1256–1264.

ACKNOWLEDGMENTS

The authors would like to acknowledge Alexander Cole, Lynn Sanders, and Kenyon Ogburn of Alexion Pharmaceuticals, Inc., for providing their respective analytical, logistical, and medical writing support and Ruth Sussman of Chameleon Communications International, who provided editorial support with funding from Alexion.

Presented at the 16th Congress of the International Pediatric Nephrology Association, August 30–September 3, 2013, Shanghai, China.