aHUS Key Facts & Information

Atypical Hemolytic Uremic Syndrome

2016 September

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About aHUS

- Atypical Hemolytic Uremic Syndrome (aHUS) is a very rare, chronic and life-threatening genetic condition
- aHUS can occur at any age, with roughly 60 per cent of children affected and 40 per cent adults [2]
- aHUS is caused by chronic, uncontrolled activation of the complement system, a part of the body's natural immune system [1]
- As a result, the immune system attacks the body's unhealthy and healthy cells, which can cause abnormal blood clotting and blood vessel damage [2, 3]
- The presence of blood clots causes damage to organs, leading to heart attack, stroke, kidney failure and death [2]
- Within a year of diagnosis, over half of patients will need dialysis, will have irreversible kidney damage, or will not survive [2]
- The majority of patients progress to end-stage kidney failure within three years of diagnosis [2,5]
- Death rates amongst aHUS patients are as high as 25 per cent, and progression to end-stage kidney disease occurs in more than 50 per cent of patients [2, 5]
- Kidneys are often transplanted in aHUS patients with permanent kidney failure, however, the disease recurs in 60 per cent of patients, and more than 90 per cent of patients experience failure of transplanted kidney [2]

Diagnosis

- Atypical HUS encompasses a group of diseases that share in the clinical features of a microangiopathic hemolytic anemia associated with thrombocytopenia and renal failure. In practice there is little agreement on what defines or limits classifying someone as an aHUS patient, given the nonspecific nature of the term aHUS. aHUS clumps together a group of diseases with very different underlying pathologies. [25]
- The causes of aHUS are not fully understood, but in 70 per cent of cases it is associated with an underlying genetic or acquired abnormality of the complement system [10]
- Doctors and their health care team must look at many factors when making a diagnosis – including clinical symptoms, lab findings, and results from more specialized tests such as gene analysis [11]

- During initial onset of aHUS, or during recurring episodes, tell-tale signs can be detected from lab findings relating to [9]
    - platelet levels
    - hemoglobin and haptoglobin levels
    - creatinine levels
    - BUN (blood urea nitrogen) levels

Symptoms

- aHUS disease can be characterized by three key features:[12]
    - thrombocytopenia (low platelet count in the blood)
    - anemia (low red blood cell/platelet count in the blood)
    - kidney symptoms (starting as acute kidney failure but can progress to end-stage kidney disease)

- There are a number of symptoms secondary to kidney failure, which include [10]
    - nausea and vomiting
    - confusion
    - shortness of breath (dyspnea)
    - fatigue

- In aHUS, patients present with symptoms of diarrhea, fatigue, irritability, and lethargy to a point where hospitalization is needed [12]
- The majority of patients have genetic abnormalities that impair cell surface control of complement [18]

Treatment

Plasma Therapy & Dialysis

- The prognosis for patients with aHUS is very poor,[13] with existing supportive therapies unproven and unreliable
- The management of aHUS has relied on plasma infusion and plasma exchange therapies with variable results[14]
- To date, there have been no well-controlled trials that show plasma exchange or plasma infusion to be safe or effective in aHUS [15]
- In studies where the majority of patients with aHUS were treated with plasma therapy, patient outcomes were reported as being poo r[16]
- Despite plasma exchange or plasma infusion, 65 per cent of all aHUS patients die, require dialysis, or have permanent renal damage within the first year after diagnosis [6]
- Dialysis cannot completely compensate for the loss of kidney function, and can lead to deadly infections and shortened life expectancy [17]
- Complications related to plasma exchange have been reported to occur in up to 55 per cent of plasma exchange sessions in children and in 15 per cent of sessions in adults [16]

Eculizumab

- Eculizumab has shown greater efficacy than plasma therapy in the prevention and treatment of aHUS [16, 19]
- Experts recommend the use of eculizumab as first-line therapy in children with aHUS, and for adults with an unequivocal diagnosis of aHUS [16]
- Clinicians advise that patients with native or transplanted kidneys whose aHUS recurs be treated with eculizumab [16], and that treatment be initiated as early as possible for optimal recovery of renal function[19]
- Switching from plasma therapy to eculizumab has been shown to improve renal function even in patients with long-lasting and stable chronic kidney disease [16]
- In clinical trials, eculizumab has been proven effective in preventing blood vessel damage and abnormal blood clotting [20, 21]
- In June 2013, an international study in the *New England Journal of Medicine* showed aHUS patients treated with eculizumab were able to discontinue plasma infusion/exchange and dialysis therapies, and saw improved kidney function, reduced blood vessel damage and decreased risk of blood clots [22]

Access to Treatment

- As of April 2016 aHUS patients in many nations still do not have access to eculizumab, and coverage within some of those countries is further restricted: dependent on the aHUS patient's location within their nation or their individual health status. [26,28]

- In September 2013, National Health Service (NHS) England recommended that eculizumab be funded for aHUS patients, following a positive reimbursement recommendation from the Clinical Priorities Advisory Group (CPAG). The final draft guidance recommending eculizumab for funding for treating aHUS was issued by the National Institute for Health and Care Excellence (NICE) in November of 2014.

- Inequality in Treatment Options among Nations - Access to eculizumab for treatment of aHUS patients worldwide plummets from 77% to only 37% for poll respondents in nations outside of the US & EU. [28] (White Paper at **http://ow.ly/Dbzb303ZqhU**, with 2016 Poll Results: http://ow.ly/1DA7303FoJx)

Note: The aHUS Alliance wishes to extend thanks to aHUS Canada for their efforts in providing core facts contained in this document.

SOURCES: See our CITATIONS section later in this document

A Short Version of this Document is Available

aHUS Facts- a Brief Look

Future in aHUS Treatment- Pipeline of Investigational Orphan Drug Therapies

(Table created Sept 2016) [26,27]

Company	Molecule	Mechanism	Indications	Stage*
Alexion	ALXN1210, (TT30, acquired from Taligen)	Anti-C5 inhibitor	PNH, others	Phase 1/2
Achillion	ACH-4471	Sm Molecule: Factor D inhibitor	PNH, C3G, others	Phase 1/2
AKARI Therapeutics (formerly Volution)	Coversin®	C5 inhibitor	PNH, aHUS, Guillain Barre Syndrome	Phase 1B
Alnylam	ALN-CC5	C5 (RNAi therapeutic)	PNH	Phase 1/2
Amgen	**ABP 959**	BioSimilar to eculizumab	Same targeted diseases as for eculizumab	Unknown
Apellis	Compstatin® / APL-2	C3 inhibitor	PNH	Phase 1B
Chemo Centryx	CCX168	Small Molecule Targeting C5aR	AAV, aHUS, IgAN	P II for AAV
Epirus Biopharmaceuticals	BOW080	BioSimilar to eculizumab	Same targeted diseases as for eculizumab	Unknown
Omeros	OMS721® / MASP-2	Lectin pathway inhibitor	TMAs including aHUS	Phase 2/3

Company	Molecule	Mechanism	Indications	Stage*
Ra	RA101495	C5 inhibitor	PNH, other indications	P I

**Clinical Trials, Stages of Development:* http://www.nlm.nih.gov/services/ctphases.html

Resources regarding these Investigational Drugs:

See **Alexion's** Corporate site, regarding ALXN1210: http://ow.ly/h0Id303SdEb

See **Achillion's** Corporate site, regarding ACH4471: http://ow.ly/vXej303SdHd

See **Akari Therapeutics**'s Corporate site, regarding Coversin®: http://akaritx.com/coversin/

See **Alnylam's** Corporate site, regarding ALN-CC5®: http://ow.ly/VkHs303Tnra

See **Amgen**'s Pipeline: http://www.amgenpipeline.com/pipeline/ Article re ABP 959: http://ow.ly/UVY2303TnF4

See **Apellis**' Corporate site, regarding Compstatin®/APL-2: http://www.apellis.com/focus.html PR: http://ow.ly/zvSd303ToqZ

See **ChemoCentryx**'s Corporate site, regarding CCX168: http://ow.ly/JoUE303ToKA

See **Epirus Biopharmaceuticals**' Corporate site, regarding BOW080: http://ow.ly/vp7s303TnPV Article: http://ow.ly/UVY2303TnF4

See **Omeros**' Corporate site, regarding OMS721®/MASP-2: http://www.omeros.com/pipeline/masp2.htm PR: http://ow.ly/LYGq303Tp8p

See **Akari Therapeutics**'s Corporate site, regarding Conversin®: http://akaritx.com/coversin/

See **Ra Pharmaceutical** 's Corporate site, regarding RA101495®: http://rapharma.com/programs.html PR: http://ow.ly/TdN7303TpgJ

LEARN about Clinical Trials for aHUS,with updated information on ClinicalTrials.gov: http://ow.ly/NmCh303Tmzs

2016 aHUS Global Poll: aHUS Patient Voice [28]

An international poll of aHUS patients and pediatric caregivers was launched on 29 February 2016 (world Rare Disease Day) and was completed 15 April 2016. The poll was offered in 6 languages and contained 45 questions to include patient profiles as well as diagnosis and treatment experiences. Additional information and insights were sought regarding aHUS challenges, patient engagement views, clinical trials, and orphan drug development issues.

233 respondents from 23 countries provided data for the 2016 aHUS Global Poll, with results reported within these assets, graphs and commentary:

- 2016 aHUS Global Poll OVERVIEW: http://ow.ly/gSj8303GcdH
- 2016 aHUS Global Poll, RESULTS & Graphs: http://ow.ly/1DA7303FoJx
- RareConnect 2016 aHUS Poll Webinar (commentary by Dr. C Licht): http://ow.ly/ACiN303GajE

2014 aHUS Poll: *In Collaboration with RareConnect, previous aHUS poll Results & Webinar with commentary by Dr. T Goodship: http://ow.ly/hRau303OZG2*

aHUS Insights – Select Info from the 2016 Global Poll [28] ***– (View Complete Data at Links above)***

Poll respondent Profile - 48% of responses were from caregivers of pediatric aHUS patients, with the remaining 52% of data representing adult patients. 66% of people completing the 2016 aHUS global poll were female, 34% were male.

- *Response rate by Nation* – Of the 23 countries participating in the 2016 poll, respondents living in these three countries had the highest participation rates with the other 20 nations created less than 10% of survey responses. (The poll was available in 6 languages:EN, ES, FR, RUS, IT and JPN)

  USA - 43% UK - 18% Canada - 11%

- *Genetic Testing* – 84% have or are awaiting Genetic Test Results

- *aHUS Info Sources* - When seeking Information, most:

  Check aHUS Patient Organizations– 37% Rely on their Doctor – 17% Utilize Search Engines – 26%

- *Dialysis* - 46% of poll respondents stated the most significant dialysis issue was it interferes with normal routines. Other dialysis issues:

  - Impact on Other ORGANS 29%
  - Negative affect on QUALITY at Work/School 28%
  - Issues with ANXIETY or DEPRESSION 27%

- *aHUS Research - Participation* 50% of Respondents have already done so, and 36% more would like participate but don't know how to engage.

- *Inequality in Treatment Options among Nations* - Access to eculizumab for treatment of aHUS patients worldwide plummets from 77% to only 37% for poll respondents in nations outside of the US & EU. (White Paper at **http://ow.ly/Dbzb303ZqhU**)

- *COST Impact* - 7 out of 10 state their specialist or medical team mention COST of aHUS treatment in discussing patient care options. 16% state cost concerns affect their treatment options or medical care.

- *COST Treatment Access* **-** 24% of respondents state aHUS medical care or treatment is limited by their National or Heath Ministry policies. 29% note that cost of medical care and treatment concern them and their family.

- *Advancements in aHUS treatment or drug therapies*- Factors or key considerations for use:
    - Cost of new drugs would likely affect our usage - 33%
    - Recommendation of our medical team - 28%
    - Type of drug delivery/Ease & Convenience of New Treatment - 24%

2016 aHUS Global Poll, RESULTS & Graphs: http://ow.ly/1DA7303FoJx

DIRECTORY of aHUS Patient Organizations: http://ow.ly/TlLw303QQGn

Resources – Learn More about aHUS

*In ENGLISH: Disease OVERVIEW with definitions & research links

NCBI GeneReviews©, affiliated with the National Institutes of Health (NIH)
http://www.ncbi.nlm.nih.gov/books/NBK1367/

*In ENGLISH: OVERVIEW with detailed Info & Tables on aHUS triggers, genetics, extra-renal involvement (aHUS affecting other organs), and other topics

Kavanagh D, Goodship T H, and Richards A. Atypical Hemolytic Uremic Syndrome. Semin Nephrol 2013 Nov; 33(6): 508–530. doi: 10.1016/j.semnephrol.2013.08.003 http://ow.ly/QjUD303Tqlp

*In ENGLISH: Pediatric Focus

An international consensus approach to the management of atypical hemolytic uremic syndrome in children, Abstract: http://www.ncbi.nlm.nih.gov/pubmed/25859752

*In ENGLISH and Multiple Languages: KDIGO GLOBAL CONSENSUS

An international consensus approach to the diagnosis and management of patients with complement-mediated kidney disease, such as aHUS. *EXPECTED IN LATE 2016, THIS DOCUMENT HAS NOT YET BEEN RELEASED*. (Check www.KDIGO.org for updates)

*aHUS Clinical & Diagnostic Checklist, Courtesy of www.RareRenal.org (UK): http://ow.ly/BuOR303SaLv

*Atypical HUS Clinical Channel - YouTube: http://ow.ly/mSyT303ZDch

Rare Disease Day

Rare Diseases – Fast Facts

- There are approximately 7,000 diseases and conditions designated as a rare disease, each affecting fewer than 200,000 Americans. In Europe, a disease is considered rare if it affects fewer than 1 in 2,000 people.
- Rare diseases as a group affect an estimated 25 to 30 million Americans, 1 out of 10 people. Eighty percent of rare diseases are genetic in origin, and it is estimated that about half of all rare diseases affect children.

EURORDIS: Founders of Global Rare Disease Day: Info & Resources www.eurordis.org
NORD: Rare Disease Day Info & Resources, specific to the USA www.rarediseases.org
RareConnect : Disease-Specific Webpages, sponsored by NORD and EURORDIS www.rareconnect.org

These organizations provide information, services, resources, and support to the rare disease community. Their Rare Disease Day resources include press kits, social media tools, Rare Disease Day graphics and more.

World Rare Disease Day, recognized annually on the last day of February, encourages patients and their families, medical professionals, researchers, government officials, and companies developing treatments for rare diseases to join together to focus attention on rare diseases as a public health issue.

aHUS Awareness Day is 24 September

Created by the aHUS Alliance in 2015, and marked in various nations around the world, aHUS Awareness Day provides an opportunity for individuals and organizations around the world to join together in support of people living with aHUS. An opportunity to provide aHUS insights, information and outreach, we encourage participation of all stakeholders who seek to provide advancement for patients globally. Learn More about aHUS Awareness Day aHUS Alliance http://ow.ly/yuMA303Vosx

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[28] 2016 aHUS Global Poll. Conducted by the aHUS Alliance, 45 questions were offered in a poll for aHUS adult patients and pediatric caregivers, made available in 6 languages. (N=233, from 23 countries) Poll Overview: http://ow.ly/gSj8303GcdH Poll Questions & Results: http://ow.ly/1DA7303FoJx Poll Webinar, courtesy of RareConnect with commentary by Dr. C. Licht: http://ow.ly/ACiN303GajE

An Outreach and Education Initiative of the aHUS Alliance (Sept 2016)

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