Author/s:
Soraru, J;Isbel, N;Wong, G;Coates, PT;Mantha, M;Abraham, A;Juneja, R;Hsu, D;Brown, F;Bose, B;Mudge, D;Carroll, R;Kausman, J;Hughes, P;Barbour, T;Durkan, A;Mount, P;Lee, D;Larkins, N;Ranganathan, D;Lim, WH

Title:
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Date:
2020-09-01

Citation:
Soraru, J., Isbel, N., Wong, G., Coates, P. T., Mantha, M., Abraham, A., Juneja, R., Hsu, D., Brown, F., Bose, B., Mudge, D., Carroll, R., Kausman, J., Hughes, P., Barbour, T., Durkan, A., Mount, P., Lee, D., Larkins, N. ,... Lim, W. H. (2020). Baseline characteristics of patients with atypical haemolytic uraemic syndrome (aHUS): The Australian cohort in a global aHUS registry. Nephrology, 25 (9), pp.683-690. https://doi.org/10.1111/nep.13722.

Soraru Jacqueline (Orcid ID: 0000-0001-6308-0691)
Mudge David (Orcid ID: 0000-0002-4112-5550)
Barbour Thomas (Orcid ID: 0000-0002-3610-5053)
Mount Peter (Orcid ID: 0000-0001-7637-3661)
Lee Darren (Orcid ID: 0000-0002-3771-9102)

Baseline characteristics of patients with atypical haemolytic uraemic syndrome (aHUS): the Australian cohort in a global aHUS registry

Jacqueline Soraru[1#], Nicole Isbel[2], Germaine Wong[3,4,5], Patrick Toby Coates[6,7], Murty Mantha[8], Abu Abraham[9], Rajiv Juneja[10], Danny Hsu[11], Fiona Brown[12], Bhadran Bose[13], David Mudge[2], Robert Carroll[6], Joshua Kausman[14], Peter Hughes[15], Thomas Barbour[15], Anne Durkan[16], Peter Mount[17], Darren Lee[18], Nicholas Larkins[19,20], Dwarakanathan Ranganathan[21], Wai H Lim[1,20]

[1]Department of Renal Medicine, Sir Charles Gairdner Hospital, Perth, Australia; [2]Department of Nephrology, Princess Alexandra Hospital, Brisbane, Australia; [3]Centre for Transplant and Renal Research, Westmead Hospital, Sydney, Australia; [4]Centre for Kidney Research, The Children's Hospital at Westmead, Sydney, Australia; [5]School of Public Health, University of Sydney, Sydney, Australia; [6]Central and Northern Renal and Transplantation Service, Royal Adelaide Hospital, Adelaide, Australia; [7]Adelaide Health and Medical Sciences, University of Adelaide, Adelaide, Australia; [8]Department of Nephrology, Cairns Base Hospital, Cairns, Australia; [9]Department of Nephrology and Renal Transplant, Fiona Stanley Hospital, Perth, Australia; [10]Flinders Medical Centre, Adelaide, Australia; [11]Department of Haematology, Liverpool Hospital, Sydney, Australia; [12]Department of Nephrology, Monash Medical Centre, Melbourne, Australia; [13]Department of Nephrology, Nepean Hospital, Blue Mountains, Australia; [14]Department of Nephrology and Renal Transplantation, The Royal

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/nep.13722

Children's Hospital, Melbourne, Australia; [15]Department of Nephrology and Transplantation, The Royal Melbourne Hospital, Melbourne, Australia; [16]Department of Nephrology, The Children's Hospital at Westmead, Sydney, Australia; [17]Department of Nephrology, Austin Health, Melbourne, Australia; [18]Department of Renal Medicine, Eastern Health Clinical School, Monash University Melbourne, Victoria; [19]Department of Nephrology and Hypertension, Perth Children's Hospital, Perth, Australia; [20]School of Medicine, University of Western Australia, Perth, Australia; [21]Kidney Health Service, Royal Brisbane and Women's Hospital, Brisbane, School of Medicine, Griffith University, Australia.

Running title: Atypical HUS in Australia

#Corresponding author:

Jacqueline Soraru

Email: jacqueline.soraru@health.wa.gov.au

Address: Department of Renal Medicine, Sir Charles Gairdner Hospital, Hospital Avenue, Nedlands, WA 6009

Word count: Abstract - 255, Text – 3060 Tables - 5

Abstract

Aims: To describe the baseline characteristics and treatment of Australian patients diagnosed with atypical haemolytic uraemic syndrome (aHUS) reported to the Global aHUS Registry. **Methods**: Descriptive analysis of the Australian cohort with aHUS (n=106) was undertaken for demographics, disease characteristics and prior treatment with eculizumab; comparing with the global cohort (n=1688) for certain pre-specified disease characteristics. **Results**: In Australia, almost two-thirds of patients diagnosed with aHUS were female and over 80% of patients were Caucasians, with similar proportions reported in the global cohort. Less than 6% of patients in the Australia and global cohorts were reported to have a history of autoimmune disease (4% vs. 2%, respectively; p=0.21) or cancer (5% vs. 5%, respectively; p=0.93), conditions that have been associated with secondary HUS. In the Australian cohort, 26% had received a kidney transplant and 68% of patients had received eculizumab. Kidneys were the most common organ involvement, followed by

gastrointestinal tract (26%) and cardiovascular system (19%), with 35% of patients reported to have had at least 2 organs involved within 6 months prior to baseline visit or entry into the registry. Complement factor H (CFH) was the most common pathogenic complement gene variant in the Australian patients. **Conclusion**: Data from the aHUS registry confirms and defines region-specific disease characteristics among a selected group of Australian children and adults with aHUS reported to the registry. Ongoing and more inclusive data will provide further information about temporal trends and treatment outcomes, representing a unique opportunity for clinicians and researchers to further develop knowledge surrounding this rare disease.

Keywords: atypical haemolytic uraemic syndrome, registry, complement gene mutation, eculizumab, kidney transplant.

Introduction

Atypical haemolytic uraemic syndrome (aHUS) is a rare, genetic, systemic, complement-mediated disease characterized by thrombotic microangiopathy (TMA), manifesting clinically as microangiopathic haemolytic anaemia, thrombocytopaenia and tissue injury [1-3]. With a greater understanding of the role of the complement system in the pathogenesis of aHUS, combined with the availability of specific treatment with anti-C5 monoclonal antibody (eculizumab) for this disease, the incidence of aHUS has substantially increased worldwide [4,5]. Despite this, it is possible that the true incidence of aHUS, reported to be 1-2 cases per million population, remains underestimated because of the varied presentation of

patients with aHUS, ranging from asymptomatic haematological and biochemical abnormalities to severe end organ complications [6].

Registries of rare diseases such as aHUS are critical in understanding the characteristics, presentation and outcomes of patients affected by these diseases, providing clinicians with the knowledge to assist in the identification of such infrequent patients [7-9]. aHUS is fundamentally a diagnosis of exclusion that can affect both adults and children, with dissimilar clinical presentations and patient characteristics across geographical regions, making region-specific data important. In 2012, a global registry was initiated to collect demographic and clinical information of all patients with aHUS, regardless of whether the patients had received treatment with eculizumab or whether the patients had reached end-stage kidney disease (ESKD) [7]. The aim of this analysis is to describe the characteristics of Australian patients diagnosed with aHUS reported in the global aHUS registry.

Methods

Study population

Data of the Australian aHUS patients were recorded within the Global aHUS Registry (United States National Institutes of Health; www.ClinicalTrials.gov Identifier: NCT01522183), with details of the methodology published in 2015 [7]. In brief, the Global aHUS Registry is sponsored by Alexion Pharmaceuticals (Boston, Massachusetts, USA), with all retrospective

and prospective cases of patients with aHUS across 22 countries (351 sites) recorded in the Registry. Informed consent was provided at study inclusion, following local institutional ethics committee approval at each participating site. Eligible patients included individuals of all ages with a clinical diagnosis of aHUS as determined by the treating clinicians at each site. The Registry does not verify the diagnosis of aHUS of each patient; and genetic abnormalities, tissue evidence of TMA or the evidence supporting the exclusion of secondary TMA were not requirements of study enrolment. However, patients with thrombocytopaenic purpura (TTP) or Shiga-toxin producing *Escherichia coli* (STEC) HUS were not eligible for study inclusion. For Australian patients with aHUS in the registry, the investigators have confirmed that all patients fulfilled the clinical diagnosis for aHUS. Data of each patient were recorded at study entry, and with prospective data collection until the 1st April 2019.

Data collection

Data collected included age, gender, ethnicity; characteristics at disease presentation such as organ(s) involvement including the presence of ESKD, the number of TMA complications since disease diagnosis, family history of aHUS, history of malignancy or autoimmune diseases, and the presence of pathogenic genetic variants in complement genes (where available); treatments including the administration of eculizumab and plasmapheresis; and prior kidney transplantation. Serological testing for C3-nephritic factor, complement activity classical (CH50) and alternative pathway (AH50) were not reported to the Registry.

Statistics

Descriptive analysis of the Australian cohort with aHUS was undertaken for demographics, disease characteristics and prior treatment with eculizumab. The data were expressed as number (proportion), mean (standard deviation [SD]), and median (interquartile range [IQR]), where appropriate. Comparison of baseline characteristics between Australia and "other countries" was undertaken using chi-square test for categorical data, with p-values of <0.05 considered statistically significant. Data analyses were performed using SPSS Version 23 software program and SAS version 9.4 (SAS Institute, Cary, NC).

Results

There were a total of 1794 patients with aHUS recorded in the global Registry, of which 106 (5.9%) were from Australia. Of the 106 patients recruited from 17 sites across all states and territories in Australia, the median (IQR) number of patients at each site was 4 (2-7, range 1-37).

When comparing the characteristics of the Australian cohort to other countries (Table 1), a greater proportion of patients were diagnosed with aHUS in childhood/adolescence (aged less than 18 years) in other countries compared to Australia (42% vs. 22%, respectively). This may be directly related to adult patients more likely being reported to the Registry in the Australian cohort. Compared to patients in other countries, Australian patients were more likely to be female (63% vs. 55% respectively) with similar number of Caucasian patients in the two groups (82% vs. 80% respectively). Family history of aHUS was reported in 10% and 12% of patients in Australia and other countries, respectively; with less than 5% of patients in both cohorts with a history of autoimmune disease and/or cancers. Of the 4 patients with autoimmune conditions in Australia, 1 patient was reported to have rheumatoid arthritis, 1 with systemic lupus erythematosus, 1 with essential thrombocytosis and the cause of autoimmune condition in 1 patient was not specified. Of the 5 patients with cancers in Australia, 2 were reported to have haematological malignancy (1 with chronic lymphocytic leukaemia, and 1 with Hodgkin's lymphoma), and 3 were reported to have solid cancers (2 with ampullary carcinoma and 1 with pancreatic cancer). Of the 2 patients with a prior

diagnosis of malignant hypertension in Australia, blood pressure readings at time of diagnosis of aHUS were not reported to the Registry. Blood pressure trend for one patient ranged between 107/90mmHg to 150/80mmHg over the follow-up period, whereas the trend was between 110/60mmHg to 140/90mmHg over the follow-up period in the second patient. Both of these patients were reported to have a pathogenic mutation in Complement Factor H gene.

A similar proportion of patients in Australia and other countries had received a kidney transplant (26% vs. 23% respectively). Over 65% of patients in both cohorts had received eculizumab treatment, and 12 (11%) patients with aHUS were reported to have died in the Australian cohort, as compared to 88 (5%) patients in the global cohort.

Organ involvement

Table 2 summarises the patient data relating to aHUS-related symptoms and morbidities (as reported by clinicians) within the *6 months* prior to the baseline visit or entry into the registry and therefore likely to underestimate the true prevalence of these end organ complications. For Australian patients with aHUS, investigators have confirmed that all patients reported to the registry had kidney involvement during the course of disease. This is followed by symptoms or morbidities relating to the gastrointestinal tract (25%), cardiovascular system (19%) and neurological system (16%). There were 37 (35%) patients

reported to have had at least 2 organ systems affected by aHUS, with 8 (8%) patients reported to have had 4 or more organ systems involvement.

Identifiable pathogenic genetic variants in complement genes

Of the patients with available genetic data, complement factor H (CFH) gene abnormality was the most common pathogenic variant with 17 out of 50 (34%) of patients tested for this gene having an identifiable mutation. This was followed by the detection of anti-CFH antibody in 5 out of 43 patients (11%). Of note, variants in complement factor H-related protein 1-3 was present in in 6 out of 37 (CFHR1-3; 16%), with the deficiency in complement factor H-related protein often associated with the occurrence of anti-CFH antibody [10,11]. Two patients had at least two identifiable pathogenic genetic variants in the complement genes or the presence of anti-CFH antibody (Table 3). Of those patients tested, only 37% had a pathogenic gene mutation identified. The registry does not verify the accuracy of the genetic reports.

Treatment with eculizumab

The characteristics of the patients who were treated (n=72) and not treated (n=30) with eculizumab are shown in Table 4. In both groups, over 50% and 70% of patients had received dialysis and plasmapheresis, respectively. Patients treated with eculizumab were older and had a greater mean number of TMA events compared to those who did not receive eculizumab.

Characteristics of patients with ESKD

Table 5 shows the characteristics of patients with a kidney transplant before and after the baseline visit/enrolment into the registry. Of the 12 (of 23; 52%) patients who had received kidney transplants prior to baseline/enrolment and had received eculizumab treatment, 1 (4%) had discontinued treatment, with "investigator decision" reported as the main reason. Of the 5 patients who had not received a kidney transplant at baseline/enrolment (i.e. received a kidney transplant after enrolment into the registry), 3 (60%) had received eculizumab, with 2 (40%) discontinuing eculizumab treatment with reasons cited as "alternative diagnosis" and "symptom stabilisation". However, both of these patients re-started eculizumab treatment. The registry does not record the reasons for reinstituting treatment with eculizumab nor collect detailed information on the circumstances relating to eculizumab treatment termination.

Discussion

This report describes the baseline characteristics, treatment patterns and outcome of patients with aHUS in Australia. Analyses of the data from this industry-sponsored registry showed that patients with aHUS (as reported to the registry) in Australia were predominantly adults, with almost 70% of patients having received treatment with eculizumab. This study complements findings from other country-specific registry reports, providing information and novel insight on the occurrence, characteristics and progression of this rare disease.

The long-held belief that aHUS predominantly affects the kidneys are mistaken, as reflected by the varied clinical presentations and difficulties in establishing and differentiating aHUS from other TMA-related diseases. Consistent with other studies, kidneys were the most common organ involved, but gastrointestinal, neurological and cardiovascular disease were not infrequent [1,2,12-14]. However, it must be emphasized that the true prevalence of aHUS-related organ involvement is likely to be underestimated in this study because the registry only captures symptoms and morbidities related to aHUS within the 6 months prior to baseline visit/enrolment into the registry. The report by investigators that 100% of patients in the registry have kidney involvement related to aHUS (as compared with 52% reported in Table 2) highlights the limitations of the data capture in the registry. In Australia, almost 80% of patients with aHUS were adults at presentation, which is considerably higher than other countries but given the retrospective nature of data capture of patients with aHUS , this observation is likely to represent reporting or referral bias. Given that not all patients with aHUS in all Australian centres were enrolled in the registry (and with more patients from adult compared to paediatric centres enrolled), it is possible that the true characteristics of the prevalent aHUS patients in Australia is dissimilar to those included in the registry.

The presentation of patients with aHUS is often sporadic, with family history of the disease present in only 1 of 10 patients [2]. Consistent with this, in the aHUS registry, family history

was present in 10% and 12% of patients with aHUS in Australia and other countries respectively. Over 70% of patients with aHUS first manifest disease following a triggering "complement amplifying" event, typically following a systemic infection, but 30% of patients with aHUS have no reports of any triggering events [1,15]. Even though genetic complement abnormalities may be more common in patients with a family history, genetic abnormalities are not detected in up to 50% of patients with aHUS [12,16]. Furthermore, genetic complement abnormalities can be identified in up to 30% of patients presenting with secondary TMA as associated with malignant hypertension, kidney transplantation, pregnancy and other systemic disease, suggesting the possibility that these secondary conditions may unmask aHUS in genetically susceptible patients [12]. In a European study of 110 patients with secondary HUS, genetic variants in complement genes were identified in 5% of patients, which was similar to that detected in healthy subjects (6-8%). This compared with pathogenic complement genetic variants in 40-70% of aHUS patients reported in other studies suggesting that secondary HUS may not be directly attributed to genetic complement dysregulation [6,12,17]. In the European study, the relapse rate was 1% in patients with secondary HUS, but almost 40% of patients had reached ESKD. In a recent study of 55 aHUS patients from Spain, 35% had malignant hypertension on presentation, with pathogenic variants in the complement genes identified in 37% of those with malignant hypertension. In this study, the authors showed that thrombotic microangiopathy was infrequent (<5%) among patients presenting with malignant hypertension caused by diseases other than aHUS, indicating the likely differential pathogenesis of these two

disease pathways [18]. In the Australian cohort of patients with aHUS, less than 5% were reported to have had a secondary disease state that could potentially initiate HUS and less than 2% had a prior history of malignant hypertension, but we were unable to distinguish whether these represented secondary HUS or coincidental diseases unrelated to the diagnosis of aHUS. Of the patients with genetic screening performed, complement factor H mutation was the most frequent pathogenic genetic abnormality. Given that genetic screening was not undertaken in a proportion of patients in the registry, this is an underestimation of the true incidence of pathogenic genetic complement abnormalities. Nevertheless, these data do indicate the need to consider genetic screening as part of the management strategy for patients with aHUS or possibly presumed secondary HUS given prognostic implications. It also highlights the importance of re-reviewing patients as testing technologies and understanding of pathogenic and non-pathogenic gene variants improves.

Prior to the availability of disease-specific treatment with complement inhibition [19,20], the treatment of aHUS typically comprised of plasmapheresis or plasma infusion, which has variable effect in influencing patient outcomes [21]. The Australian Pharmaceutical Benefits Scheme funded eculizumab for the treatment of aHUS in Australia in 2014. However, a small number of patients with aHUS were able to access this drug for compassionate use through the Patient Access Program prior to 2014. The baseline data showed that 68% of patients in the aHUS registry received eculizumab, which is similar to global data. Previously, kidney transplantation was considered a relative contraindication for patients with aHUS because

of high rates of disease recurrence and premature allograft failure. With the availability of eculizumab (prophylactic or when clinically indicated), kidney transplant outcomes have markedly improved but successful transplantation without prophylactic eculizumab has also been reported [22-25]. In the Australian aHUS registry, 23 patients with ESKD had received a prior kidney transplant, of which 12 (52%) had received eculizumab treatment. There was one drug discontinuation but the registry does not capture the reason for discontinuation or the allograft outcomes of these recipients. Interestingly, of the 5 patients with ESKD who had received a kidney transplant after enrolment, 3 (60%) had received treatment with eculizumab, with 2 patients reported to have discontinued treatment but both had restarted treatment on follow-up. It will be critical for investigators to provide granular details regarding the diagnosis of such patients and the reasons for discontinuation (recorded as symptoms stabilization and alternative diagnosis) and reinstitution of eculizumab treatment to provide a greater understanding of the disease process, as it remains unclear as to whether the cessation of treatment is possible in certain situations [26-28].

Registry data of rare disease are important in understanding and providing clinical insights into people living with these conditions, and are essential to provide strategic planning in the development of support networks for clinicians and patients, allocation of health care resources, and to inform the need for novel treatment options and research[8,9,29]. There are several rare disease registries operating in Australia, which includes the Australian TTP/TMA

registry (n=57) [30], Fabry's disease registry (n=67) [31] and cystic fibrosis data registry [32]. The majority of these were established with limited funding support or in-kind support provided by local investigators/institutions, which may explain the small number of patients or limited data captured in some of these registries. Even though the funding model for registries vary widely between countries and disease types, it is likely that a joint funding model including government agencies, industries and clinical care providers will be most cost-effective, providing sufficient autonomy of the clinicians and investigators in collecting and analysing (without restriction) data relating to the diseases and treatments, as well as providing an accurate landscape of the true incidence and health resource utilisation relating to the management of these rare diseases.

There are inherent limitations with registry data, which must be carefully considered when interpreting these data. The comparison of the point estimates for baseline characteristics between Australia and other countries must be interpreted with caution, as these estimations are subjected to a high degree of uncertainty. For Australian patients with aHUS, there is a risk of reporting and selection bias given that not all hospital centres were included and often, there was not a complete capture of all patients with aHUS (even in the same hospital centre). The registry does not require the verification of the accuracy of aHUS diagnosis or other details regarding the clinical, laboratory and treatment data for these patients. Patient data relating to aHUS-related symptoms and morbidities (as reported by clinicians) were required to be recorded if these occurred within the 6 months prior to the

baseline visit or entry into the registry, but these data were often incomplete or were missing. The registry does not capture whether eculizumab was given prophylactically or as treatment in aHUS who have received kidney transplants. However, it is unlikely that eculizumab was given prophylactically given that the Pharmaceutical Benefits Scheme in Australia for government-subsidised prescription medications only allows eculizumab to be prescribed as treatment for aHUS. In addition, information regarding timing of eculizumab treatment, reasons for discontinuation and long term renal outcomes in patients as well as allograft loss in kidney transplant recipients would have been useful in gaining a better understanding of disease characteristics in this population.

Baseline data from the cohort of Australian patients in the global aHUS registry represent a unique opportunity for clinicians and researchers to facilitate and recognise knowledge gaps typical of the management of rare diseases. Recruitment to the registry has now concluded, however the inclusion of affected patients, with varying characteristics, presentations and treatment exposure allows the characterisation of the long-term health outcomes and effectiveness of disease-specific treatment of this rare disease, and should translate to improved patient care. Nevertheless, an alternative collaborative funding model for a national registry that will capture accurate and more granular clinical data for all patients with aHUS from both adult and paediatric centres are urgently required for this high-cost rare disease. This will allow for future health service planning and provide a repository of

relevant clinical information that may assist in improving clinical decision-making process and the lives of those people living with this rare disease.

Disclosures and Acknowledgments

WH Lim is supported by a Clinical Research Fellowship from the Raine Foundation (University of Western Australia and Health Department of Western Australia) and Jacquot Research Foundation (Royal Australasian College of Physicians). N Larkins is also supported by a Raine Clinical Research Fellowship. G Wong is supported by a National Health and Medical Research Council Career Development Fellowship. N Isbel, D Mudge and WH Lim have received funding from Alexion with honoraria for advisory board membership and educational lectures.

Conflict of Interest

There are no conflicts of interest for any of the authors.

Acknowledgments

The Global aHUS registry is supported by Alexion Pharmaceuticals, Inc. The authors would like to thank the Alexion global medical team for review and approval of the manuscript and also Imad Al-Dakkak and his team at Global Epidemiology (Alexion Pharmaceuticals, Boston, MA, US) for undertaking the data extraction for this study. The authors would also like to thank all sites (investigators, research coordinators) for reporting of the data to the registry, and patients and their families for participation in the registry.

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Table 1. Comparison of baseline characteristics of patients with atypical haemolytic uremic syndrome in Australia versus other countries.

	Australia (n=106)	Other countries (n=1688)	Difference in proportion (95%CI)	P-value
Age at diagnosis				
<18 years (%)	23 (21.7)	701 (41.5)	19.8% (10.7% to 27.0%)	<0.01
Female (n, %)	67 (63.2)	932 (55.2)	8% (-1.8% to 16.9%)	0.11
Ethnicity (%)				
Caucasian	87 (82.0)	1353 (80.2)	1.9% (-6.7% to 8.3%)	0.63
Asian	7 (6.6)	113 (6.7)	0.1% (-6.4% to 3.7%)	0.97
Black	0 (0.0)	85 (5.0)	5% (1.4% to 6.1%)	0.02
Others	6 (5.7)	111 (6.6)	0.9% (-5.3% to 4.2%)	0.72
Not recorded	6 (5.7)	26 (1.5)	4.2% (1.1% to 10.4%)	<0.01
Family history (%)	11 (10.4)	201 (11.9)	1.5% (-5.9% to 6.3%	0.64
Kidney transplant ever (%)	28 (26.4)	392 (23.2)	3.2% (-4.5% to 12.5%	0.45
Dialysis prior to baseline (%)	55 (51.9)	858 (50.8)	1.1% (-8.6% to 10.7%)	0.83
Ever treated with eculizumab (%)	72 (67.9)	1118 (66.2)	1.7% (-7.9% to 10.1%)	0.71
Deceased (%)	12 (11.3)	88 (5.2)	6.1% (1.2% to 13.6%)	<0.01
History of autoimmune disease (%)[†]	4 (3.8)	34 (2.0)	1.8% (-0.6% to 7.4%)	0.21
History of cancers (%)[†]	5 (4.7)	82 (4.9)	0.2% (-5.7% to 3.1%)	0.93

Data presented as number (%), with comparison of the difference in proportions and (95% confidence intervals [95%CI]) examined by chi-square test. [†]*Types of autoimmune diseases and cancers not available for "other countries".*

Table 2. Types of organ involvement in Australian patients with atypical haemolytic uremic syndrome [†].

	Number N=106
Systemic organ involvement(s) (%)	
Cardiovascular system	20 (18.9)
Kidneys	55 (51.9)
Respiratory system	10 (9.4)
Neurological system	17 (16.0)
Gastrointestinal system	27 (25.5)
Multiple organ systems involvement:	
2 sites	15 (14.2)
3 sites	14 (13.2)
>3 sites	8 (7.5)

[†]*The aHUS-related symptoms and morbidities (as reported by clinicians) within the 6 months prior to the baseline visit or entry into the registry. Data expressed as number (%).*

Table 3. Types of identifiable pathogenic complement gene abnormalities or the presence of anti-complement factor H antibody in Australian patients with atypical haemolytic uremic syndrome.

Complement gene abnormalities *(denominator[†])* (%)	Number
Complement Factor H *(n=50)*	17 (34.0)
Complement Factor I *(n=48)*	1 (2.1)
Membrane Co-Factor Protein *(n=49)*	3 (6.1)
Complement factor H-related protein 1-3 deletion *(n=37)*	6 (16.2)
Anti-Complement Factor H antibody *(n=43)*	5 (11.6)
Complement Factor B *(n=45)*	1 (2.2)
Thrombomodulin *(n=12)*	1 (8.3)

Diacylglycerol kinase-ε *(n=10)*	1 (10.0)

Data expressed as number (%). There were 2 patients with 2 or more pathogenic complement gene abnormalities identified. †Represents the number of patients who were tested for pathogenic complement gene variant(s) or the presence of anti-complement factor H antibody (denominator).

Table 4. Characteristics of Australian patients with atypical haemolytic uremic syndrome with and without treatment with eculizumab.

	Ever treated (n=72)†	Never treated (n=30)
Age at diagnosis		
Mean (SD)	36.2 (22.3)	27.2 (21.4)
Median (IQR)	32.2 (24.7 – 51.2)	25.4 (6.3-35.6)
Number of TMA events since diagnosis		

Mean (SD)	2.2 (2.0)	1.5 (0.9)
Median (IQR)	1.5 (1.0-3.0)	1.0 (1.0-2.0)
Family history of aHUS (%)	9 (12.5)	2 (6.7)
Kidney transplant ever (%)	15 (20.8)	13 (43.3)
Dialysis prior to baseline (%)	36 (50.5)	19 (63.3)
Plasma exchange prior to baseline (%)	52 (72.2)	21 (70.0)
Time from disease start to eculizumab treatment in years		
Mean (SD)	2.1 (4.7)	-
Median (IQR)	0.02 (0.01-0.4)	-
Prior diagnosis of malignant hypertension (%)	1 (1.4)	1 (3.3)
Past history of autoimmune disease/cancer (%)[‡]	7 (9.7)	2 (6.7)

Data presented as number (%), mean (standard deviation [SD]), or median (interquartile range [IQR] as 25-75th quartiles). TMA – thrombotic microangiopathy. [†]Treatment defined as at least one dose of eculizumab. [‡]Types of autoimmune disease/cancers not presented. There were 4 cases without recorded treatment data and therefore were not included.

Table 5. Characteristics of Australian patients with atypical haemolytic uremic syndrome and ESKD, with and without prior kidney transplant at time of enrolment into the registry.

	Prior kidney transplant(s) (n=23)	No prior kidney transplant (n=5)[†]
Age at disease start		
Mean (SD)	36.2 (15.2)	36.2 (10.4)
Median (IQR)	33.3 (22.5-41.3)	33.4 (29.0-43.4)
Deceased (n, %)	3 (13.0)	0
Ever received eculizumab (n, %)	12 (52.2)	3 (60.0)
	Prior kidney transplant(s) treated with eculizumab (n=12)	**No prior kidney transplant treated with eculizumab (n=3)[†]**
Discontinuation of eculizumab (n, %)		
"Lack of efficacy"	0	0
Alternative diagnosis	0	1 (20.0)
Investigator decision	1 (4.3)	0
Patients/parents decision	0	0
Symptom stabilisation	0	1 (20.0)
Adverse event(s)	0	0
Restarted treatment with eculizumab (n, %)	0	2 (40.0)

Data presented as number (%), mean (standard deviation [SD]), or median (interquartile range [IQR] as 25-75th quartiles). [†]Represents patients without prior kidney transplant at time of enrolment in the registry (i.e. received a kidney transplant after enrolment in the registry).