RaDaR Rare Disease Group Annual Report

April 2017 – March 2018

Rare Disease Group	**aHUS**
Lead Clinician	**David Kavanagh**
Summary of RDG Activity (Meetings, patient events, grants, research studies, conference papers etc)	**Meetings/Patient Engagement** In October 2017 a patient focus group was held at the National Renal Complement Therapeutics Centre in Newcastle. aHUS patient representatives from across all of the UK were present to discuss their ideas for generating a National Service for aHUS with patients at its core. To help facilitate discussion staff from the NRCTC, members of the rare disease group and Sandra Currie from Kidney Research UK were present. The key wishes from the patient group were: **1.** Patient information- One of our key remits is to provide high quality advice to patients and clinicians about C3G and aHUS. We have developed a website (http://www.atypicalhus.co.uk/) providing both lay and professional advice **2.** Publicising recent research - an NRCTC Newsletter is now produced on a quarterly basis highlighting recent research, changes to the aHUS service, and a questions to the expert feature. This is available on line (http://www.atypicalhus.co.uk/), by e-mail or by post to all patients, family, friends and clinicians. **3.** Regional patient roadshows. It was suggested that aHUS staff and RDG members could hold patient information meetings around the UK. The first NRCTC regional roadshow was held on the 10th March in Durham with patients attending from the North East and Yorkshire. The next planned event will be in Liverpool.

4. Patient handheld record - To ensure equality of access, in addition to our digital platforms, we are creating a written version of our aHUS and C3G patient information. This will be included in our aHUS Patient Handheld Record which will be sent to all our patients on initial diagnosis. In addition to providing information this will act as record of important blood monitoring tests and contact information.

Selected Grant Awards from the aHUS rare disease group

1. Medical Research Council IMPC Exploration of the potential of C7 blockade as a target for immune therapy in complement mediated kidney disease £37,944 (2017-2018)

2. Medical Research Council Personalised management of atypical haemolytic uraemic syndrome £212,466 (2017-2021)

3. Medical Research Council The Role of Membrane Attack Complex in Atypical Haemolytic Uraemic Syndrome £ 292,330 (2017-2021)

4. HTA - Multicentre, open label, prospective, single arm study of safety impact of Eculizumab withdrawal National Institute for Health Research (NIHR) £821,941 (2017-2020)

Selected Manuscripts from the aHUS rare disease group

1. Walsh PR, Johnson S. 2017 Treatment and management of children with haemolytic uraemic syndrome. Arch Dis Child.

2. Legendre CM, Campistol JM, Feldkamp T, Remuzzi G, Kincaid JF, Lommele A, et al. 2017 Outcomes of patients with atypical haemolytic uraemic syndrome with native and transplanted kidneys treated with eculizumab: a pooled post hoc analysis. Transpl Int.

3. Kerr H, Wong E, Makou E, Yang Y, Marchbank K, Kavanagh D, et al. 2017 Disease-linked mutations in factor H reveal pivotal role of cofactor activity in self-surface-selective regulation of complement activation. J Biol Chem;292:13345-13360.

4. Hallam D, Collin J, Bojic S, Chichagova V, Buskin A, Xu Y, et al. 2017 An Induced Pluripotent Stem Cell Patient Specific Model of Complement Factor H (Y402H) Polymorphism Displays Characteristic Features of Age-Related Macular Degeneration and Indicates a Beneficial Role for UV Light Exposure. Stem Cells;35:2305-2320.

5. Goodship TH, Cook HT, Fakhouri F, Fervenza FC, Fremeaux-Bacchi V, Kavanagh D, et al. 2017 Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. Kidney Int;91:539-551.

6. Dowen F, Wood K, Brown AL, Palfrey J, Kavanagh D, Brocklebank V. 2017 Rare genetic variants in Shiga toxin-associated haemolytic uraemic syndrome: genetic analysis prior to transplantation is essential. Clin Kidney J;10:490-493.

7. Challis RC, Ring T, Xu Y, Wong EK, Flossmann O, Roberts IS, et al. 2017 Thrombotic Microangiopathy in Inverted Formin 2-Mediated Renal Disease. J Am Soc Nephrol;28:1084-1091.

8. Bruel A, Kavanagh D, Noris M, Delmas Y, Wong EKS, Bresin E, et al. 2017 Hemolytic Uremic Syndrome in Pregnancy and Postpartum. Clin J Am Soc Nephrol;12:1237-1247.

9. Brocklebank V, Wood KM, Kavanagh D. 2017 Thrombotic Microangiopathy and the Kidney. Clin J Am Soc Nephrol.

10. Brocklebank V, Kavanagh D. 2017 Complement C5-inhibiting therapy for the thrombotic microangiopathies: accumulating evidence, but not a panacea. Clin Kidney J;10:600-624.

11. Brocklebank V, Johnson S, Sheerin TP, Marks SD, Gilbert RD, Tyerman K, et al. 2017 Factor H autoantibody is associated with atypical hemolytic uremic syndrome in children in the United Kingdom and Ireland. Kidney Int;92:1261-1271.

12. Woodward L, Johnson S, Walle JV, Beck J, Gasteyger C, Licht C, et al. 2016 An innovative and collaborative partnership between patients with rare disease and industry-supported registries: the Global aHUS Registry. Orphanet J Rare Dis;11:154.

13. Wong E, Challis R, Sheerin N, Johnson S, Kavanagh D, Goodship TH. 2016 Patient stratification and therapy in atypical haemolytic uraemic syndrome (aHUS). Immunobiology;221:715-718.

14. Sheerin NS, Kavanagh D, Goodship TH, Johnson S. 2016 A national specialized service in England for atypical haemolytic uraemic syndrome-the first year's experience. QJM;109:27-33.

15. Phillips EH, Westwood JP, Brocklebank V, Wong EK, Tellez JO, Marchbank KJ, et al. 2016 The role of ADAMTS-13 activity and complement mutational analysis in differentiating acute thrombotic microangiopathies. J Thromb Haemost;14:175-185.

16. Kavanagh D, Smith-Jackson K. 2016 Eculizumab in children with hemolytic uremic syndrome. Kidney Int;89:537-538.

17. Kavanagh D, McGlasson S, Jury A, Williams J, Scolding N, Bellamy C, et al. 2016 Type I interferon causes thrombotic microangiopathy by a dose-dependent toxic effect on the microvasculature. Blood;128:2824-2833.

18. Gleeson PJ, Wilson V, Cox TE, Sharma SD, Smith-Jackson K, Strain L, et al. 2016 Chromosomal rearrangement-A rare cause of complement factor I associated atypical haemolytic uraemic syndrome. Immunobiology;221:1124-1130.

19. Challis RC, Araujo GS, Wong EK, Anderson HE, Awan A, Dorman AM, et al. 2016 A De Novo Deletion in the Regulators of Complement Activation Cluster Producing a Hybrid Complement Factor H/Complement Factor H-Related 3 Gene in Atypical Hemolytic Uremic Syndrome. J Am Soc Nephrol;27:1617-1624.

20. Zipfel PF, Skerka C, Chen Q, Wiech T, Goodship T, Johnson S, et al. 2015 The role of complement in C3 glomerulopathy. Mol Immunol;67:21-30.

21. Wong EK, Kavanagh D. 2015 Anticomplement C5 therapy with eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome. Transl Res;165:306-320.

22. Sevinc M, Basturk T, Sahutoglu T, Sakaci T, Koc Y, Ahbap E, et al. 2015 Plasma resistant atypical hemolytic uremic syndrome associated with a CFH mutation treated with eculizumab: a case report. J Med Case Rep;9:92.

23. Nichols EM, Barbour TD, Pappworth IY, Wong EK, Palmer JM, Sheerin NS, et al. 2015 An extended mini-complement factor H molecule ameliorates experimental C3 glomerulopathy. Kidney Int;88:1314-1322.

24. Nester CM, Barbour T, de Cordoba SR, Dragon-Durey MA, Fremeaux-Bacchi V, Goodship TH, et al. 2015 Atypical aHUS: State of the art. Mol Immunol;67:31-42.

25. Kavanagh D, Yu Y, Schramm EC, Triebwasser M, Wagner EK, Raychaudhuri S, et al. 2015 Rare genetic variants in the CFI gene are associated with advanced age-related macular degeneration and commonly result in reduced serum factor I levels. Hum Mol Genet;24:3861-3870.

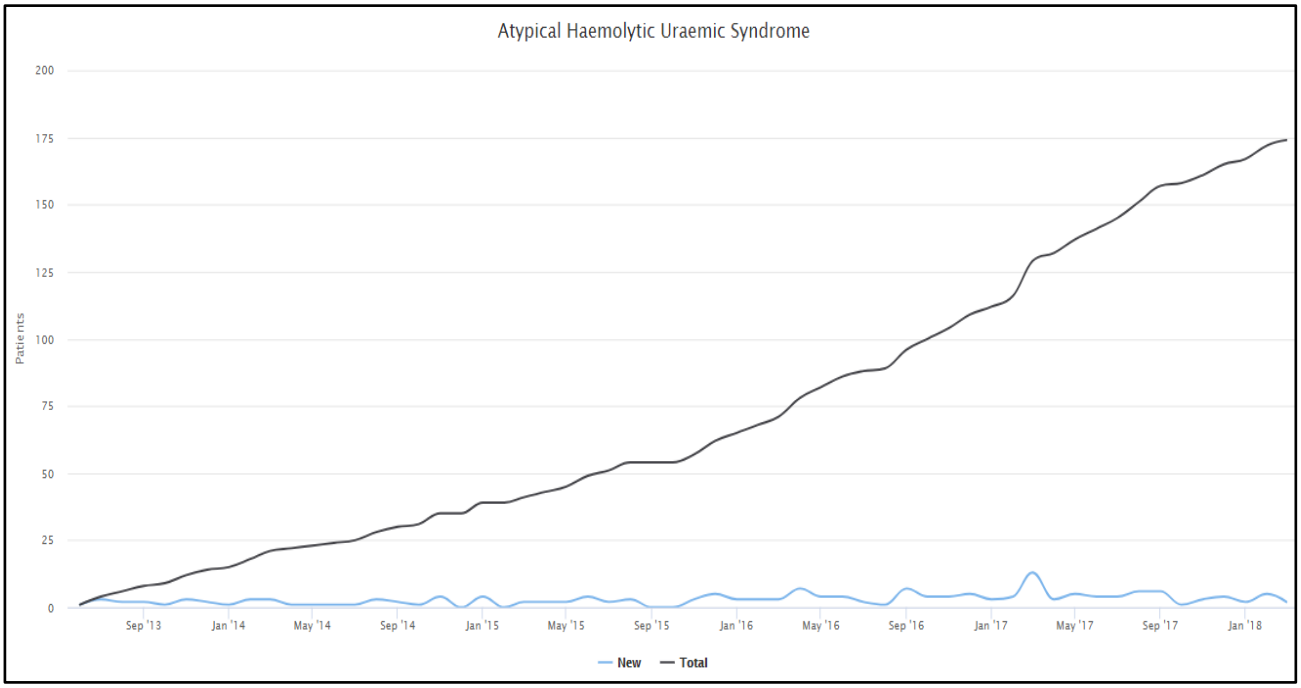
26. Iqbal Z, Wood K, Carter V, Goodship TH, Brown AL, Sheerin NS. 2015 Thrombotic Microangiopathy as a Cause of Chronic Kidney Transplant Dysfunction: Case Report Demonstrating Successful Treatment with Eculizumab. Transplant Proc;47:2258-2261.

27. Fearn A, Sheerin NS. 2015 Complement activation in progressive renal disease. World J Nephrol;4:31-40.

28. Blaum BS, Hannan JP, Herbert AP, Kavanagh D, Uhrin D, Stehle T. 2015 Structural basis for sialic acid-mediated self-recognition by complement factor H. Nat Chem Biol;11:77-82.

	29. Hunt D, Kavanagh D, Drummond I, Weller B, Bellamy C, Overell J, et al. 2014 Thrombotic microangiopathy associated with interferon beta. N Engl J Med;370:1270-1271. **30.** Osborne AJ, Breno M, Borsa NG, Bu F, Frémeaux-Bacchi V, Gale DP, van den Heuvel LP, Kavanagh D, Noris M, Pinto S, Rallapalli PM, Remuzzi G, Rodríguez de Cordoba S, Ruiz A, Smith RJ, Vieira-Martins P, Volokhina E, Wilson V, Goodship THJ, Perkins SJ.(2018) Statistical Validation of Rare Complement Variants Provides Insights into the Molecular Basis of Atypical Hemolytic Uremic Syndrome and C3 Glomerulopathy. J Immunol. 2018 Apr 1;200(7):2464-2478.
Recruits as of 1st April 2017	129
Recruits as of 31st March 2018	174
New recruits	45

Recruitment Overview Graph



Recruits by site

Hospital	Patients
Birmingham Childrens Hospital	21
Exeter	13
Newcastle upon Tyne	12
Brighton - Sussex Kidney Unit	10
Glasgow - Queen Elizabeth University Hospital	9
London - Royal Free Hospital	9
Leeds - Childrens Hospital	8
Hull	7
Birmingham - Queen Elizabeth Hospital	6
London - Guy's and St. Thomas' Hospital	5
Southampton General Hospital - Paediatrics	5
Nottingham - QMC - Children's Kidney Unit	5
Nottingham University Hospitals NHS Trust	4
Coventry and Warwickshire	4
Plymouth	4
Kent and Canterbury Hospital	3
Cardiff - UHW (Adult and Paediatrics)	3
Stoke	3
Derby	3
Bristol - Southmead Hospital	3
Stevenage - Lister Hospital	3
London - Barts Health	3
Peterborough	2
Taunton - Musgrove Park Hospital	2
Manchester Childrens Hospital	2
Leeds - St James's Hospital	2
Manchester Royal Infirmary	2
Sunderland Royal Hospital	2
Wolverhampton - New Cross Hospital	2
Leicester	2
Middlesbrough - James Cook	2

Hospital	Patients
York	2
Carshalton - St Helier Renal Unit	2
Macclesfield	1
Kilmarnock - Crosshouse - John Stevenson Lynch Renal Unit	1
London - West - Imperial	1
London- Great Ormond Street Hospital for Children	1
Oxford - Churchill	1
Norfolk and Norwich University Hospital	1
Sheffield	1
Cambridge Kidney Unit	1
Colchester General Hospital	1