Institution: Newcastle University

Unit of Assessment: UoA 1

Title of case study: Approval of eculizumab and establishment of a national service to treat patients with Atypical Haemolytic Uraemic Syndrome (aHUS)

Period when the underpinning research was undertaken: 2005-2020

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Professor Tim Goodship	Professor of Renal Medicine	1982-2016
Professor Judith Goodship	Professor of Medical Genetics	1990-2015
Professor Neil Sheerin	Professor of Nephrology	2007-present
Professor David Kavanagh	Professor of Complement Therapeutics	2007-present
Dr Yaobo Xu	Research Associate	2013-2016
Dr Edwin Wong	Clinical Fellow	2012-2016
Dr Vicky Brocklebank	Clinical Research Fellow	2013-present
Professor Kevin Marchbank	Professor of Complement Biology	2006-present
Dr Mauro Santibanez-Koref	Senior Lecturer	2002-present
Dr Kate Smith-Jackson	Clinical Research Fellow	2017-present
Dr Patrick Walsh	Clinical Fellow	2019-present
Professor Claire Harris	Professor of Molecular Immunology	2016-present

Period when the claimed impact occurred: January 2015-present

Is this case study continued from a case study submitted in 2014? Yes. The 2014 case focussed on the discovery of the molecular mechanisms underlying the disease, the identification of eculizumab as a potential treatment, its approval by the FDA and EMA and the subsequent establishment of a temporary UK aHUS Service to coordinate patient care. However, the high cost of the drug and risk of infection by encapsulated organisms meant that only patients who would respond should be treated, which hampered NICE approval. Further Newcastle research found that such patients could be identified through genetic testing. This case discusses the 2015 NICE recommendation of eculizumab and the aHUS Service being awarded an ongoing contract to co-ordinate treatment in 2016, including rapid genetic identification of patients who would not respond to the drug.

1. Summary of the impact

Atypical Haemolytic Uraemic Syndrome (aHUS) is a rare kidney disease which, left untreated, has high morbidity and a mortality rate of 10-15%. Since kidney transplantation does not correct the underlying genetic defect, recurrence is common and used to mean a lifetime on dialysis. Research in Newcastle discovered that aHUS resulted from mutations in complement system genes. Further work found that eculizumab, an inhibitor of the complement pathway, was an effective treatment and also that patients who would respond to it could be identified through genetic testing. These findings underpinned the 2015 NICE recommendation of eculizumab. In 2016, NHS England awarded the contract to coordinate aHUS treatment to the Newcastle-based National aHUS Service, who also perform genetic testing to identify patients who will respond. Of the 969 patients referred to the Service so far, around 280 have successfully received eculizumab without adverse effect, to either prevent end-stage renal failure or allow curative renal transplantation, and there have been zero aHUS-related deaths.

2. Underpinning research

Background and unmet need

Atypical Haemolytic Uraemic Syndrome (aHUS) is a rare disease with an incidence of 0.4-0.5 per million per year, currently affecting around 300 people in the UK[1]. aHUS results from mutations in the genes responsible for the complement pathway, which plays a central role in the immune system. In aHUS, these mutations cause uncontrolled activation of the complement system, which

[1]2019/20 report as below.

then attacks the endothelium of renal blood vessels, causing inflammation and clot formation in the glomeruli and leading to kidney failure.

Without treatment, the prognosis for people with aHUS is poor. Patients are at lifelong risk of an acute episode of aHUS, leading to end-stage renal failure (ESRF) and multiorgan damage. Mortality rates range from 10–15% in the acute phase of the disease, and up to 70% of patients die or progress to ESRF requiring dialysis within a year of diagnosis[2]. Since most complement proteins are produced in the liver, kidney transplantation does not correct the underlying genetic defect and recurrent aHUS with transplant loss is common.

Newcastle research (R3) directly informed the FDA and EMA approval of eculizumab in 2011, but the drug still lacked NICE approval in the UK. Its high cost means that it should only be given to patients who it would benefit, and therefore further research was required to determine if these patients could be identified via genetic testing.

Newcastle research into a treatment for aHUS

Research by Newcastle University and Newcastle Upon Tyne Hospitals NHS Foundation Trust ("Newcastle") was the first to link aHUS to a specific region on chromosome 1 responsible for regulating complement. The group then identified other genes and mutations associated with aHUS (R1), and showed that these underlying mutations in aHUS were strong predictors of kidney transplant outcome (R2). Genetic testing is therefore an essential part of appropriate treatment of aHUS.

The group also showed that abnormalities of the complement pathway are seen in around 70% of aHUS patients, indicating that complement is central to the pathogenesis of aHUS. Newcastle therefore investigated an inhibitor of complement component 5 (C5). Two clinical trials (C08-002A/B and C08-003A/B, published together as R3) were conducted into the effectiveness of the anti-C5 humanised monoclonal antibody eculizumab as a potential treatment for aHUS. These trials (R3) met their primary endpoint in treating aHUS and found that "eculizumab was associated with significant improvement in all secondary end points (renal function, changes in health-related quality of life [as measured by the EQ-5D, a widely-used tool to measure health status], pharmacokinetics and pharmacodynamics, and safety and tolerability)". No unexpected safety signals were seen in these trials and the known risk of infection with encapsulated organisms was low. These trials demonstrated that eculizumab could treat the majority of aHUS cases and prevent ESRF. This allowed safe renal transplantation, with pre-emptive eculizumab cover, of aHUS patients already on dialysis and deemed "untransplantable" due to the unacceptably high risk of relapse.

Newcastle research predicts patients who will not respond to eculizumab

Since some patients with aHUS do not respond to eculizumab, it is important to identify them to personalise their management. Eculizumab is expensive (annual cost of over £327,000 per patient) and increases the risk of infection by encapsulated organisms, most importantly meningococcal infection. Using genetic screening to identify patients who will not respond means that they are spared an ineffective treatment that places them at risk of infection and generates substantial cost savings for the NHS. For example, Newcastle recently found that mutations in the *INF2* gene (R6) and the *DGKE* gene (R7) led to non-responsiveness and therefore eculizumab could safely be withdrawn in these patients.

3. References to the research

SciVal field-weighted citation impact (FWCI) as at December 2020. Newcastle researchers in **bold.**

R1. **Kavanagh D**, **Kemp EJ**, **Mayland E**, Winney RJ, Duffield JS, Warwick G, **Richards A**, Ward R, **Goodship JA**, **Goodship TH**. (2005) Mutations in complement factor I predispose to development of atypical hemolytic uremic syndrome. *Journal of the*

[2]NICE HST 2015, as below.

American Society of Nephrology. 16(7):2150-5. DOI: 10.1681/ASN.2005010103. FWCI: 6.66.

R2. Bresin E, Daina E, Noris M, Castelletti F, Stefanov R, Hill P, **Goodship THJ**, Remuzzi G. (2006) Outcome of renal transplantation in patients with non-shiga toxin-associated hemolytic uremic syndrome: Prognostic significance of genetic background. *Clinical Journal of the American Society of Nephrology*. 1(1):88-99. DOI: 10.2215/CJN.00050505. FWCI: 3.44. **N.B.** Remuzzi has provided a testimonial to confirm Newcastle's role in this paper - available on request.

R3. **Goodship T**. (2013) Patient organisation submission to the National Institute for Health and Care Excellence. Eculizumab for the treatment of atypical haemolytic uraemic syndrome. aHUS Action. (Copy available on request). FWCI: N/A.

R4. Legendre CM, Licht C, Muus P, Greenbaum LA, Babu S, Bedrosian C, Bingham C, Cohen DJ, Delmas Y, Douglas K, Eitner KF, Feldkamp T, Fouque D, Furman RR, Gaber O, Herthelius M, Hourmant M, Karpman D, Lebranchu Y, Mariat C, Menne J, Moulin B, Nürnberger J, Ogawa M, Remuzzi G, Richard T, Sberro-Soussan R, Severino B, **Sheerin NS**, Trivelli A, Zimmerhackl LB, **Goodship T**, and Loirat C. (2013) Terminal Complement Inhibitor Eculizumab in Atypical Hemolytic–Uremic Syndrome. *New England Journal of Medicine*. 368: 2169-81. DOI: 10.1056/NEJMoa1208981. FWCI: 79.57. **N.B.** Legendre, Licht, Muus, **Goodship**, and Loirat contributed equally to this article as joint senior authors and **Goodship** was UK Chief Investigator.

R5. **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: An International Journal of Medicine*. 109(1):27-33. DOI: 10.1093/qjmed/hcv082. FWCI: 8.94.

R6. **Challis RC**, Ring T, **Xu Y**, **Wong EK**, Flossmann O, Roberts IS, Ahmed S, Wetherall M, Salkus G, **Brocklebank V**, Fester J, Strain L, Wilson V, Wood KM, **Marchbank KJ**, **Santibanez-Koref M**, **Goodship TH**, **Kavanagh D**. (2017) Thrombotic Microangiopathy in Inverted Formin 2-Mediated Renal Disease. *Journal of the American Society of Nephrology*. 28(4):1084-91. DOI: 10.1681/ASN.2015101189. FWCI: 1.6. Findings taken up directly into clinical practice pre-publication.

R7. **Brocklebank V**, Kumar G, Howie AJ, Chandar J, Milford DV, Craze J, Evans J, Finlay E, Freundlich M, Gale DP, Inward C, Mraz M, Jones C, Wong W, Marks SD, Connolly J, **Corner BM**, **Smith-Jackson K**, **Walsh PR**, **Marchbank KJ**, **Harris CL**, Wilson V, Wong EKS, Malina M, Johnson S, **Sheerin NS**, **Kavanagh D**. (2020) Long-term outcomes and response to treatment in diacylglycerol kinase epsilon nephropathy. *Kidney International*. 97(6):1260-74. DOI: 10.1016/j.kint.2020.01.045. FWCI: 0. **N.B.** Findings taken up directly into clinical practice pre-publication.

4. Details of the impact

<u>Impact on NICE HST recommendation</u>

Newcastle research (R2 and R3) informed the November 2013 Tappenden report (EV1), a systematic review commissioned by the NIHR. R2 underpins table 17 on page 65, which gives the interim national aHUS service criteria for withdrawing or restarting eculizumab therapy. Newcastle supplied the only two published, prospective studies (C08-002 A/B and C08-003 A/B, published together as R3), which are widely referenced throughout the document, including on page 5: "CKD [chronic kidney disease] transition probabilities were derived from the treatment phase and pre-treatment phase of two prospective eculizumab studies."

The Tappenden report was the only source of evidence underpinning the January 2015 NICE Highly Specialised Technology guidance for eculizumab (EV2, page 40). In addition, Professor Tim Goodship was one of five individuals giving their expert personal view on eculizumab by providing oral and written evidence to the Committee. This guidance recommended funding eculizumab within its marketing authorisation if certain arrangements were in place (page 3). The introduction of the drug, the only one licensed to treat aHUS, has led to widespread patient benefits, as detailed below.

Impact of eculizumab on patient benefit

Following its recommendation by NICE, eculizumab treatment has transformed the lives of patients with aHUS. A 2017 report from an international panel of experts (EV3) concluded:

"The introduction of eculizumab has changed the natural history of aHUS. Prior to eculizumab, most patients with aHUS progressed to end-stage renal disease… With complement inhibitory therapy, glomerular perfusion and function are maintained."

There is also quantitative evidence of improved patient quality of life. First, R3 found that eculizumab was associated with a significant ($p < 0.001$) improvement in EQ-5D score, a standardised instrument used to measure generic health status. Secondly, as stated in the Tappenden report, the manufacturer's model suggests that eculizumab adds an estimated 37.65 years of life and 38.47 QALYs per patient compared to standard care.

Impact on patient care: referrals and transplants

From April 2013-May 2016, 119 incident patients started treatment via an interim funding policy. Further funding was provided for 15 patients who had started eculizumab treatment prior to April 2013, either as part of a trial or on compassionate basis, and either through local funding or provided by the manufacturer. In May 2016, the success of this interim service led NHS England to award an initial five-year contract to the aHUS Service, a collaboration between Newcastle University and Newcastle Upon Tyne Hospitals NHS Foundation Trust and part of the Newcastle-based National Renal Complement Therapeutics Centre. As recommended by NICE, treatment with eculizumab is co-ordinated through this single expert centre due to the high cost of the drug, and all patients in England with suspected aHUS are referred there. Administration of eculizumab carries the risk of meningococcal infection, and therefore patients are required to have a vaccine before treatment, and long-term prophylactic antibiotics are recommended.

The table below summarises the number of patients with a possible aHUS diagnosis referred to the aHUS Service, and the number with a confirmed diagnosis who are subsequently recommended eculizumab. Of those, the number showing renal recovery is given, and of those the number where the drug was withdrawn.

Reporting period (Financial year)	Referrals	Eculizumab recommended	Renal recovery	Drug withdrawn	Percentage of eligible patients listed for renal transplant
2016/17 (EV4)	70	32	29	9	100%
2017/18 (EV5)	141	38	28	11	100%
2018/19 (EV6)	171	36	25	9	100%
2019/20 (EV7)	199	36	23	8	100%

Given the annual incidence of around 30 patients, the vast majority show renal recovery. Since the aHUS Service began, there have been zero aHUS-related deaths.

Impact on genetic screening for eculizumab non-response

Since eculizumab is expensive and administration carries a risk of meningococcal infection, its use is limited to those patients who will respond, aided by genetic screening (R6, R7). Genetic testing was therefore established by the aHUS Service in 2016 and is routinely performed to ensure that the drug is only given where appropriate. As well as confirming the diagnosis of complement-mediated aHUS and predicting prognosis, rapid genetic testing has allowed identification of over 30 individuals who would not have responded to eculizumab, preventing ineffective treatment and providing estimated NHS cost savings of > £10m.

In summary, Newcastle research provided sufficient testing and evidence for NICE to approve the use of eculizumab to treat aHUS, a rare and life-limiting disease. In 2016, Newcastle were awarded a contract to co-ordinate treatment, consequently identifying the patients who would respond to eculizumab, providing it to around 280 patients since 2016 and reducing aHUS-related deaths to zero.

5. Sources to corroborate the impact

EV1. The University of Sheffield Evidence Review Group 2013 Report by Tappenden et al. https://njl-admin.nihr.ac.uk/document/download/2022670
EV2. NICE January 2015 Highly specialised technology guidance. www.nice.org.uk/guidance/hst1
EV3. Goodship et al. 2017 Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. https://www.ncbi.nlm.nih.gov/pubmed/27989322
EV4. National Renal Complement Therapeutics Centre (NRCTC) 2016/17 Annual report http://www.atypicalhus.co.uk/wp-content/uploads/2018/03/NRCTC-Annual-Report.pdf or available on request.
EV5. NRCTC 2017/18 Annual report http://www.atypicalhus.co.uk/wp-content/uploads/2018/10/NRCTC-Annual-report-2017_18.pdf or available on request.
EV6. NRCTC 2018/19 Annual report http://www.atypicalhus.co.uk/wp-content/uploads/2019/12/Annual-Report-Final-Version-2018-2019.pdf or available on request.
EV7 NRCTC 2019/20 Annual report https://www.atypicalhus.co.uk/wp-content/uploads/2021/02/NRCTC-Annual-Report-2019-20.pdf or available on request.