Common Elements in Uncommon Kidney Diseases
Translation from Research to Clinical Care

Tim Goodship
Institute of Genetic Medicine
Newcastle University

Disclosure of Interests

- Alexion Pharmaceuticals - consultancy
- Akari Therapeutics - consultancy
- Omeros - consultancy

Translation from Research to Clinical Care

1. What are the positive practical outcomes for patients from improved translation from research to clinical care?
2. How to set up a clinical research collaborative network?
3. How to allow for successful trials in rare renal diseases?
4. How to ensure an optimal use of genetic services/genomics for the patients?
5. What is the best organization of care to ensure that clinical research develops and leads to clinical practice recommendations to the benefit of all?
6. What initiatives can boost drug development?
7. How to disseminate good practices for translational medicine?

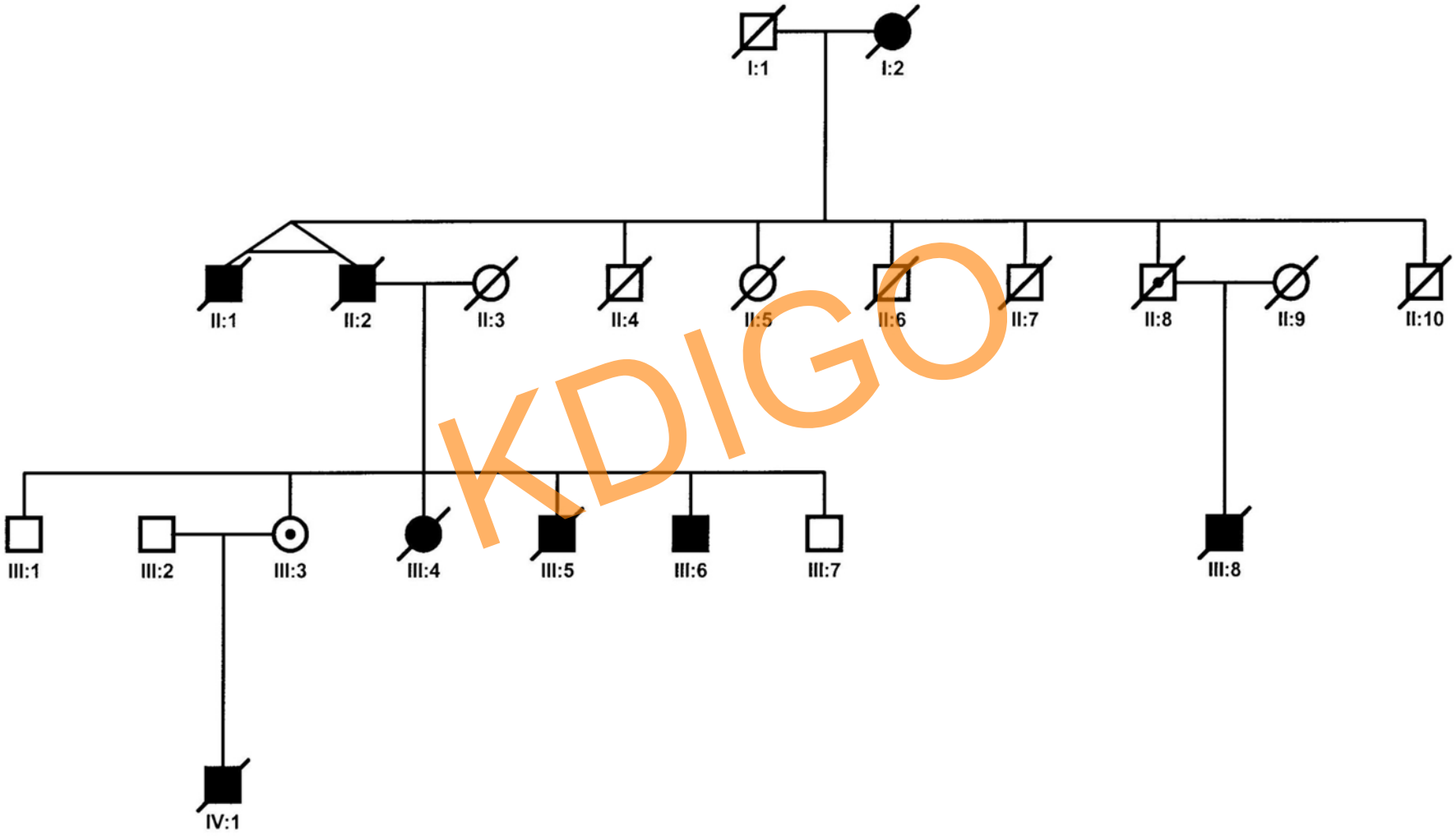
Translation from Research to Clinical Care Lessons from aHUS

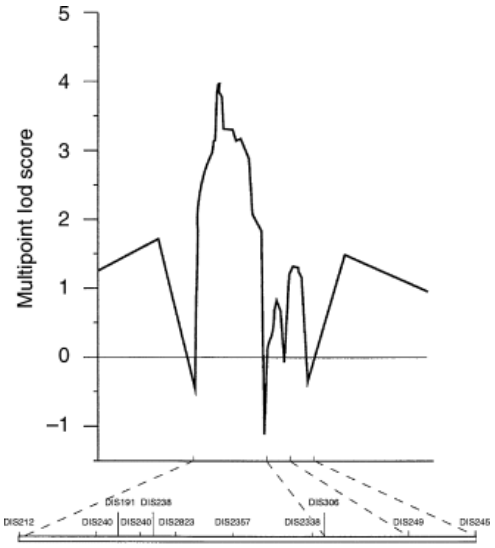
1. Studying families has been pivotal in understanding the molecular mechanisms responsible for the disease.
2. You need some luck.

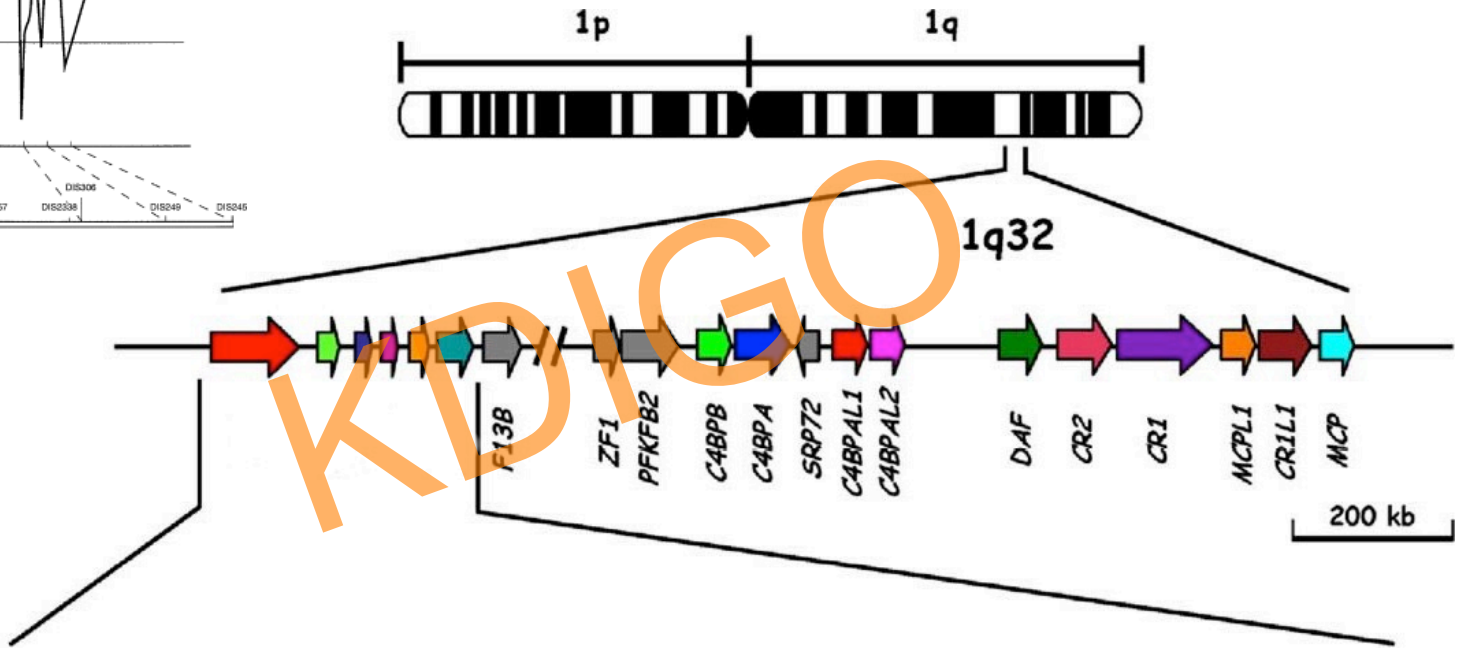
Rare condition strikes eight family members
Helen Rae, *Evening Chronicle*, July 23rd 2009

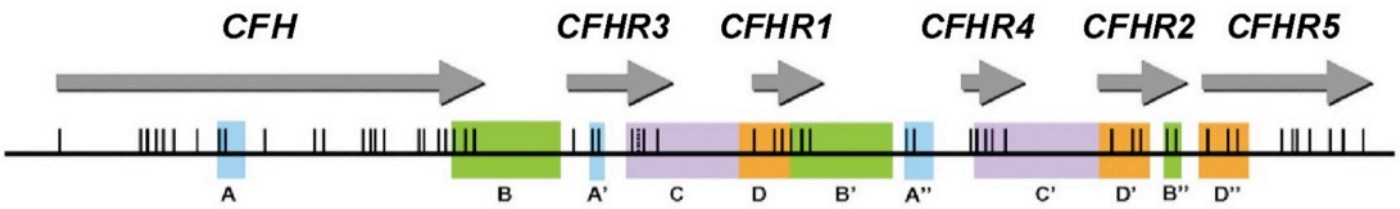
"Dad Shaun McCowie is living with a rare genetic condition that has killed seven members of his family. The 47-year-old has atypical hemolytic uremic syndrome (HUS), a form of kidney failure, and the genetic defect his family has been plagued with is believed to be one of only 10 cases in the world……. "

Newcastle Family 2016




Multipoint lod score
5
4
3
2
1
0
−1
D1S212
D1S240
D1S191
D1S238
D1S240
D1S2823
D1S2357
D1S306
D1S2338
D1S249
D1S245

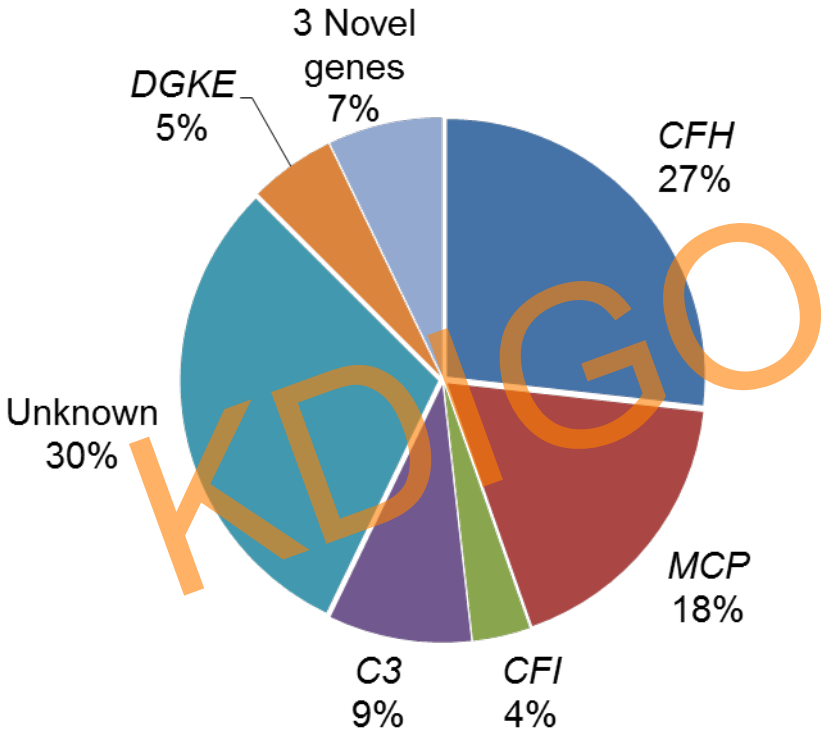

1p
1q
1q32
F13B
ZF1
PFKFB2
C4BPB
C4BPA
SRP72
C4BPAL1
C4BPAL2
DAF
CR2
CR1
MCPL1
CR1L1
MCP
200 kb


CFH
CFHR3
CFHR1
CFHR4
CFHR2
CFHR5
A
B
A'
C
D
B'
A''
C'
D'
B''
D''

Translation from Research to Clinical Care Lessons from aHUS

1. Studying families has been pivotal in understanding the molecular mechanisms responsible for the disease.
2. You need some luck.
3. Data sharing is essential for unsolved families.

Familial aHUS – Newcastle cohort

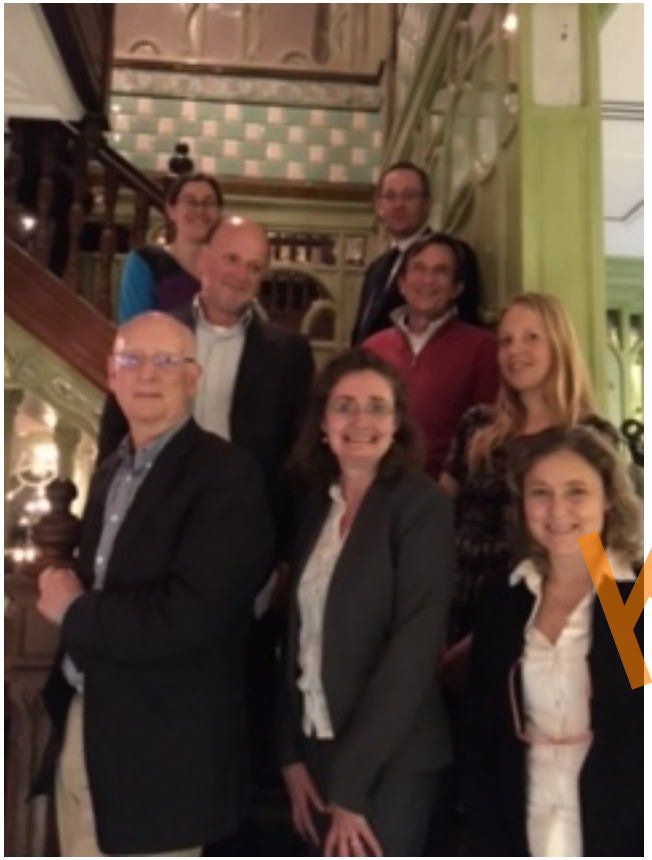


56 families in total


ClinGen
Clinical Genome Resource
ClinGen Genome Connect
AGTC
Centers for Mendelian Genomics
JOHNS HOPKINS MEDICINE
Gene Matcher
BCM
Baylor College of Medicine
CARE forRARE
Phenome Central
Phenome Central
Café Variome
Monarch
monarch INITIATIVE
DECIPHER
wellcome trust sanger institute
DECIPHER GRCh37
Matchmaker Exchange
LOVD
LOVD
Leiden Open Variation Database
Undiagnosed Diseases Network
UDN
Undiagnosed Diseases Network
BROAD RDAP
BROAD INSTITUTE
GENESIS/ GEM.app
MIAMI
PEER
RD Connect
THE GENESIS PROJECT
PrivateAccess
Genetic Alliance
PEER
RD Connect

Translation from Research to Clinical Care Lessons from aHUS

1. Studying families has been pivotal in understanding the molecular mechanisms responsible for the disease.
2. You need some luck.
3. Data sharing is essential for unsolved families.
4. Collaboration can be extraordinarily fruitful.



Database of complement gene variants

Home | Advanced Search | Variants ▼ | Structures | AA Alignments | Resources ▼ | Site Map | Log out

aHUS, C3G and AMD associated genetic variants

Since the first reports in 1998 by Warwicker et al, predisposition to aHUS is due to variants in the genes that code for proteins of the alternative pathway (AP) of complement. There are currently 1019 unique genetic variants (438 literature sourced, 617 laboratory sourced, and 190 with no patient associated) compiled within this database, corresponding to 832 literature sourced and 1143 laboratory sourced cases.

What can you do in this database?

You can search for genetic variants reported in the *ADAMTS13*, *C3*, *CD46*, *CFB*, *CFH*, *CFHR1*, *CFHR1*, *CFHR2*, *CFHR3*, *CFHR3*, *CFHR5*, *CFHR5*, *CFI*, *CFP*, *DGKE*, *PLG*, *THBD* and *THBD* genes which may have an association with aHUS, AMD, C3G, 'Healthy', TMA and TTP by using the 'Simple Search' tools on the right hand side or by clicking 'Advanced Search' on the menu bar. The search result will display variant sequence, phenotype, structural, functional and allele frequency information.

Citing us

1. Osborne AJ et al, (2016) Database of Complement Gene Variants: a comprehensive database providing insights on function, structure and allele frequency for genetic variants identified in complement-mediated diseases. ABSTRACT for EURenOmics conference, Paris, 11th-13th May 2016 (hover to display)
2. Rodriguez E et al (2014) New functional and structural insights from updated mutational databases for complement factor H, factor I, membrane cofactor protein and C3. Biosci Rep. 34(5)
3. Saunders RE et al (2007) The interactive Factor H-atypical hemolytic uremic syndrome mutation database and website: update and integration of membrane cofactor protein and Factor I mutations with structural models. Hum Mutat. 28(3):222-34
4. Saunders RE et al (2006) An interactive web database of factor H-associated hemolytic uremic syndrome mutations: insights into the structural consequences of disease-associated mutations. Hum Mutat. 27(1):21-30

HGVS numbering ▼

Transcript and protein IDs ▼

Have you or someone you know been diagnosed with aHUS, C3G or AMD? ▼

Acknowledgements ▼

News and updates; latest release: Version 3.0 ▼

Simple Search

Reset all

Source of data

---Select---

Gene

Select source first

cDNA, amino acid number or variant type

Select gene first

CFH (FH) c.2867C>T p.Thr956Met (938) The 1000 Genomes Project AF: 0.00120

Location: Exon(18) **Variant Type:** Point **Variant Effect:** Missense
Domain: SCR16 **Transcript:** ENST00000367429 **Genomic:** 196709833 [GRCh37]
Phenotype ►

ID	FH level	C3 level	FI level	MCP level	AntiFH Ab	Zygosity	Disease inheritance	Other Variants	Condition	Reference
111L1	0.87	1.76	0.069			Heterozygous	Sporadic		aHUS	L1
116L1						Heterozygous	Sporadic		aHUS	L1
159L1	0.59	0.07	0.052			Heterozygous	Sporadic	*CFI*: c.1657C>T (p.Pro553Ser)	MPGN I	L1
161L1	0.7	1.05	0.077		Negative	Heterozygous	Sporadic		aHUS	L1
171L1	0.75	1.12	0.058		Negative	Heterozygous	Sporadic		aHUS	L1
175L1						Heterozygous	Sporadic		MPGN I	L1
223L1	0.5	0.68	0.059		Negative	Heterozygous	Sporadic		C3GN	L1
1834L2						Heterozygous	Unknown		MPGN	L2
1358L2						Heterozygous	Unknown		MPGN	L2
15-20L3					Negative	Heterozygous	Sporadic	*DGKE*: c.445C>G (p.Pro149Ala)	Unknown	L3
15-85L3	52.7	1.1	20		23 AU	Heterozygous	Sporadic		aHUS	L3
15-84L3	52.7	1.1	20		Negative	Heterozygous	Sporadic		aHUS	L3
32L4						Heterozygous	Sporadic		aHUS	L4

Allele Frequency ►

aHUS population

Allele Count (AC)	No. of patients screened for *CFH*	Allele Number (AN)	Allele Frequency (AF) estimate
8	2494	4988	0.001604

C3G population

Allele Count (AC)	No. of patients screened for *CFH*	Allele Number (AN)	Allele Frequency (AF) estimate
5	450	900	0.005556

Control population

dbSNP: rs145975787

The 1000 Genomes Project:

1000 GP Alleles	1000 GP Allele	1000 GP Allele Frequency (AF)	
C/T (2)	T	0.001198080	Chi-square test

ExAC:

ExAC Ethnicity	ExAC Allele Count (AC)	ExAC Allele Number (AN)	ExAC Allele Frequency (AF)	
ALL	147	121400	0.001211000	Chi-square test
African	4	10406	0.000384	
European	87	66734	0.001304	
East Asian	0	8650	0	
Finnish	0	6614	0	
Latino	5	11576	0.000432	
Other	2	908	0.002203	
South Asian	49	16512	0.002968	

Exome Variant Server (EVS):

EVS Ethnicity	EVS Alleles	EVS Allele	EVS Allele Count (AC)	EVS Allele Number (AN)	EVS Allele Frequency (AF)	
ALL	C/T (2)	T	15	13006	0.001153	Chi-square test
European-American	C/T (2)	T	14	8600	0.001628	
African-American	C/T (2)	T	1	4406	0.000227	

Structure and Function ►

No functional or structural studies for this variant (c.2867C>T) currently exist in the database.

Please click here to view the mapping of this variant onto the latest FH structure and view the functional analysis by PolyPhen-2 and SIFT.

Translation from Research to Clinical Care Lessons from aHUS

1. Studying families has been pivotal in understanding the molecular mechanisms responsible for the disease.
2. You need some luck.
3. Data sharing is essential for unsolved families.
4. Collaboration can be extraordinarily fruitful.
5. We should aspire to undertake RCTs.

ORIGINAL ARTICLE

Terminal Complement Inhibitor Eculizumab in Atypical Hemolytic–Uremic Syndrome

C.M. Legendre, C. Licht, P. Muus, L.A. Greenbaum, S. Babu, C. Bedrosian, C. Bingham, D.J. Cohen, Y. Delmas, K. Douglas, F. Eitner, T. Feldkamp, D. Fouque, R.R. Furman, O. Gaber, M. Herthelius, M. Hourmant, D. Karpman, Y. Lebranchu, C. Mariat, J. Menne, B. Moulin, J. Nürnberger, M. Ogawa, G. Remuzzi, T. Richard, R. Sberro-Soussan, B. Severino, N.S. Sheerin, A. Trivelli, L.B. Zimmerhackl,* T. Goodship, and C. Loirat

ABSTRACT

BACKGROUND

Atypical hemolytic–uremic syndrome is a genetic, life-threatening, chronic disease of complement-mediated thrombotic microangiopathy. Plasma exchange or infusion may transiently maintain normal levels of hematologic measures but does not treat the underlying systemic disease.

METHODS

We conducted two prospective phase 2 trials in which patients with atypical hemolytic–uremic syndrome who were 12 years of age or older received eculizumab for 26 weeks and during long-term extension phases. Patients with low platelet counts and renal damage (in trial 1) and those with renal damage but no decrease in the platelet count of more than 25% for at least 8 weeks during plasma exchange or infusion (in trial 2) were recruited. The primary end points included a change in the platelet count (in trial 1) and thrombotic microangiopathy event–free status (no decrease in the platelet count of >25%, no plasma exchange or infusion, and no initiation of dialysis) (in trial 2).

RESULTS

A total of 37 patients (17 in trial 1 and 20 in trial 2) received eculizumab for a median of 64 and 62 weeks, respectively. Eculizumab resulted in increases in the platelet count; in trial 1, the mean increase in the count from baseline to week 26 was 73×10^9 per liter ($P<0.001$). In trial 2, 80% of the patients had thrombotic microangiopathy event–free status. Eculizumab was associated with significant improvement in all secondary end points, with continuous, time-dependent increases in the estimated glomerular filtration rate (GFR). In trial 1, dialysis was discontinued in 4 of 5 patients. Earlier intervention with eculizumab was associated with significantly greater improvement in the estimated GFR. Eculizumab was also associated with improvement in health-related quality of life. No cumulative toxicity of therapy or serious infection-related adverse events, including meningococcal infections, were observed through the extension period.

CONCLUSIONS

Eculizumab inhibited complement-mediated thrombotic microangiopathy and was associated with significant time-dependent improvement in renal function in patients with atypical hemolytic–uremic syndrome. (Funded by Alexion Pharmaceuticals; C08-002 ClinicalTrials.gov numbers, NCT00844545 [adults] and NCT00844844 [adolescents]; C08-003 ClinicalTrials.gov numbers, NCT00838513 [adults] and NCT00844428 [adolescents]).

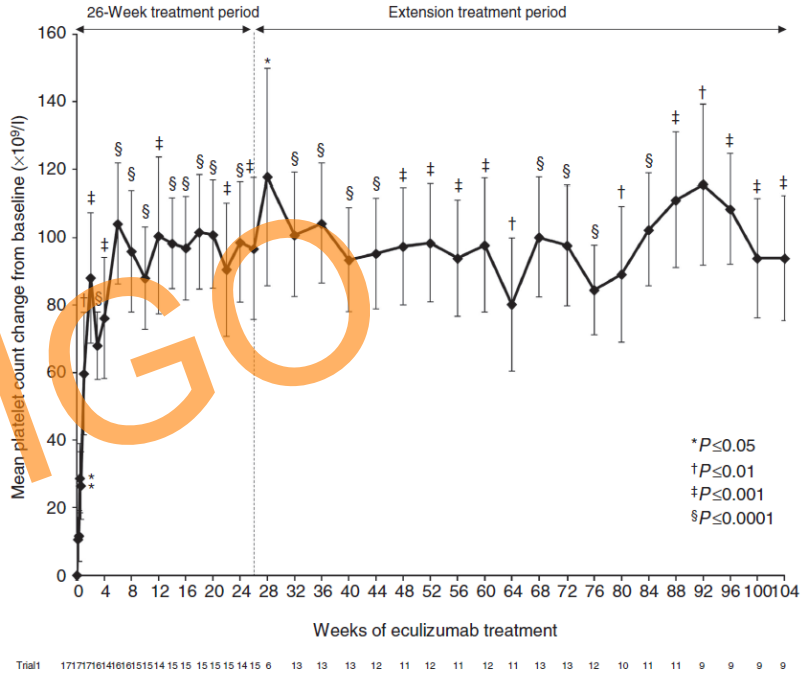


Figure 3 | Mean change from baseline in platelet counts over 2 years of eculizumab treatment in trial 1 ($P = 0.001$ at the 2-year cutoff). Bars represent s.e.

Translation from Research to Clinical Care Lessons from aHUS

1. Studying families has been pivotal in understanding the molecular mechanisms responsible for the disease.
2. You need some luck.
3. Data sharing is essential for unsolved families.
4. Collaboration can be extraordinarily fruitful.
5. We should aspire to undertake RCTs.
6. Be prepared for a tortuous, painful journey to obtain approval for the use of expensive therapies.

NICE National Institute for Health and Care Excellence

Eculizumab for treating atypical haemolytic uraemic syndrome

NICE guidance

Highly specialised technology guidance

Published: 26 January 2015

nice.org.uk/guidance/hst1

THE TIMES

Max 12C min -8C

Wednesday January 28 2015 | thetimes.co.uk | No 71417

Only 60p to print members £1.20

2 You think Britain's cold, try Svalbard

Damian Whitworth braves the location of the latest Scandi thriller

What they wore at Paris couture Times2

Doctors get green light for drug costing £10m a patient

Chris Smyth Health Editor

A drug that costs up to £10 million per patient will be made available on the NHS after the treatments watchdog approved its most expensive medicine.

Eculizumab, also known as Soliris, can be the difference between life and death for about 200 people with a rare kidney condition and will cost the NHS up to £82 million a year.

The National Institute for Health and Care Excellence (NICE) said that the drug offered gains "of a magnitude that is rarely seen for any new drug treatment", allowing people to live independently for decades.

The adviser approved the drug through a process for ultra-rare conditions, which does not involve assessment by its standard value-for-money formula. NICE says that it is unfair to apply normal cost standards to such a rare condition, where drug companies have to recoup their research costs from only a handful of patients.

The decision comes amid dissatisfaction over the NHS system for funding cancer drugs that can offer a few extra months of life at a cost of tens of thousands of pounds per patient. Drugs rejected by NICE are then paid for by the government's Cancer Drugs Fund, which itself stopped a quarter of its treatments this month on cost grounds.

Eculizumab has been described as a "significant breakthrough", which, on average, offers patients with atypical Haemolytic Uraemic Syndrome (aHUS) an extra 25 years of good-quality life.

NICE judged that this made it worth the annual £340,000 cost per patient to the NHS, even as it criticised the drug's maker for not fully justifying the

Continued on page 6, col 4

Translation from Research to Clinical Care Lessons from aHUS

1. Studying families has been pivotal in understanding the molecular mechanisms responsible for the disease.
2. You need some luck.
3. Data sharing is essential for unsolved families.
4. Collaboration can be extraordinarily fruitful.
5. We should aspire to undertake RCTs.
6. Be prepared for a tortuous, painful journey to obtain approval for the use of expensive therapies.
7. Patient/family/carer organisations are absolutely essential.


Save Lives
Not
Money


Third aHUS alliance meeting
28th june 2015 - LONDON
www.ahusalliance.org
UK - USA - Russia - Italy - France - Belgium - Australia
Germany - India - Sweden - Canada - Spain - Netherlands
KDIGO
aHUS alliance

Translation from Research to Clinical Care
Lessons from aHUS

1. Studying families has been pivotal in understanding the molecular mechanisms responsible for the disease.
2. You need some luck.
3. Data sharing is essential for unsolved families.
4. Collaboration can be extraordinarily fruitful.
5. We should aspire to undertake RCTs.
6. Be prepared for a tortuous, painful journey to obtain approval for the use of expensive therapies.
7. Patient/family/carer organisations are absolutely essential.
8. A national expert centre can help to optimise translation from research to clinical care.

Benefits of a national expert centre
Lessons from the aHUS expert centre in England

- 3 year period (April 2013 – March 2016) provided an aHUS expert centre for England
- 119 patients treated with eculizumab, 31 children and 88 adults, 76 incident and 43 prevalent, 81 still receiving treatment
- 28 patients transplanted with prophylactic eculizumab
- 35% mutation detection in incident patients. Mutation negative patients being entered into national WGS study (100,000 genomes)
- Provide all the specialist investigations
- Provide a service for the counselling of family members
- Hopefully a national study of withdrawal of treatment will start in 2017
- A national service for aHUS provides an infrastructure for patients to be treated with eculizumab when they need it for as long as they need it
- A locally delivered national service with oversight from an expert centre provides both local and national accountability

Translation from Research to Clinical Care Lessons from aHUS

1. Studying families has been pivotal in understanding the molecular mechanisms responsible for the disease.
2. You need some luck.
3. Data sharing is essential for unsolved families.
4. Collaboration can be extraordinarily fruitful.
5. We should aspire to undertake RCTs.
6. Be prepared for a tortuous, painful journey to obtain approval for the use of expensive therapies.
7. Patient/family/carer organisations are absolutely essential.
8. A national expert centre can help to optimise translation from research to clinical care.
9. Establish an appropriate, professional relationship with pharma.

Newcastle family 2016