aHUS: What are the challenges in short-term and long-term patient management?

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Disclosure of Interests

Research Grants

Wellcome Trust, Medical Research Council; Kidney Research UK, Northern Counties Kidney Research Fund; Fight for Sight, Macular Disease Society,

Consultancy

Syncon, Gemini, Biomarin, Alexion
Pathogenesis of aHUS

- Rare Genetic Complement Mutations
- Common Genetic SNPs
- Trigger

Eculizumab

KDIGO Controversies Conference on Complement-Mediated Kidney Diseases
November 19-21, 2015 | Barcelona, Spain
Short term- making the diagnosis

Multiple associations
Unmasking latent complement defect
Or
Direct effect
Short Term Management Challenges

Making the diagnosis

Currently diagnosis of exclusion

Clinical exclusion difficult

  e.g. malignant hypertension vs chronic TMA

  HELLP vs pregnancy associated aHUS

Currently no biomarker for disease

Genetics not immediately available

  Absence of a mutation not necessarily guide to treatment outcome

What subtypes should we currently be treating
How do we assess response

1st & 2nd Year UK National aHUS Service Incident patients
n=52

- Dialysis
  - n=37
  - No recovery of renal function
    - n=18
  - Recovery of renal function
    - n=19
- No Dialysis
  - n=15

Non Responders vs Late presenters
e.g. Polymorphism in C5 (p.R885H), DGKE
Monitoring eculizumab levels /complement blockade
Long Term Management Challenges

For patients with atypical Hemolytic Uremic Syndrome: (aHUS) Soliris® aHUS Dosing Guide

All patients must be vaccinated against Neisseria meningitidis at least 2 weeks prior to the first dose of Soliris therapy. Do not initiate Soliris therapy in patients with unresolved serious Neisseria meningitidis infection or who are not currently vaccinated, unless the risks of delaying Soliris treatment outweigh the risk of developing a meningococcal infection.¹

Soliris is a therapy for aHUS—a chronic disease needing chronic treatment¹
What is the evidence that aHUS is a chronic disorder requiring long term treatment?

Penetrance is low

Age of onset variable

Normal renal function until presentation with aHUS.
Long Term Management Challenges

Can Eculizumab be stopped?

AJKD
Case Report

Discontinuation of Eculizumab Maintenance Treatment for Atypical Hemolytic Uremic Syndrome: A Report of 10 Cases
Gianluigi Ardissino, MD, PhD, Sara Testa, MD, Ilaria Possenti, MD, Francesca Tel, MD, Fabio Pagliaroni, MD, Stefania Salardi, BS, Silvana Tedeschi, MD, Mirco Belingheri, MD, and Massimo Cugno, MD

ORIGINAL PAPER
A national specialized service in England for atypical haemolytic uraemic syndrome—the first year’s experience
N.S. Sheerin¹,³,*, D. Kavanagh²,³,*, T.H.J. Goodship²,³,*, and S. Johnson³,*
From the ¹Institute of Cellular Medicine, ²the Institute of Genetic Medicine Newcastle University and ³the Newcastle Upon Tyne Hospitals NHS Foundation Trust, UK
Long Term Management Strategies

When to stop
- If ESRF
- If dialysis independent

How do we monitor disease driven treatment
- LDH
- Platelets
- Hb
- Urinalysis
- What else

How Frequently?

Monitoring extra-renal manifestations
1st & 2nd Year UK National aHUS Service Incident patients

**Dialysis**
- n=37
  - No recovery of renal function
    - n=18
      - Ecu withdrawn
        - n=18
          - Extrarenal relapse
            - n=2
              - Ecu reintroduced
                - n=2
          - Death
            - n=3
              - Non compliant
              - Ponto-cerebellar hypoplasia I
              - Myocardial Infarction
      - Ecu continued
        - n=18
    - Ecu withdrawn
      - n=1

**No Dialysis**
- n=15
  - Ecu continued
    - n=10
  - Ecu withdrawn
    - n=5
    - Renal relapse
      - n=1
    - Ecu reintroduced
      - n=1
Extra-renal manifestations

- Cerebral (n=9/104)
  - CJASN 5:1844
- Pulmonary*
  - JASN 18:2392
- Hepatitis*
  - JASN 16:555
- Pancreatitis*
  - JASN 16:555
- Vascular Stenosis
  - NDT25:3421
- Cardiac (n=5/104)
  - CJASN 5:1844
- Ocular*
- Renal
- Intestinal

*Extra-renal manifestations
Extra-renal manifestations

Are the acute extra-renal manifestations secondary to:

1) the thrombotic microangiopathy
2) complement activation
3) uraemia and hypertension

Are the chronic extra-renal manifestations caused by:

1) long term renal failure / dialysis access
2) complement activation

If it is a consequence of complement activation how many of the sequelae will be treated by blockade at the level of C5
Whole-exome sequencing identifies rare, functional
CFH variants in families with macular degeneration

Yi Yu¹,², Michael P. Triebwasser²,¹, Edwin K. S. Wong³,⁴, Elizabeth C. Schramm²,¹, Brett Thomas⁴,
Robyn Reynolds¹, Elaine R. Mardis⁵, John P. Atkinson², Mark Daly⁶,⁷, Soumya
Raychaudhuri⁸,⁹,¹⁰, David Kavanagh³ and Johanna M. Seddon¹,¹¹,¹²,*

Rare genetic variants in the CFI gene are associated
with advanced age-related macular degeneration
and commonly result in reduced serum factor I levels

David Kavanagh¹, Yi Yu², Elizabeth C. Schramm³, Michael Triebwasser³,
Erin K. Wagner², Soumya Raychaudhuri⁴,⁵,⁶,⁷, Mark J. Daly⁴,⁵,⁸,
John P. Atkinson³ and Johanna M. Seddon²,⁹,¹⁰,*

Molecular Basis of Factor H R1210C Association with
Ocular and Renal Diseases

Sergio Recalde,* Agustín Tortajada, Marta Subias, Jaouad Anter, Miquel Blasco,
Ramona Maranta, Rosa Coco, Sheila Pinto, Marina Noris, Alfredo García-Layana,* and
Santiago Rodríguez de Córdoba†

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Ranica, Bergamo, Italy; and Institute of Applied Ophthalmology, University of Valladolid, Valladolid, Spain
Discussion points

• Short Term Management
  • Making the diagnosis
    • What tests are required
    • In a multiple hit model how can we be sure we are not undertreating
  • Can the classification of TMAs reflect treatment pathways
  • Identifying non responders

• Long Term Management
  • What is the evidence for chronic complement activation in aHUS?
  • What is the evidence for long term eculizumab treatment?
  • When should Eculizumab be stopped?
  • Should withdrawal be stratified
    • By genetics/autoantibodies
  • How should disease driven treatment be monitored

• Extra-renal manifestations
  • What symptoms are a direct effect of a TMA and what are a secondary effect of CRF/dialysis
  • In ESRF what symptoms require treatment
  • How do we monitor patients for extra-renal manifestations