aHUS: a chronic, systemic disease with life-threatening consequences

Dr Peter Hughes – Nephrologist, Royal Melbourne Hospital

aHUS is a disease of complement-mediated TMA largely caused by genetic deficiencies of complement regulators. It is defined by a decreased platelet count and evidence of both microangiopathic haemolysis and organ impairment/damage. The majority of patients with aHUS (63%) have organs other than just the kidneys involved, with progression of extrarenal vascular lesions without other symptoms of TMA. Many conditions may unmask aHUS. Due to incomplete genetic penetrance, it is a complex disease to recognise, as it can occur in the context of other diseases, which often precipitate the start of aHUS. This can occur at any age (although there appears to be a cluster of patients who present before 5 years of age).

Outcomes associated with aHUS have been poor, with death or progression to ESRD associated with the initial clinical manifestation in 33–40% of patients, a 10–15% mortality rate in the initial phase of the disease, and 65–70% of all patients dying, requiring dialysis or having permanent renal damage within the first year despite receiving plasma exchange or infusions.

aHUS is associated with chronic uncontrolled activation of complement on endothelial cell surfaces leading to devastating consequences (Figure 1). The complement system may be activated by the lectin, classical or alternative system. Genetic mutations in aHUS predominantly affect plasma or cell surface factors that are involved in control of the alternative pathway. The uncontrolled complement activity results in ongoing vascular endothelial injury, leading to TMA lesions that may progress to irreversible damage (Figure 2).

Figure 1. Complement pathways involved in aHUS

Figure 2. Endothelial damage leading to TMA

Abbreviations used in this review:

aHUS = atypical haemolytic uraemic syndrome
CV = cardiovascular
ESRD = end-stage renal disease
GFR = glomerular filtration rate
GI = gastrointestinal
LDH = lactate dehydrogenase
QOL = quality of life
TMA = thrombotic microangiopathy
TTP = thrombotic thrombocytopenic purpura

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Knowledge of the different aetiologies of TMAs has increased over the last 15 years. The clinical presentations of the different types are similar, but the underlying causes differ.\(^8,23,25,27,29,36–43\) Besides aHUS, important differentials are: i) TTP, which is mostly seen in adults and is caused by defects in the cleavage of von Willebrand factor multimers due to severe deficiency of ADAMTS13 activity. This can be congenital or due to an inhibitory antibody; and ii) particularly in children, Shiga toxin-producing bacteria (STEC-HUS, e.g. *Escherichia coli*), which bind directly to and damage endothelial cells, triggering uncontrolled complement activation.

**Differential diagnosis of TMA**

Differentiating between the types of TMA is becoming increasingly clinically important as the treatments are starting to differ; e.g. there are agents now being trialled that are specific for TTP and a specific treatment for aHUS is available (Figure 3).\(^2,8,23,25,27,29,36–43\) Three diagnostic tests are useful for achieving a quick and accurate diagnosis (Table 1).\(^2\) It is important to do an ADAMTS13 test in all patients at presentation, as treatment before the test can interfere with the results. ADAMTS13 tests can be done at a number of laboratories across Australia, and results can usually be obtained in 1–2 days. Complement level testing can also be considered, but doesn’t always help achieve a diagnosis as serum C3 and CFH levels are often normal in patients with aHUS.\(^1\) While genetic tests are becoming available in Australia now, they are not very helpful for the initial diagnosis and management of patients, as 30–50% of patients with aHUS have no genetic mutation identified, not all mutations are known and the results can take weeks to months.\(^2,16,39,44\) However, genetic testing may be important if considering a transplant in a patient with aHUS. A reliance on clinical features alone to differentiate between TMAs can also prove problematic; historically it was considered that neurological features were more characteristic of TTP and kidney involvement of aHUS; however, a recent analysis of French registry data showed that neurological features are just as common in both diseases. Similarly, the presence of GI symptoms has been used to diagnose STEC-HUS, but patients with aHUS frequently have diarrhoea and other GI symptoms. Patients with ADAMTS13 activity <5–10% are classified as having TTP, those who are Shiga toxin-positive have STEC-HUS, and the remainder can be classified as having aHUS.\(^2,8,23,40–43\)

**Clinical symptoms and organs involved**

The clinical picture of TMA can be difficult to elucidate, particularly due to patients presenting with another illness, multiple organ involvement and the presence of chronic complement activation. Clinical symptoms are varied (Table 2), with neurological symptoms seen in around half of patients and >50% progressing to ESRD.\(^1,25\) CV abnormalities are probably under-recognised, but are increasingly being reported. Reported rates of complications in a retrospective chart review of 30 patients with aHUS were 100% renal, 47% CV, 37% GI and 20% neurological, with 63% having complications in >1 system.\(^9\)

<table>
<thead>
<tr>
<th>Renal</th>
<th>Neurological</th>
<th>Haematological</th>
<th>CV</th>
<th>GI</th>
<th>Pulmonary</th>
<th>Visual</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESRD; Elevated creatinine level; Proteinuria; Deterioration due to convulsion; Encephalopathy; Seizures</td>
<td>Confusion; Stroke; Encephalopathy; Seizures</td>
<td>Thrombocytopenia; Decreased haptoglobin or haemoglobin level; Elevated LDH level; Schistocytes</td>
<td>Myocardial infarction; Hypertension; Diffuse vasculopathy; Peripheral gangrene; Cardiomyopathy</td>
<td>Colitis; Nausea/vomiting; Pancreatitis; Abdominal pain; Gastroenteritis; Hepatic necrosis</td>
<td>Dyspnoea; Pulmonary haemorrhage; Pulmonary oedema</td>
<td>Ocular occlusion</td>
</tr>
</tbody>
</table>

**Table 1. Important tests for TMA differential diagnosis**

<table>
<thead>
<tr>
<th>Test</th>
<th>Use</th>
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</thead>
<tbody>
<tr>
<td>ADAMTS13</td>
<td>Recommended to differentiate aHUS from severe ADAMTS13 deficiency</td>
</tr>
<tr>
<td>Clinical assessment</td>
<td>Platelet count &gt;30×10^9/L Serum creatinine level &gt;150–200 µmol/L almost eliminates a diagnosis of severe ADAMTS13 deficiency (while waiting for ADAMTS13 test results)(^6)</td>
</tr>
<tr>
<td>Shiga toxin test</td>
<td>Recommended for patients with historical or current GI symptoms to differentiate aHUS from STEC-HUS</td>
</tr>
</tbody>
</table>

**Figure 3. Schema of differential diagnosis of TMA**\(^2,8,23,25,27,29,36–43\)
Of note, anaphylactoid type reactions appear to 

Table 3.

<table>
<thead>
<tr>
<th>Complications of plasma exchange/infusion</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Hypotension requiring fluid infusion</td>
<td>48%</td>
</tr>
<tr>
<td>Hypocalcaemia</td>
<td>64%</td>
</tr>
<tr>
<td>Allergic reactions</td>
<td>24%</td>
</tr>
<tr>
<td>Serious vascular complications during 1632 apheresis procedures</td>
<td>48%</td>
</tr>
</tbody>
</table>

Complications in children receiving 1093 plasma exchange procedures

Dialysis

Patients receiving dialysis may still exhibit symptoms of TMA, with systemic complement activation likely to be ongoing, the degree of which depends on mutation. They also have significant rates of other organ involvement (e.g. gut disease, cardiomyopathy), which might be effective includes replacement of dysfunctional or absent regulatory proteins and removal of antibodies, if present.

Overall, plasma exchange/infusion is of limited success for treating aHUS, as it is often ineffective. There are also many complications associated with its use, such as line- or access-related complications, and it is an extremely difficult treatment to undertake in children. There are also significant associated cost factors. Outcomes associated with standard of care therapy are highly variable according to which high-risk patients with factor H mutations typically having very poor outcomes (predominantly driven by ESRD during the first 12 months).

Audits have shown numerous problems associated with plasma exchange. Around a quarter of adults experience major complications, including life-threatening complications, while such issues are seen in around half of children receiving this treatment (Table 3). Of note, anaphylactoid type reactions appear to be more common in aHUS than transplanted patients, possibly due to less immunosuppression. Asssoc Prof Isbel showed that data for five patients treated at her institution, which illustrated how much plasma product is required to treat patients contrasted against consistently poor outcomes (Figure 4).
Transplantation

Historical data show that transplanted adults have a 60% aHUS recurrence rate if the mutation is unknown, which is associated with 90% graft loss. Over half of these (60%) occur within 1 month of transplantation and are usually unresponsive to plasma exchange. Lack of response to plasma exchange in early recurrence is probably due to the use of calcineurin inhibitors, but the relapse rate is the same if a calcineurin inhibitor-free regimen is used. Patients with early recurrence probably also have a higher risk of antibody-mediated rejection.

The risk of aHUS recurrence can be better assessed when genetic mutations are known. Factor H mutations have the higher relapse rate (75–90%), while MCP mutations have a recurrence rate of 15–20%, due to the fact that theoretically normal MCP is introduced with the graft (being a membrane-bound protein). However, many patients have >1 mutation and some ‘extra’ mutations are not initially identified with older sequencing methods. As gene sequencing technologies continue to improve, more comprehensive results should follow.

Combined liver-kidney transplants may be considered, as the liver has an important role in synthesising circulating complement components (e.g. factors I and H). However, liver transplantation is associated with a great deal of procoagulant activity and endothelial disturbance. Profound haemolysis was a limiting feature of early combined transplants, but modified protocols have meant that seven of eight such transplants in patients with factor H mutations were successful, and only one was not due to hepatic artery thrombus.

Clinical trial experience with eculizumab

A new approach for treating aHUS is needed, and based on the known mechanisms of the disease, a monoclonal antibody logically should offer a solution. Eculizumab is a humanised monoclonal antibody directed at C5 (the pivotal point in the complement pathway for the development of aHUS) that prevents its cleavage and therefore the formation of membrane attack complex (Figure 1). The advantage of blocking C5 is that the early part of the complement cascade is preserved, allowing for continued opsonisation of micro-organisms and clearance of immune complexes and apoptotic bodies.

Eculizumab’s half-life is 11–12 days, allowing for long intervals between doses. The standard regimen is weekly 35-minute IV infusions at 900mg for adults for 4 weeks’ induction, followed by maintenance dosing at 1200mg every 2 weeks. The dose is bodyweight adjusted for adolescent and paediatric patients.

The Alexion Pharmaceuticals multinational clinical programme of 26-week prospective trials of eculizumab for aHUS has now recruited 100 participants (Table 4). Thirty-two participants from the two CO8 trials were enrolled in long-term extension studies of chronic eculizumab, and participants from the two C10 trials are also involved in ongoing long-term extension periods. C11-003 is a long-term follow-up study of all four trials. There were subtle differences across the trials for the primary endpoints, and secondary endpoints across the trials included haematological normalisation, renal function normalisation, platelet count normalisation, health-related QOL measures and safety/tolerability.

Table 4. Characteristics of trials of eculizumab for aHUS

<table>
<thead>
<tr>
<th>Trial</th>
<th>Participants</th>
<th>Primary endpoint(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C10-003&lt;sup&gt;11&lt;/sup&gt;</td>
<td>22 paediatric patients with earlier diagnosis and treatment</td>
<td>Complete TMA response at 26 weeks*</td>
</tr>
<tr>
<td>C10-004&lt;sup&gt;11&lt;/sup&gt;</td>
<td>41 adults with earlier diagnosis and treatment</td>
<td>Change in platelet count Haematological normalisation*</td>
</tr>
<tr>
<td>C08-002&lt;sup&gt;11,13&lt;/sup&gt;</td>
<td>17 adults and adolescents with aHUS with active progressing TMA</td>
<td>TMA event-free status Haematological normalisation**</td>
</tr>
<tr>
<td>C08-003&lt;sup&gt;11,10&lt;/sup&gt;</td>
<td>20 adults and adolescents with long duration of aHUS and chronic kidney disease</td>
<td></td>
</tr>
</tbody>
</table>

* normal platelet count and LDH level, and ≥25% improvement in baseline serum creatinine level on 2 consecutive measurements ≥4 wks apart

** normal platelet count and LDH level for ≥2 consecutive measurements ≥4 wks apart

Data from the C08 and the C10 trials provide some interesting insights in terms of the drug’s mechanism depending on how long the disease has been present. In the C08-002 and C08-003 trials, the median times from diagnosis to baseline were 9.7 and 48.3 months, respectively. Less than one-third of participants were receiving dialysis and all had received plasma exchange/infusions prior to eculizumab. In the C10-003 and C10-004 studies, the median duration from diagnosis to baseline visit was <1 month<sup>14,15</sup>. Over half the C10 trial participants were receiving dialysis and not all had received plasma exchange/infusions, with more (especially the paediatric participants) receiving eculizumab as first-line treatment. The length of time the patients were treated helps explain differences seen in renal outcomes and illustrates the importance of prompt diagnosis and treatment of aHUS.

There are a number of key benefits of eculizumab therapy. Primarily, it quickly, completely and sustainably inhibits uncontrolled complement activity in all patients with aHUS (Figure 5), regardless of genetic mutations. An important consideration is to stop plasma exchange/infusion so that the agent is not removed. There is a differential response to eculizumab with regard to the various features of aHUS, with haematological markers initially improving quickly; all four trials showed normalisation of haematological parameters and platelet counts at 26 weeks in over three-quarters of participants.”

<sup>1</sup>Transplant (27 Nov 2011)
<sup>2</sup>Dialysis (25 Mar 2005)
<sup>3</sup>Declining graft function (Chronic TMA)
<sup>4</sup>Haematological normalisation**
<sup>5</sup>Change in platelet count
<sup>6</sup>Complete TMA response at 26 weeks*
Renal function
Response to treatment with eculizumab varies according to the duration of the disease prior to treatment. It is clear that patients treated early experience greater improvements in renal function than those with long disease duration (Figure 6).\textsuperscript{9,10,13–15} In the C10-003 trial, participants were younger and diagnosed earlier. These patients typically exhibited a steady increase in estimated GFR over ~2 months after starting eculizumab, after which it stabilised at a mean 64 mL/min/1.73m\(^2\) above baseline.\textsuperscript{11} In contrast, adult patients from C10-004 exhibited a slower, but still steady, increase in estimated GFR to a mean of 29 mL/min/1.73m\(^2\) above baseline.\textsuperscript{12,13} with sustained improvements in the follow-up studies. The data also suggest that patients presenting with anuria can improve with eculizumab. Dialysis discontinuation rates were 80–83% among the participants in the C08-002, C10-003 and the C10-004 trials in those with anuria can improve with eculizumab. Dialysis discontinuation rates were 80–83% among the patients in the C08-002, C10-003 and the C10-004 trials in those diagnosed early.\textsuperscript{9,10,13–15} Data out to 2 years do suggest that patients continue to have improved renal function with chronic eculizumab therapy. Although it is still not clear if/when patients receiving eculizumab while on dialysis should discontinue treatment, there still appears to be hope their renal function can improve.

The case of a 38-year-old woman with symptoms and a family history of aHUS was presented. After eculizumab was started (and plasma exchange discontinued), her platelet count quickly normalised, followed by her LDH level, and her renal function had also improved considerably at ~8 months. After eculizumab was started (and plasma exchange discontinued), her platelet count quickly normalised, followed by her LDH level, and her renal function had also improved considerably at ~8 months.

Figure 6. Renal function improvements with eculizumab treatment\textsuperscript{9,10,13–15}

Safety
Eculizumab’s safety and tolerability profile is well established and most trial-reported adverse events have been moderate to mild with no new safety concerns or deaths reported.\textsuperscript{11,12,15} In the C10-003 trial, there was one withdrawal due to severe agitation, but no meningococcal infections, while two C10-004 participants experienced a meningococcal infection, both of whom recovered (one discontinued the trial). Current data suggest that meningococcal infection occurs at a rate of 4 per 1000 patient-years among eculizumab recipients, and the drug comes with a Boxed Warning advising of the risk. Vaccination is advised and antibiotic cover is recommended if eculizumab is started before vaccination is complete. Because of this risk, the importance of prompt medical advice in the event of feeling unwell should be emphasised to patients receiving eculizumab.

Difficult questions and unknowns
How to approach the presentation of aHUS is something that is becoming well understood; e.g., assessment, excluding TTP and STEC-HUS. There is no need to demonstrate a genetic mutation before starting treatment. In the UK and France, eculizumab is now recommended as first-line therapy for children with aHUS. There are also a number of papers suggesting that transplanting with eculizumab for patients on dialysis with high-risk mutations (factor H, factor I, C3) or previous graft loss from recurrence should be standard of care.

Another important unknown is if and when eculizumab therapy should be stopped, bearing in mind patients with aHUS have a persistent underlying complement disorder. The frequency of relapses is very unpredictable, and recognition of subclinical injury and other organ damage is important. It is not known if restarting eculizumab for a relapse after withdrawal will be effective. Data from Alexion Pharmaceuticals show that 5/18 patients with longstanding/relapsing disease in the original registration studies who deviated from the approved dosing schedule experienced severe TMA-related complications, whereas patients who adhered to the protocol had complete inhibition of terminal complement out to 2 years. A number of regulatory bodies have suggested that eculizumab should be lifelong therapy due to the high risk of severe TMA complications and loss of significant, continuous, time-dependent clinical improvements on discontinuation.

A paper recently published has reported on 10/22 eculizumab-treated patients with aHUS who discontinued the agent; all patients had undergone genetic testing.\textsuperscript{17} It was found that patients with factor H mutations relapsed earlier after treatment discontinuation and resumed eculizumab. Patients with other mutations stayed off drug for longer. The issue that is not fully understood is what the implications are for relapse in the long term, particularly if patients develop other illnesses or become injured or pregnant.

Assoc Prof Isbel finished her presentation by talking about the importance of the multinational Alexion-sponsored aHUS registry and the Melbourne-based TTP/TMA registry for collecting data on the disease.

Figure 5. Quick, complete and sustained inhibition of complement activity in patient with aHUS\textsuperscript{9,10,13–15}
Take home points

- Treatment of aHUS with eculizumab results in significant improvements in haematological and renal outcomes
- There are case reports of improvements in extrarenal complications
- Early diagnosis and treatment is key
- Eculizumab is safe and well tolerated
- Future registry data will hopefully help answer some of the unanswered questions

References


Prof Toby Coates – Nephrologist, Royal Adelaide Hospital

The case of a 21-year-old male was presented. He had initially presented at age 13 months with aHUS and was treated with dialysis. He had numerous subsequent admissions, and was partially responsive to plasma exchange with a persistently low C3 level. He started chronic dialysis at the age of 4 years (early 1999), and later that same year he underwent bilateral nephrectomies for intractable hypertension. Living related-donor renal transplantation was performed 3 years later without complication.

Four years after his transplant, his serum creatinine level began to slowly increase. A renal biopsy revealed focal areas of scarring, and his immunosuppressant was switched from tacrolimus to sirolimus. The following year his condition deteriorated, and he was diagnosed with aHUS and renal failure and treated with plasma exchange. Thrombotic microangiopathy was confirmed on biopsy and his C3 level was low. He did not respond to plasma exchange, so his graft was eventually removed and he began long-term peritoneal dialysis, a second transplant was advised against. Genetic testing revealed a homozygous mutation of factor I, which at that time had not been described.

He underwent a deceased-donor renal transplant without complication. He received plasma exchange, tacrolimus, mycophenolate mofetil and prednisolone. His serum creatinine level decreased to 190–200 µmol/L. Two post-transplant protocol biopsies at days 7 and 14 revealed probable acute tubular necrosis with no acute rejection. He was presumed to have aHUS toxicity due to high concentrations of the drug at peak 2. Two weeks post-transplant his serum creatinine level began to increase. He experienced a bleed and became anuric on post-transplant day 18, and this haemoglobin level and platelet count then started to fall, with the latter reaching a nadir of ~28 × 10^11/L on post-transplant day 22.

He was enrolled in a multinational paediatric trial conducted by Alexion in late 2011. On post-transplant day 23, aHUS recurrence was suspected, and eculizumab was started. His creatinine level then began to quickly decrease, reaching 425 × 10^11/L within 8 days; his platelet counts before and after eculizumab treatment are presented in Figure 7. He has since been able to return to a relatively normal life at his remote home in Alice Springs receiving eculizumab every 2 weeks and three agents for ongoing hypertension. His creatinine level has been 100–120 µmol/L and there were no signs of TMA at last follow-up.

Figure 7. Platelet count response to eculizumab in a man with recurrent aHUS

This review was commissioned by Alexion Pharmaceuticals Australasia Pty Ltd. The clinical opinions expressed in this publication are those of the authors and not necessarily those of Alexion. Treatment decisions based on these data are the full responsibility of the prescribing physician.