SP283

# Risk of thrombotic microangiopathy in patients with atypical haemolytic uraemic syndrome discontinuing from chronic eculizumab therapy

Nils Heyne,[1] Fernando de Alvaro Moreno,[2] Tina Dutt,[3] Ingela Fehrman,[4] Karine Hadaya,[5] Manuel Macia[6]

[1]University of Tübingen, Tübingen, Germany; [2]University Hospital Infanta Sofia, Madrid, Spain; [3]Alder Hey Children's NHS Foundation Trust, Liverpool, UK; [4]Karolinska University Hospital, Stockholm, Sweden; [5]Geneva University Hospitals, Geneva, Switzerland; [6]University Hospital NS de Candelaria, Santa Cruz de Tenerife, Spain.

## Introduction

- Atypical haemolytic uraemic syndrome (aHUS) is a rare, genetic, life-threatening disorder characterised by thrombotic microangiopathy (TMA) and end organ damage.[1–3]
- Clinical manifestations of TMA are severe and, historically, outcomes have been poor:
  - Over half of patients die, require dialysis or develop permanent kidney damage within 1 year of diagnosis.[4]
- The efficacy and tolerability of eculizumab – a monoclonal antibody that blocks terminal complement – have been demonstrated in prospective clinical trials in adults and children with aHUS, regardless of whether a complement mutation has been identified.[5,6]
- aHUS is a chronic disease and TMA manifestations are unpredictable, occurring without warning, leading to potentially irreversible complications
  - Consequently, life-long eculizumab treatment is specified for patients with aHUS unless discontinuation is clinically indicated.[7]
  - However, there are reports in the literature of the discontinuation of eculizumab in patients with aHUS.[8]
- Here we present details of six selected cases from our clinics of patients with aHUS in whom eculizumab was discontinued or altered from the indicated dosing regimen.

## Diagnosis and treatment

- **Table 1** shows the patient characteristics and laboratory parameters at acute presentation.

Table 1.

| | Patient | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 |
| Age (years) | 37 | 22 | 16 | 37 | 38 | 39 |
| Gender | Female | Male | Female | Female | Female | Male |
| Complement mutation | MCP | No mutation identified | C3 | MCP, homozygous CFH risk haplotype | No mutation identified | No mutation identified, homozygous CFH risk haplotype |
| Medical history | Diagnosed with "TTP"; 3 previous TMA managed with plasma | Cerebral palsy; 5 yrs earlier in ICU for "diarrhoea" | Diagnosed with aHUS at 6 yrs; 3 previous TMA managed with plasma; patient in CKD since several yrs | Diagnosed with aHUS; 3 previous TMA managed with plasma; ESRD at 28 yrs, first transplant at 32 yrs and multiple miscarriages and preeclampsia with renal damage | "HELLP syndrome" and ESRD post caesarean section; transplanted but lost graft rapidly; 2nd transplant | 4H syndrome |
| ADAMTS13 activity | >75% | 60% | Normal | Normal | N/A | Normal |
| Shiga toxin | N/A | Negative | Negative | Negative | N/A | N/A |
| Platelet count (x10⁹/L) | 121 | 12 | 117 | N/A | 78 | 31 |
| LDH (U/L) | 1916 | 1049 | 1976 | N/A | 1022 | 2510 |
| Creatinine (µmol/L) | 1025 | 590 | 216 | 476 | 167 | 619 |
| Haemoglobin (g/dL) | 6.3 | 6.4 | 7.8 | N/A | 7 | 8.8 |
| Schistocytes | Yes | Yes | Yes | Yes | Yes | Yes |
| On dialysis | Yes | No | No | Yes (starting at acute presentation) | No | Yes |
| Previously transplanted | No | No | No | Yes | Yes | No |

ADAMTS, A disintegrin and metalloproteinase with thrombospondin motifs; CFH, complement factor H; CKD, chronic kidney disease; ESRD, end stage renal disease; HELLP, hemolysis, elevated liver enzymes and low platelet count; LDH, lactate dehydrogenase; ICU, intensive care unit; MCP, membrane co-factor protein; N/A, not available; TTP, thrombotic thrombocytopenic purpura

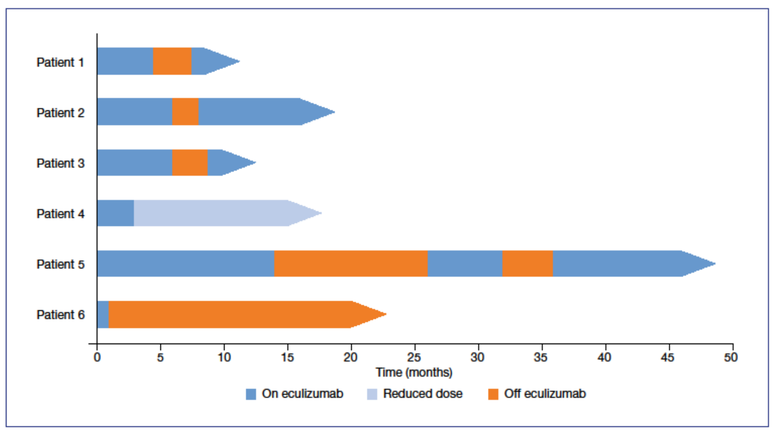
## Initial management and clinical presentation

- Patient 1 presented with weakness, elevated blood pressure (165/95 mmHg) and oedema and initially received daily plasmapheresis for 2 weeks before starting eculizumab. Two additional plasmapheresis sessions were given in week 4 and one in week 5, and weekly rituximab injections were given in weeks 4–7.
- Patient 2 was severely ill; TMA, acute $O_2$ desaturation, admitted to ICU and intubated and was initially treated with daily plasma exchange for 19 days (condition deteriorating) before switching to eculizumab. Dialysis started on day 19.
- Patient 3 presented with foot pain, headache, seizures and cramps; was admitted to ICU and managed with intensive plasma exchange for 2 months prior to eculizumab initiation.
- Patient 4 presented with TMA and AKI needing dialysis after infection. She was then re-transplanted with eculizumab from day 0.
- Patient 5 had just been re-transplanted, but rapidly developed recurrent TMA (Day 7) and initiated eculizumab at Day 8.
- Patient 6 initiated eculizumab very rapidly after initial symptoms of TMA (Day 2). He received one session of plasma exchange before starting eculizumab.

## Eculizumab treatment

- All patients received eculizumab treatment at the indicated dose regimen:
  - Induction: 900 mg/week for 4 weeks.
  - Maintenance: 1200 mg at week 5, then 1200 mg every 2 weeks.
- In all six patients, eculizumab treatment was associated with improvement or normalisation of haematological parameters and no new TMA manifestations.
  - Four patients had improved renal function, while two remained on dialysis.
- Duration of eculizumab treatment at the indicated dose ranged from 1–14 months.
  - A timeline of eculizumab treatment is shown in **Figure 1**.

Figure 1. Eculizumab treatment and discontinuation over time




## Eculizumab discontinuation and follow-up

### Patient 1

- The patient remained stable with a serum creatinine of 256 µmol/L for 3 months after discontinuation, before reporting weakness and slight oedema of the ankles at a routine visit after an upper-airway infection.
- Laboratory tests at 3 months post discontinuation of eculizumab:
  - Platelets: 110 x 10⁹/L
  - Lactate dehydrogenase (LDH): 540 U/L
  - Estimated glomerular filtration rate (eGFR): 17 mL/min/1.73 m², and serum creatinine of 286 µmol/L.
- Eculizumab was restarted the next day. After 13 months, laboratory values had improved but not normalized:
  - Platelets: 228 x 10⁹/L
  - Haemoglobin: 12.8 g/dL
  - LDH: 107 U/L
  - eGFR: 42 mL/min/1.73 m²
  - Serum creatinine: 124 µmol/L

### Patient 2

- After 6 months, the patient had shown no recovery in eGFR, and eculizumab was discontinued.
- Two months later he was admitted with bloody diarrhoea, abdominal pain and vomiting.
  - Platelets: 18 x 10⁹/L
  - Haemoglobin: 7 g/dL
  - LDH: 1300 U/L.
- After initial plasma exchange, eculizumab was restarted on Day 4, and the patient was discharged on Day 10 with a platelet count of 113 x 10⁹/L.
- Twelve months later, he remains on eculizumab and is a candidate for renal transplantation.
  - Platelets: 60 x 10⁹/L
  - Haemoglobin: 11 g/dL
  - LDH: 550 U/L.

### Patient 3

- The patient received eculizumab for 6 months as part of a clinical trial, at which time her parents declined to participate in the extension study.
- Eleven weeks after discontinuation, the patient presented with malaise, fatigue, severe headache after an upper-airway infection.
  - Platelets: 139 x 10⁹/L
  - Haemoglobin: 12 g/dL
  - LDH: 383 U/L
  - eGFR: 10 mL/min/1.73 m².
- Eculizumab was restarted, and after over 2 years of treatment, eGFR is maintained at 45 mL/min1.73 m².

### Patient 4

- After 3 months of eculizumab treatment, the dose was reduced to 900 mg/month as there had been no change in renal function.
- The patient has since remained on reduced dosing with no overt TMA manifestations for 12 months.

### Patient 5

- The patient had received eculizumab for 14 months post-transplantation before requesting to stop treatment.
  - Twelve months later there was a new TMA manifestation in the allograft after influenza vaccination.
- Re-initiation of eculizumab was associated with recovery of renal function. Treatment was stopped again at the patient's request after 6 months.
  - Four months after discontinuation there was again a TMA manifestation in the allograft after a urinary tract infection.
- Re-initiation of eculizumab was again associated with recovery of renal function and the patient remains on long-term eculizumab treatment with a current eGFR of 44 mL/min/1.73m².

### Patient 6

- The patient received eculizumab for 1 month, after which platelets had stabilized above 200 x 10⁹/L, haemoglobin at ~11 g/dL, LDH at ~400 U/L and serum creatinine at 530 µmol/L.
- The patient has now been followed up for 19 months after discontinuation, with no new TMA manifestations.

## Summary of outcomes after eculizumab discontinuation

- Two of the six patients have had no new TMA manifestations since alteration or discontinuation of the approved eculizumab dosing regimen, both of these started eculizumab very rapidly after current TMA manifestation (within 1 day).
- In patients who had new TMA manifestations, the time to new TMA post-discontinuation ranged from 2 to 12 months.
- The cause of new TMA manifestations was an upper airway infection in two patients (1 and 3), influenza vaccination and urinary tract infection in Patient 5, and was unknown in Patient 2.
- Of those experiencing new TMA manifestations two had no identified complement mutation, one had an MCP mutation and one a C3 mutation.

Table 2. Summary of eculizumab discontinuation

| | Patient | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 |
| Time to eculizumab start from current TMA | 2 weeks | 19 days | 2 months | 0 | 1 day | 1 day |
| Reason for discontinuation/ reduced dose | Clinical improvement | No recovery of eGFR | Parental request | Considered stable | Patient request | Clinical improvement |
| Time to new TMA, months | 3 | 2 | 3 | – | 12 | – |
| Reason for new TMA event | Upper airway infection | Unknown | Upper airway infection | – | a, Influenza vaccination b, UTI | – |
| Outcome | Long-term eculizumab | Long-term eculizumab (>12 months from last TMA event) | Long-term eculizumab | No new overt TMA on reduced dose for 12 months | Long-term eculizumab | Latest follow-up 19 months without overt TMA |

eGFR, estimated glomerular filtration rate; TMA, thrombotic microangiopathy; UTI, urinary tract infection

## Conclusions

- Patients with aHUS who discontinue eculizumab are at risk of experiencing new TMA manifestations.
- Reasons for new TMA manifestations varied from patient to patient, and onset could not be predicted.
- TMA manifestations were not characteristic to specific mutations in this cohort.
- These findings highlight the importance of sustained complement blockade in patients with aHUS.

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