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Title:
Long-term remission with eculizumab in atypical haemolytic uraemic syndrome

Date:
2017-02-01

Citation:
Carter, S., Hewitt, I. & Kausman, J. (2017). Long-term remission with eculizumab in atypical haemolytic uraemic syndrome. Nephrology, 22 (S1), pp.7-10. https://doi.org/10.1111/nep.12932.

Persistent Link:
https://hdl.handle.net/11343/292420

Title. Long term remission with eculizumab in atypical haemolytic uremic syndrome.

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Abstract. The understanding of the role of complement dysregulation in atypical haemolytic uremic syndrome (aHUS) has led to major changes in therapeutic approaches and outcomes. Eculizumab is a humanized anti-C5 monoclonal antibody that inhibits the terminal complement pathway and has revolutionized the treatment and prognosis of aHUS. However, published reports to date have had relatively short term follow-up. We report two pediatric cases of aHUS successfully treated with eculizumab longer than six years with no serious adverse events and preservation of renal function.

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/nep.12932

Introduction. The understanding of the role of complement dysregulation in atypical haemolytic uremic syndrome (aHUS) has led to major changes in therapeutic approaches and outcomes. Eculizumab is a humanized anti-C5 monoclonal antibody that inhibits the terminal complement pathway and has revolutionized the treatment and prognosis of aHUS. However, published reports to date have had relatively short term follow-up. We report two paediatric cases of aHUS successfully treated with eculizumab longer than 6 years with no serious adverse events and preservation of renal function.

Case 1. A seven month old male was diagnosed with aHUS having presented with microangiopathic haemolytic anemia, thrombocytopenia and oliguric acute kidney injury (AKI). Upon presentation investigations were as follows: haemoglobin 53g/l, platelets 144 $x10^9$/l with schistocytes apparent on the blood film, LDH 3805 U/l, C3 0.94, C4 0.12, creatinine 130µmol/l. Peritoneal dialysis (PD) was commenced, however hypertension and oliguria persisted. Weekly plasma infusions of 10ml/kg commenced at one month, then increased to twice weekly due to recurrent aHUS activity. There was no evidence of Shigatoxin production or anti-factor H antibody. There were normal serum levels of factors H, I B, ADAMTS13 and normal CD46 (membrane co-factor protein) expression on leukocytes by fluorescein-activated cell sorting analysis. Gene mutation analysis was negative for pathogenic mutations of factors H, I, B, C3, thrombomodulin, CFHR proteins and CD46. Biopsy at four months showed a thrombotic microangiopathy with bloodless, ischaemic glomeruli with marked endothelial swelling and membrane duplication. Three of 23 glomeruli were globally sclerosed, two segmentally with relatively preserved tubulointerstitium. Due to recurrent AKI and failure of plasma infusions (peak creatinine 240 µmol/l; estimated GFR 12.1ml/min/1.73m^2) plasma exchange was started at eight months. This initially allowed PD to be withdrawn, however plasma exchange was then escalated to thrice weekly exchanges due to deteriorating renal function. Eculizumab was obtained 13 months post presentation with serum creatinine 220µmol/l and commenced following antibiotic prophylaxis and Meningococcal immunization, following which plasma exchange was also withdrawn. Haematological remission was characterized by a stable haemoglobin and platelet count within the normal range for age. There was a sustained renal recovery with creatinine level falling to 50 µmol/l with improvement of urine output, but he remained on erythropoietin and

lisinopril. At 6.5 years post commencement of eculizumab he remains in remission, while maintained on a dose of 300mg fortnightly via a subcutaneous tunneled central venous catheter, with a creatinine of 64 µmol/l (estimated GFR 70.2ml/min/1.73m^2). No adverse reaction to eculizumab has been observed, however there was one episode of idiopathic pancreatitis (lipase 1624U/l) immediately following eculizumab infusion that did not recur and was not associated with any evidence of aHUS flare. There has been no evidence of the development of anti-eculizumab antibodies. He has had recurrent admissions for empiric antibiotic treatment in the context of febrile episodes, however no recurrence of aHUS with these intercurrent illnesses. He has required revision of his central venous catheter on three occasions due to growth.

Figure 1. Long term renal remission with eculizumab.

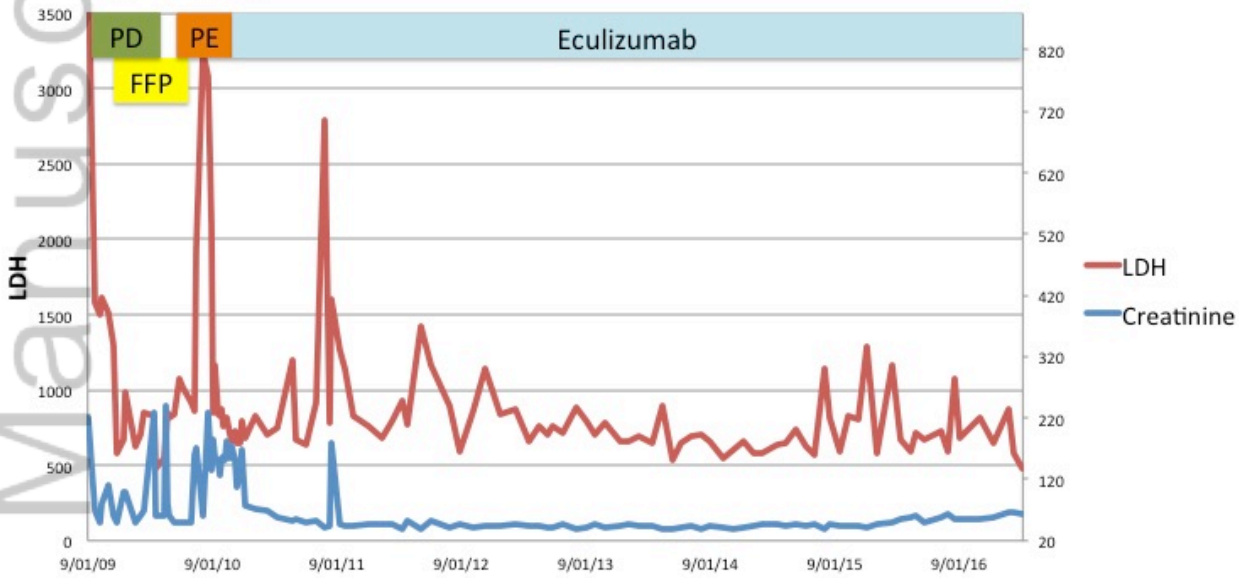
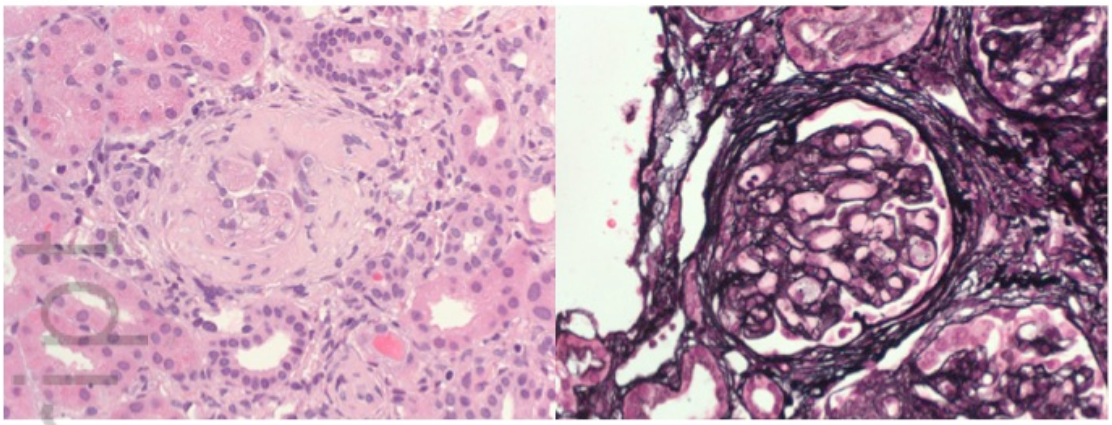


Figure 2. Renal biopsy in aHUS showing acute-on-chronic endothelial injury

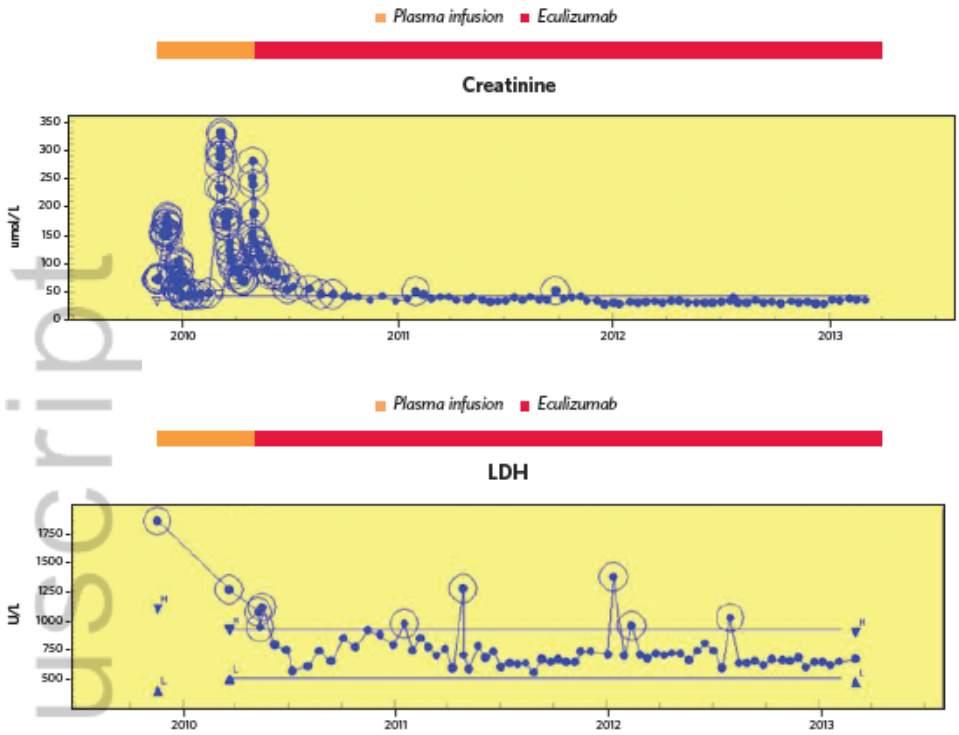


Histologically, there were bloodless glomeruli with ischaemic retraction, endothelial swelling and accompanying membrane reduplication. The tubulointerstitium was largely preserved.

Case 2.

A nine month old girl presented with aHUS mildly hypertensive with a microangiopathic haemolytic anemia (haemoglobin 56 g/l) and elevated LDH (1850 U/l). Her creatinine at presentation was 72µmol/L with microscopic hematuria and nephrotic range proteinuria. No Shigatoxin was isolated, her ADAMTS13 assay and assessment of her complement pathways were normal. She subsequently had an acute aHUS flare with worsening renal impairment (creatinine 154µmol/l) and required multiple antihypertensive agents. A renal biopsy was consistent with thrombotic microangiopathy. She was commenced on thrice weekly plasma infusions at four weeks. Despite this, she remained clinically unstable with three subsequent flares over five months necessitating ventilation secondary to pulmonary edema and malignant hypertension. Eculizumab was provided on compassionate grounds nine months after presentation and was commenced following vaccination and commencement of prophylaxis against Meningococcus. After six years of receiving eculizumab, she remains clinically quiescent on fortnightly eculizumab infusions via a subcutaneously implanted venous access port. Control of her aHUS is shown graphically in figure 3; her current creatinine is 40µmol/l. No adverse reactions or resistance to eculizumab have occurred, but multiple revisions of her central venous catheter were necessary. She remains on an ACE inhibitor.

Figure 3. Long term eculizumab treatment maintains aHUS remission and renal function.



Discussion.

Eculizumab is the empiric therapy of choice for aHUS, where available, even before the complement pathway abnormality is elucidated [1]. It is also indicated as either a prophylactic or rescue therapy for renal transplant in aHUS. Where it is not available, therapy with plasmapheresis is still indicated within 48 hours. Eculizumab allows for sustained renal recovery as evidence by improvement in GFR and reduction in proteinuria. Haematological remission is more rapid than renal recovery with most patients normalizing their cell counts on treatment. Renal recovery is more complete when eculizumab is instituted early, however there may still be a dramatic response to treatment years after disease onset. In case 1, despite institution of therapy 12 months after initial presentation and severe renal impairment, the patient had an excellent response with normalization of serum creatinine. Failure to institute eculizumab promptly may however lead to irreversible renal damage and renal failure. There is evidence for significant improvement in quality of life following treatment commencement.

The prognosis of aHUS was poor in the pre-eculizumab era. There was an 85% risk of mortality or end stage renal disease and 61% risk of recurrence post renal transplantation [2]. With eculizumab independence from plasmapheresis, plasma infusion and/or dialysis are well reported [3, 4]. In a total of 37 patients treated for 2

years, eculizumab had a favourable safety profile with new onset of adverse events uncommon after 6 months of therapy [5]. In children with aHUS, there has been a recent case series of acute derangement in liver function tests leading to discontinuation of therapy in one of seven patients [6]. Whist eculizumab is generally well tolerated, most children remain dependent on long term central venous access with recurrent hospital attendances. There may be complications relating to venous access, severe hypertension or infectious complications including overwhelming meningococcal sepsis. However the largest barrier limiting access to widespread, long term maintenance therapy with eculizumab remains its cost.

The long term safety of eculizumab is promising yet remains uncertain. Safety has been previously reported in children with aHUS treated for up to 4 years [7, 8]. In patients with paroxysmal nocturnal haemoglobinuria, long term safety data is available in excess of 8 years [9]. There has been histological evidence of eculizumab deposition in glomeruli, the long term significance of which is unclear [10]. Although there have been reports of anti-eculizumab antibody production, none have led to treatment failure [11, 12].

Conclusion.
Long term treatment with eculizumab is a safe and effective in children with aHUS. Therapeutic strategies include using implanted subcutaneous ports for long term venous access, monitoring for disease recurrence during viral illnesses and prophylaxis against meningococcal infection. The question of optimal dosing and frequency of administration remains uncertain.

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