Title: Genetic Atypical Hemolytic-Uremic Syndrome *GeneReview* – Treatment of Manifestations: Eculizumab
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Eculizumab

In two prospective Phase II clinical trials using eculizumab for a median of 64 and 62 weeks, respectively, in 37 adult and adolescent individuals with aHUS, eculizumab resulted in increased platelet counts and significant improvement in all secondary end points, with continuous, time-dependent increases in the estimated glomerular filtration rate (GFR) [Legendre et al 2013]. In trial 1, 4/5 affected individuals treated with eculizumab were able to discontinued dialysis. 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, was observed through the extension period.

Two subsequent trials comprising 22 children and 41 adults, respectively, allowed early treatment initiation. Fifty-five percent of children received eculizumab as first-line therapy without prior plasma exchange or infusion, compared to 15% of adults. Complete response with improved renal function was maintained after 26 weeks of treatment in 64% of children [Greenbaum et al 2013], while 80% of adults had complete response with preserved renal function over one year treatment duration [Fakhouri et al 2014]. Renal function recovery was greater in the pediatric compared to the adult cohort. Only 9% of children and 12% of adults required dialysis at 26 weeks and 1 year of continued eculizumab therapy, respectively. Mean gains in eGFR were less in transplanted than in non-transplanted adults [Loirat et al 2014].

The four trials overall indicate that eculizumab is effective to stop the thrombotic microangiopathy process in individuals with aHUS, allowing sustained remission of the disease and improved or preserved renal function in the majority of individuals, including those resistant to plasma exchange or infusion. Results also suggest that an early switch from plasma exchange or infusion to eculizumab or the use of eculizumab as initial therapy may increase the chance of full recovery of renal function [Loirat et al 2016]. Except for the occurrence of meningococcal meningitis in two of the 100 individuals who entered these trials [Fakhouri et al 2014], treatment was well tolerated, with no treatment emergent adverse events.

- In children with a first episode of aHUS, eculizumab therapy avoids the complications associated with apheresis and central venous catheters.
- In adults, eculizumab can be used as a first-line therapy when the aHUS diagnosis is undisputable, although plasma therapy should be used as a first-line therapy if uncertainty in the diagnosis warrants further investigation.
- Evidence of plasma resistance or dependence should lead to a prompt shift to eculizumab therapy [Zuber et al 2012].

Notes:(1) A small number of reports have suggested that eculizumab could also reverse extra-renal aHUS-related organ failure, including neurologic involvement and digital ischemia [Ariceta et al 2012, Ohanian et al 2011]; (2) individuals with pathogenic variants in *DGKE* may not benefit from treatment with eculizumab [Zuber et al 2012, Lemaire et al 2013]; (3) a number of important issues require further study, including the appropriate duration of treatment according to an individual's genetic background and medical history, and a cost-efficacy analysis. Among 18 individuals with aHUS from the first two trials who discontinued eculizumab therapy, five experienced relapse after withdrawal. Similarly, among 24 published cases of eculizumab withdrawal, six experienced relapse [Nester et al 2015]. The individuals who experienced relapse had *CFH* pathogenic variants or high titer of FH autoantibodies. One individual had a *C3* pathogenic variant and in another individual no variant was identified.

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