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LETTER TO THE EDITORS

Eculizumab for aHUS post-transplantation: when and how to stop a good thing

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Dear Sirs,

Atypical hemolytic uremic syndrome (aHUS) is characterized by mutations in the alternative complement pathway. It is associated with a 50% rate of mortality/dialysis dependence at 5 years. A recurrence rate >80% following renal transplantation has historically discouraged kidney-alone transplantation. Eculizumab, a monoclonal antibody to C5, has caused a paradigm shift in the management of these patients [1].

We report the case of a 30-year-old woman with uniquely acquired aHUS who was subsequently received a renal transplant. She presented in 2010 at the age of 26 years, 4 weeks postpartum, with intravascular hemolysis and advanced renal failure [2]. Five years previously, she had a successful liver transplant following hepatic vein thrombosis. Genetic analysis subsequently revealed a mutation in complement factor H (*CFH*) gene in the liver donor, such that hepatic synthesis of factor H was reduced [2]; the patient herself was homozygous for the "at-risk" *CD46GGAAC* haplotype, insufficient in itself to result in aHUS.

In 2014, after 4 years of hemodialysis, she underwent a successful renal transplant from her mother with eculizumab cover. There was an immediate primary graft function with markers of hemolysis remaining negative. Creatinine 1 year post-transplant is 1.0 mg/dl. Her thrombocytopenia, which persisted throughout the dialysis period, normalized following transplantation with eculizumab. This suggests there was persistent low-level hemolysis from presentation despite being clinically well.

Important questions regarding the duration of eculizumab therapy now arise. The annual cost of maintenance therapy is approximately £300 000 [3], far in excess of maintenance hemodialysis treatment. The estimated nonrecurrence rate is 10–20%, meaning that costly long-term eculizumab is unnecessary for some patients.

Interestingly, in this patient, the defective *CFH* gene was tolerated for 5 years before manifestation of disease. This is consistent with the accepted pathophysiology of aHUS; the patient had an "at-risk" phenotype (*CD46GGAAC* homozygosity), acquired a CFH mutation from her liver donor, and then experienced the final trigger of pregnancy [2]. *CD46* codes for a transmembrane complement regulator expressed widely in renal endothelium. The transplanted kidney may not have homozygosity for the at-risk haplotype. So should there be a trial withdrawal off eculizumab?

In one report, withdrawal of eculizumab in 16 patients resulted in clinical recurrence in 6, half of whom had a CFH mutation [4]. However, the risk of aHUS recurrence differs depending on the genetic mutation.

Healthcare providers, who have a moral obligation to provide the best care for the majority in the setting of finite resources, are also tasked with providing optimal treatment for young patients with rare diseases. However, drugs for orphan diseases, such as aHUS, are often expensive and exclusive, at least initially. As development expenditure must be regained from a small number of patients, often there is no correlation between price and manufacturing costs, molecular complexity, and therapeutic benefit [5]. The use of eculizumab in the treatment of paroxysmal nocturnal hemoglobinuria is reportedly not cost-effective [6].

There are currently pharmaceutically sponsored randomized control trials exploring the role of eculizumab in delayed graft function and also in high immunological risk renal transplants. The notable difference between intervention in these scenarios and aHUS is the duration of treatment with eculizumab. A potential finite duration of therapy in post-transplant aHUS may maximize access to those who would benefit from this revolutionary therapy. Given rising healthcare costs, we suggest a carefully planned randomized controlled trial exploring eculizumab treatment withdrawal in post-transplant patients with aHUS, initially those with the lower risk mutations, is necessary.

Agnes Masengu and Aisling Courtney
Regional Nephrology Unit, Belfast City Hospital, Belfast, Northern Ireland
e-mail: amasengu@gmail.com

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Conflicts of interest

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