Paroxysmal nocturnal hemoglobinuria (PNH) is rare acquired bone marrow disease characterized by a clone of cells lacking glycosyl phosphatidylinositol (GPI)-anchored proteins. Deficiency of the GPI-anchored complement inhibitors CD55 and CD59 on erythrocytes leads to intravascular hemolysis upon complement activation. In addition to hemolysis, a high risk of thrombosis is a major problem in PNH patients. Eculizumab (Soliris®) is a humanized monomeric antibody that targets complement factor C5 and inhibits the production of C5a and formation of the terminal complement membrane attack complex. It is registered for the treatment of PNH and atypical hemolytic uremic syndrome (aHUS). Eculizumab results in significant reduction of hemolysis in PNH, improves symptoms and quality of life and reduces the incidence of PNH related thrombosis. A poor response, defined as sustained high levels of LDH during treatment with Eculizumab irrespective of improvement of clinical symptoms, has been reported in a subgroup of PNH patients (Nishimura et al. NEJM 2014;370:632-639). These patients had a genetic variant of C5 which occurs in approximately 3.5% of the Japanese and 1% of the Chinese Han populations and interferes with binding of eculizumab to C5. We describe the first patient with no known Asian ancestry with a poor response to Eculizumab.

A 30-year old male Caucasian patient commenced treatment with Eculizumab because of PNH (granulocyte clone size: 90%), severe hemolytic (LDH 3.6x upper limit of normal, and peak values of 17xULN), transient renal failure, extreme fatigue and erectile dysfunction. He had no history of thrombosis and no underlying bone marrow disease. During eculizumab treatment (dosed 600 mg iv every 7 days, weeks 1-4 and 900 mg b.i.w.k starting in week 5) he felt better, seemed less fatigued and experienced less erectile dysfunction. However, laboratory examination showed sustained elevated markers of hemolysis (Figure 1). Other causes of hemolysis were excluded. Underdosing of eculizumab was ruled out by demonstrating sustained high LDH levels at different time points in between subsequent eculizumab infusions and by measuring trough levels of eculizumab (>100ug/ml). In vitro terminal complement complex blockade by eculizumab through antibody-coated chicken red blood cell lysis was indicative of ongoing active hemolysis in our patient’s serum. The presence of Human Anti-D沪指nteracting with binding of approximately 3.5% of the Japanese and 1% of the Chinese Han populations and has been reported in a subgroup of PNH patients (Nishimura et al. NEJM 2014;370:632-639). These patients had a genetic variant of C5 which occurs in approximately 3.5% of the Japanese and 1% of the Chinese Han populations and interferes with binding of eculizumab to C5. We describe the first patient with no known Asian ancestry with a poor response to Eculizumab.

Conclusions

- We describe the first Caucasian patient with no known Asian ancestry who showed resistance to treatment with Eculizumab due to a C5 polymorphism.
- Eculizumab blocks complement cleavage in vitro by binding to C5 remote from the Eculizumab binding site and blocks complement cleavage in our index patient.
- Eculizumab may prove a useful alternative to eculizumab for patients with resistance due to C5 polymorphisms.

Contact Information

Saskia Langemeijer
Radboud UMC
Nijmegen, The Netherlands
Phone: +31 (0)24 36 14703
Fax: +31 (0)24 36 42080
E-mail: saskia.langemeijer@radboudumc.nl