12 weeks safety and efficacy results of the novel C5 inhibitor coversin in PNH with resistance to eculizumab due to complement C5 polymorphism

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Introduction

Paroxysmal Nocturnal Haemoglobinuria (PNH) is a rare acquired life-threatening disease characterized by complement induced haemolysis and its sequelae and a high incidence of thrombosis. The monoclonal antibody eculizumab binds to C5 and prevents its activation and cleavage into C5a and C5b and is an established treatment for PNH and aHUS. However, for patients with the rare amino acid polymorphism p.Arg885His or p.Arg885Ser, which interferes with the binding and efficacy of eculizumab (Nishimura et al, 2014, Langemeijer et al, 2015), there is still no effective treatment. A new small protein complement inhibitor named Coversin is in Phase 1-2 clinical development. Coversin also prevents cleavage and activation of C5 but binds to C5 at a different site than eculizumab. In vitro Coversin inhibits C5 activation in both wild type C5 and C5 with a polymorphism at the Eculizumab binding site. Coversin studies in healthy volunteers proved safe and demonstrated inhibition of terminal complement activation.

We report safety and preliminary efficacy data of the novel C5 inhibitor Coversin in a severely haemolytic PNH patient with a C5 polymorphism.

Patient

The patient is a 30 year old male with PNH, (granulocyte clone size: 90%) and severe haemolysis (LDH 3 to 17 x upper limit of normal), transient renal failure, extreme fatigue and symptoms of muscle dystonia and no history of thrombosis. He remained severely haemolytic during eculizumab treatment despite adequate drug levels and no human anti-djug antibodies. Other causes of haemolysis were excluded. The patient was shown to have a p.Arg885Ser polymorphism in the C5 gene rendering him resistant to eculizumab therapy (Figure 1).

Coversin was administered by s.c. injection at an ablating dose of 0.57 mg/kg on day 1, followed by a maintenance dose of 0.14 mg/kg per day thereafter. Peripheral blood samples were drawn for PK/PD. Protocol specified doubling of the dose and/or shortening of the dose interval were allowed on the basis of clinical symptoms and CH50 levels to achieve adequate and sustained complement inhibition.

Coversin administration resulted in an initial suppression of haemolysis with a further decrease of his LDH (Figure 2). LDH decreased to approximately 1.5xUNL. There was a good initial response to an ablating dose of 0.57 mg/kg Coversin with CH50 levels decreasing below 8 U Eq/ml, which is the lower limit of qualification of the ELISA assay. Clinical symptoms and laboratory markers of haemoysis improved during the maintenance treatment of 0.14mg/kg every 24 hours. However, 6 days into the treatment, the patient again experienced haemolysis-associated symptoms with dark urine hours before the next s.c. injection and no further decrease of his LDH. The same occurred after doubling of the dose to 0.29 mg/kg per day.

Conclusions

- Over a period of 12 weeks Coversin has proven safe and effective in the first PNH-patient treated with the drug.
- Coversin may prove a useful alternative to Eculizumab for patients with resistance due to C5 polymorphisms.

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Figure 1: Sequence analysis of exon 21 of C5 in index patient

DNA analysis of the coding region of C5 was performed in our index patient. This showed a single C5 heterozygous missense mutation, c.2653C>A, which predicts p.Arg885Ser. The same mutation was demonstrated in the DNA of our patient’s healthy father.

Figure 2: LDH level and complement activity (CH50) during the first 17 days of treatment with Coversin

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Figure 3: LDH level and complement activity (CH50) after changing the dosing schedule to 0.14 mg/kg every 12 hours