

Ravulizumab: A Review in Atypical Haemolytic Uraemic Syndrome

Atypical haemolytic uraemic syndrome, known as aHUS, is a rare type of thrombotic microangiopathy, or TMA. aHUS is characterized by thrombocytopaenia; microangiopathic haemolytic anaemia; and damage to end organs, particularly the kidneys. The disease is caused by dysregulation of the complement system resulting in overactivation of the terminal complement pathway. This leads to endothelial cell damage and platelet activation, causing thrombosis in micro blood vessels. Encounter of red blood cells with thrombi leads to their mechanical fragmentation. The disease can thus be treated with complement C5 inhibition.

Eculizumab, a complement protein C5-inhibiting antibody, was the first approved treatment for aHUS. Although it's effective, it must be infused intravenously every two to three weeks. This high frequency of administration may be inconvenient for patients, while also increasing the infusion burden and the risk of infusion-related reactions. As a result, eculizumab has been re-engineered into the longer-lasting inhibitor ravulizumab.

Like eculizumab, ravulizumab binds to C5, preventing C5's cleavage into C5a and C5b. Therefore, it inhibits formation of the terminal complement complex C5b9. In this way, ravulizumab removes C5 from the bloodstream without interfering with early steps of complement activation.

However, ravulizumab's pharmacokinetics differ from eculizumab's in a very important way, which extends the terminal elimination half-life of ravulizumab. While eculizumab is degraded along with C5, ravulizumab is instead released and recycled, after which it binds to more C5 molecules in the blood. Because of this recycling process, the half-life of ravulizumab is more than four times that of eculizumab, which means the drug can be administered less frequently. After an initial loading dose, a maintenance dose of ravulizumab, which is dependent upon body weight, is given every four to eight weeks instead of the every two to three weeks required for eculizumab.

In two clinical trials, ravulizumab was found to be effective in adults with aHUS who had never received complement inhibitors and in paediatric patients who had either never received complement inhibitors or had previously responded to eculizumab.

In the trial in adults, over half of patients achieved a complete TMA response by 26 weeks, and the rate increased with prolonged treatment. Even greater

percentages of patients exhibited improvements in the individual response parameters. The median time to complete TMA response was 86 days.

In the paediatric trial, over three-quarters of treatment-naïve patients achieved a complete TMA response by 26 weeks. As in adults, the response rate increased with prolonged treatment. The median time to complete TMA response was 30 days. In paediatric patients who switched from eculizumab, renal and haematological parameters remained stable.

Ravulizumab was well-tolerated in both trials. The most common treatment-emergent adverse events were headache, diarrhoea, and vomiting in adults and fever, colds, diarrhoea, vomiting, and headache in paediatric patients.

Overall, the data show that ravulizumab is an effective option for aHUS treatment with longer intervals between treatments that make it less burdensome for patients than eculizumab.