NEW DRUGS

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Ravulizumab

Approved indication: paroxysmal nocturnal haemoglobinuria

Ultomiris (Alexion)
vials containing 10 mg/mL, 100 mg/mL concentrated solution

Paroxysmal nocturnal haemoglobinuria is a rare cause of haemolytic anaemia. Affected patients have a mutation that results in a loss of function of a critical enzyme involved in linking proteins to the plasma membrane of haematopoietic cells. These proteins include the complement inhibitory proteins, so patients are vulnerable to complement-mediated intravascular haemolysis. They are also at risk of thrombosis and bone marrow failure. Management was generally limited to supportive care, such as transfusions of red blood cells, unless a bone marrow transplant was possible. Treatment changed with the approval of eculizumab. This is a monoclonal antibody that binds to complement protein C5 to stop the complement cascade. Although eculizumab has improved outcomes for patients, it has to be infused every two weeks. This is one of the reasons for the development of ravulizumab.

Ravulizumab is a genetically engineered monoclonal antibody. It binds with high affinity to complement protein C5. Ravulizumab is diluted then slowly infused according to protocol. A loading dose enables immediate achievement of a steady state and inhibition of C5. As ravulizumab has a half-life of about 50 days, maintenance doses only need to be infused every eight weeks. Ravulizumab is expected to be metabolised like other immunoglobulins, so no dose adjustments have been recommended for patients with liver or kidney disease.

Ravulizumab has been evaluated in patients with paroxysmal nocturnal haemoglobinuria who had not previously received a complement inhibitor and in those who were being treated with eculizumab. These two open-label trials assessed haemolysis by measuring concentrations of lactate dehydrogenase.[1,2]

The trial of previously untreated patients randomised 125 to receive ravulizumab and 121 to receive eculizumab for 26 weeks. Treatment resulted in lactate dehydrogenase concentrations returning to normal in 53.6% of the ravulizumab group and 49.4% of the eculizumab group. Breakthrough haemolysis affected 4% and 10.7%. No transfusions were needed in 73.6% of the ravulizumab group and 66.1% of the eculizumab group.[1]

In the trial of patients receiving eculizumab, 98 were randomised to continue while 97 were switched to infusions of ravulizumab. After 26 weeks, 66% of the ravulizumab group had normal concentrations of lactate dehydrogenase compared with 59.2% of the eculizumab group. The mean change in concentration was a decrease of 0.82% with ravulizumab and an increase of 8.39% with eculizumab. None of the patients taking ravulizumab had breakthrough haemolysis compared to five of the eculizumab group. Fewer patients (12 vs 17) in the ravulizumab group required transfusions.[2]

Headache was a frequent adverse effect reported in the trials. It affected 32% of the patients given ravulizumab and 26% of those given eculizumab. Other adverse events occurred at similar rates in both groups. The effect on the complement system increases the susceptibility of patients to meningococcal infection. Meningococcal vaccine before treatment with ravulizumab is therefore recommended.

Statistical analysis shows that ravulizumab is non-inferior to eculizumab.[1,2] Although the duration of each infusion is longer, patients are likely to prefer the reduced frequency of ravulizumab infusions. The current approval is limited to adults, but ravulizumab is being studied in children.

T manufacturer provided the AusPAR and the product information

REFERENCES

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The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, the European Medicines Agency and the Therapeutic Goods Administration.