Caplacizumab

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Approved indication: thrombotic thrombocytopenic purpura

Cablivi (Sanofi-Aventis)
vials containing 10 mg as powder for reconstitution

The von Willebrand factor is a glycoprotein involved in coagulation. In acquired thrombotic thrombocytopenic purpura there is an autoantibody that prevents the cleaving of multimers of von Willebrand factor. These multimers then accumulate resulting in excessive platelet aggregation. This leads to thrombosis, haemolytic anaemia and thrombocytopenia. Patients may present with cerebrovascular or cardiovascular events, kidney injury or gut ischaemia. The mortality rate was high, but has been greatly reduced by plasma exchange therapy and immunosuppression.

Caplacizumab is an antibody fragment that has been genetically engineered to bind with von Willebrand factor. This blocks the interaction between the multimers and platelets so should reduce platelet aggregation.

The first dose of caplacizumab is given intravenously before plasma exchange. Patients are then given daily subcutaneous injections of caplacizumab after each plasma exchange. They continue these daily injections into the abdomen for 30 days after plasma exchange therapy is stopped. The antibody reaches a peak concentration 6–7 hours after injection and markers of platelet aggregation decrease rapidly. The pharmacokinetics of caplacizumab are influenced by the concentration of von Willebrand factor. The half-life will therefore vary depending on how much antibody is bound to the factor. Bound antibody will be catabolised while unbound caplacizumab is thought to be excreted in the urine. No dose adjustments have been advised for patients with liver or kidney disease.

The efficacy of caplacizumab was initially assessed in a phase II trial involving patients requiring plasma exchange for acquired thrombotic thrombocytopenic purpura. In addition to standard care, 36 patients were given caplacizumab and 39 received injections of placebo. The primary end point of this trial was the normalisation of the platelet count. This took a median of three days with caplacizumab and 4.9 days with placebo. There was complete remission, with no subsequent exacerbations, in 81% of the caplacizumab group and 46% of the placebo group. Two patients died in the placebo group.[1]

To confirm the effect of treatment, a double-blind phase III trial studied patients who had already received a single plasma exchange. There were 72 patients in the caplacizumab group and 73 in the placebo group. Compared to the standard of care, patients given caplacizumab were 1.55 times more likely to have normalisation of their platelet count. The composite end point of death, thromboembolism or a recurrence of thrombotic thrombocytopenic purpura during treatment occurred in 12% of the caplacizumab group and 49% of the placebo group. The three deaths during treatment were all in the placebo group. Markers of organ damage, such as cardiac troponin I, returned to normal in a median of 2.86 days with caplacizumab and 3.36 days with placebo.[2]

As von Willebrand factor has a key role in haemostasis, bleeding is an adverse effect of caplacizumab. In the phase III trial 65% of the caplacizumab group had bleeding compared with 48% of the placebo group. Epistaxis, haematuria, vaginal haemorrhage and gingival bleeding are common. In severe cases it may be necessary to consider giving von Willebrand factor if it is available. Bleeding can also occur at the injection sites and some patients will develop a haematoma in the wall of the abdomen. Consecutive injections should not be given into the same quadrant of the abdomen. Other very common adverse events in patients injecting caplacizumab include headache, urticaria, fever and fatigue.[2]

It is important to note that caplacizumab is not aimed at the autoantibody that causes thrombotic thrombocytopenic purpura. Ongoing autoimmune activity can lead to recurrences. Continuing treatment after plasma exchange could be where the main benefit of caplacizumab is. In the phase III trial the median time to normalisation of the platelet count was 2.69 days with caplacizumab and 2.88 days with placebo. However, during the treatment period there was an exacerbation in 38% of the placebo group versus 4% of the caplacizumab group. The patients given caplacizumab also needed less plasma exchange and fewer days of intensive care. Their average hospital stay was 9.9 days versus 14.4 days for the placebo group.[2]

T manufacturer provided the product information

REFERENCES

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2. Scully M, Cataland SR, Peyvandi F, Coppo P, Knobl P, Kremer Hovinga JA, et al. for the HERCULES investigators. Caplacizumab treatment for acquired thrombotic thrombocytopenic purpura. New Engl J Med 2019;380:335-46. https://doi.org/10.1056/NEJMoa1806311

NEW DRUGS

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, and the European Medicines Agency and the Therapeutic Goods Administration.