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CAPLACIZUMAB FOR ACQUIRED THROMBOTIC THROMBOCYTOPENIC PURPURA: A REVIEW

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ABSTRACT

Acquired Thrombotic Thrombocytopenic Purpura (aTTP) is a rare disorder of blood coagulation system causing extensive microscopic clot formation in the small blood vessels throughout the body. Caplacizumab, anti- von Willebrand factor Nanobody is the first drug specially approved for its treatment. In this phase 2, controlled study, the patients who were included in the case were given with subcutaneous drug and the control were received only placebo in addition to plasma exchange for 30 days. The primary and the secondary endpoints were analysed by Kaplan–Meier analysis and significance level was done by one-sided log rank test. Complete remission after the initial course of daily plasma exchange was observed more frequently in the Case group than in the control. Caplacizumab, which shows a greater reduction in acute TTP than placebo. It was well tolerable with a manageable risk of increased bleeding and is free of other potential hematologic problems.

KEYWORDS: Thrombocytopenic purpura, exacerbation, microangiopathy.

BACKGROUND

Thrombotic Thrombocytopenic Purpura (TTP) aggressive form of thrombotic microangiopathy which results in multiorgan dysfunction as a consequence of widespread microvascular ischemia.[1] Two main types of TTP, Acquired and Inherited, the former that accounts for >90% of the patients[2]. Inherited means those that passing from parents. This

affects mainly in new-borns and children. It occurs due to the defect of the gene ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 repeats, member 13) gene and doesn't prompt the body to make a ADAMTS13 enzyme. As a result the enzyme activity is lacking. Lack of the activity of enzyme causes TTP. This enzyme which is involved in blood clotting. The enzyme breaks up a large protein called von Willebrand factor that clumps together with platelet to form blood clot.[4]

Acquired Thrombotic Thrombocytopenic Purpura (aTTP) is an Ultra-rare, acute, life-threatening blood clotting disorder that leads to extensive micro-clot formation in the small blood vessels throughout the body and tissue ischemia and damage to vital organs including the heart, brain and kidney. Mortality is high at 10-20%, with vast majority within 2 week post diagnosis and about 36% of patients suffer from recurrences after initial treatment with the current standard of care, which consist of plasma exchange and immune suppressive treatment.[2]

Caplacizumab is the first drug specially approved for the treatment of acquired thrombotic thrombocytopenic purpura (aTTP). It is highly potent and selective an anti-vWF Nanobody that received orphan drug designation in the US and EU in 2009. It inhibit the interaction between vWF and platelet by targeting the A1 domain of vWF and thus has the potential to immediately block the ULvWF mediated platelet interactions and formation of the string like clots in the blood of aTTP.[2]

SUMMARY

It is a single-blind, randomized, placebo-controlled study were a total of seventy-five patients enrolled. Adults with an acute episode of acquired TTP with platelet count less than 100,000 per cubic millimetre, without active bleeding, and required plasma exchange were included. They were assigned to active or placebo in a 1:1 ratio, with the use of a computerized randomization schedule in which 36 patients were assigned to the test group and 39 to the control. In addition to standard-of-care treatment (daily plasma exchange and immunosuppressive therapy), sample patients received an intravenous loading dose of caplacizumab 10 mg. The drug (10 mg) was further administered subcutaneous daily within 30 minutes after the end of each plasma exchange and was continued for 30 days after the last exchange.

The median time response or the primary end point was evaluated with the use of a Kaplan–Meier analysis stratified for the absence or presence of one plasma-exchange session before randomization, with a one-sided log-rank test used to assess superiority at a 2.5% significance level. All efficacy analyses were performed on the intention-to-treat population, and safety and immunogenicity analyses were performed on the safety population. On the basis of the stratified log-rank test, caplacizumab produce a 39% reduction in median time to response as compared with placebo.

After one month follow up, patients were analysed for the secondary end points such as exacerbations, relapses, remission, and mortality. Complete remission after the initial course of daily plasma exchange was observed more frequently in the Caplacizumab group (81% of patients) than in the placebo group (46% of patients). Three drug- treated patients had exacerbations with a baseline ADAMTS13 activity of less than 10%, but out of 11 patients in the placebo group, 90% have an activity less than 10%. After cessation of the study drug, 8 patients in the study group had a relapse during the 1-month follow-up period (with 7 of them having a relapse within 10 days after cessation of the study drug and have a baseline activity of less than 10%), as compared with no patients in the placebo group. Two deaths occurred during the study, both in the placebo group; one due to severe, refractory TTP, and the other was due to cerebral haemorrhage.

During the treatment period, 34 of the case group and 37 of the control produced adverse effects. Headache and epistaxis were the most common adverse events related to the study drug. The number and percentage of patients with bleeding-related adverse events were higher in the sample population than in the placebo. Serious bleeding-related adverse events were reported in 2 patients in each study group: subarachnoid and retinal haemorrhage and metrorrhagia in the Caplacizumab group and cerebral haemorrhage and haematuria in the placebo group. Serious adverse events were reported in 13 patients in the Caplacizumab group and 12 patients in the placebo group. Immune-related adverse events were reported in 17 patients (49%) in the Caplacizumab group and 12 patients (32%) in the placebo group. In the sample group, drug-induced antidrug- antibody responses were confirmed in three patients (9%).

RELEVANCE OF STUDY

Thrombotic thrombocytopenic purpura (TTP) is rare, with a reported incidence of six cases per million per year in the UK.[4] It is an important diagnosis to make because the untreated

mortality is 90%, which can only be reduced with the prompt delivery of plasma exchange (PEX). So it is inevitable to find a recognized and appropriate medical therapy. The available treatment of TTP includes Plasma therapy, Steroids and Rituximab. But in certain condition such as refractory and remitting cases, drugs such as vincristine and cyclophosphamide is indicated irrespective of its side effects.[3] The drug used in TTP have higher adverse effects that produce serious problems to the patients. That increase the demand for finding the newer drug to the patient.

CONCLUSION

Caplacizumab, an anti–von Willebrand factor Nanobody which shows a faster reduction in the symptoms than placebo to patients with Acquired Thrombotic Thrombocytopenic Purpura (aTTP). Major problem that limiting the use of the risk is its increased risk of bleeding. But when considering the risk-benefit ratio, including the severity of disease. Caplacizumab is one of the good choice of drug to a TTP.

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