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Review Article

A SYSTEMATIC REVIEW ON CAPLACIZUMAB FOR THE TREATMENT OF ACQUIRED THROMBOTIC THROMBOCYTOPENIC PURPURA

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ABSTRACT

A systematic review of literature addressing the efficacy and safety of caplacizumab for patients with acquired thrombotic thrombocytopenic purpura (aTTP) was done. The literature search for 5 years (2017–2021) was conducted using particular search terms in databases/search engines (PubMed, Cochrane), and articles were screened based on inclusion and exclusion criteria. A total of 394 peoples were involved in the selected studies. With caplacizumab, the median time to normalization of the platelet count was faster than with a placebo. In comparison to those who received a placebo, patients who received caplacizumab required fewer plasma exchanges and spent less time in the hospital. Mucocutaneous bleeding was reported by 65% of participants receiving caplacizumab and 48% of patients receiving a placebo as the most frequent side effect. Three patients died in the placebo group. After the trial period, one patient died due to cerebral ischemia in the caplacizumab group. Caplacizumab was efficacious and well tolerated in patients with aTTP who experienced a diseases exacerbation.

Keywords: Acquired thrombotic thrombocytopenic purpura, Plasma exchange, Caplacizumab.

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INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP), a rare life-threatening blood disorder may be acquired or inherited [1-4]. Inherited TTP is caused due to the variants in the ADAMTS13 gene. The acquired TTP (aTTP) is caused by a severe deficiency of ADAMTS13 gene [4-9]. A rare, life-threatening autoimmune blood clotting disorder, manifested by systemic microvascular thrombosis leading to profound thrombocytopenia, hemolyticanemia, and organ ischemia, is known as aTTP [1,2,8,10,11]. Inhibitory autoantibodies to the von Willebrand Factor (vWF)- cleaving protease, ADAMTS13, results in aTTP [3]. The reduction in ADAMTS13 activity results in the accumulation of ultra-large (UL) Vwf multimers, which bind to platelets and induce the formation of microthrombi, causing tissue ischemia and organ dysfunction, and may result in major thromboembolic complications such as stroke, myocardial infarction, and arterial and venous thrombosis [12-14]. The chance of recurrence is possible when there is a severe deficiency in ADAMTS13. Caplacizumab, an anti-VWF nanobody appeared recently as a new treatment in aTTP [15]. Caplacizumab is changing the standard of care of aTTP by opening the perspective of a dramatic decrease of unfavorable outcomes while substantially alleviating the burden of care. Caplacizumab improves organ failure and stabilizes platelet count until immunosuppression (corticosteroids and rituximab) improves durably ADAMTS13 activity by inhibiting anti-ADAMTS13 antibodies production [16-19]. Hence, we proposed to conduct a systematic review on efficacy and safety of caplacizumab for the treatment of patients with aTTP.

METHODS

Search strategy and study selection

This systematic review followed the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) standards. The searched database includes PUBMED, Cochrane Library from 2017 to 2022. Search terms used were TTP, aTTP, ADAMTS13, caplacizumab,and vWF. Full text randomized controlled trial article on caplacizumab for the treatment of acquired thrombotic thrombocytopenic purpura, full text articles published in English language were included. The exclusion criteria include articles with no full text, duplication, review articles, case reports, brief reports, conference proceedings, observational cohort studies, and non-randomized control trails.

Data extraction and analysis

The literature screening and data extraction were done independently by two authors. Differences in the summary of the results were discussed and dealt with by the two authors. Reading the title and abstract and the full text were done for both the initial and secondary screenings. PRISMA flow chart was used to describe the selection of studies. Two authors independently extracted the following information from each study which includes author name, year of study, study design, number of subjects, inclusion criteria, exclusion criteria, treatment, duration of treatment, outcomes of treatment, and adverse effects of caplacizumab.

RESULTS AND DISCUSSION

A total of 268 records were identified, and following the screening process, a total of 4 articles were included in the review chart. There was one duplication of literature. Fig. 1 shows PRISMA chart of the study selection process.

The clinical benefit of caplacizumab was investigated and observed that there were four events of which 1 pulmonary embolism and 3 aTTP exacerbations were accounted for in 4 patients of caplacizumab group and there were 20 events such as 2 acute myocardial infarctions, one event of ischemia, hemorrhagic stroke, pulmonary embolism, deep vein thrombosis, venous thrombosis, and 13 aTTP exacerbations were accounted in 14 patients who have been in the placebo group and two of the placebo-treated patients died from aTTP [20]. Caplacizumab took

Table 1: Characteristics of selected studies of caplacizumab in acquired thrombotic thrombocytopenic purpura

S. No	Author name	Year	Study design	Subject (n)	Treatment	Treatment durations	Outcomes	Adverse effects
1.	Peyvandi *et al.*	2016	Single blind, parallel design, randomized, placebo-controlled, multicentre study.	75	Caplacizumab	30 days	Caplacizumab reduce the risk of major thromboembolic morbidities and mortalities associated with aTTP.	Mild anaemia
2.	Scully *et al.*	2019	Double-blind, controlled trial	145	Caplacizumab versus placebo	30 days	Normalization of platelet count	Mucocutaneous bleeding
3.	Estcourt *et al.*	2019	Double-blind, superiority randomised controlled trial	145	Caplacizumab versus placebo	30 days	Reduce the number of aTTP death.	Mucosal bleeding (epistaxis, gingival)
4.	Knoebl *et al.*	2020	Double-blind, Hercules study	31	Caplacizumab versus placebo (n=31)	25 days	Controlling platelet consumption and aTTP propagation	Splenectomy, meningitis

aTTP: Acquired thrombotic thrombocytopenic purpura

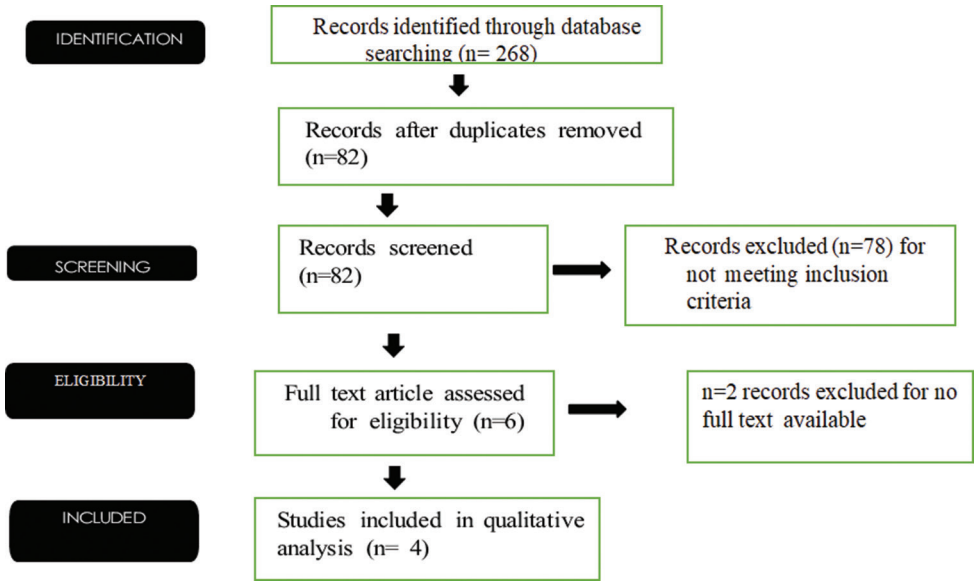

Fig. 1: PRISMA chart of the study selection process

less time for the platelet count to normalize (2.69 days vs. 2.88 days, p=0.01. With caplacizumab, recurrence of aTTP at any point in the trial was 67% lower than the placebo (12% vs. 38%, p<0.001). In caplacizumab group, no patients developed refractory disease and also received less plasma exchange and had a shorter hospitalization than the placebo group [18,19]. Nearly, 65% of patients had mucocutaneous bleeding, the most common adverse event, while 48% of patients experienced the same in placebo [18,19]. During the trial period, death of three patients was recorded in placebo group and death of one patient was recorded in the caplacizumab group. Time that the patients were thrombocytopenic was reduced with caplacizumab {2·69 days [95% confidence interval (CI) 1.89–2.83] vs. 2.88 days [95% CI 2.68–3.56], p=0·01}. In the period of study, at any instance of time, caplacizumab treated patients were 1.5 times more likely to have normal platelet count [18]. The reduction in TTP-related deaths (0 vs. 4%) and recurrence of TTP (4 vs. 38%) was influenced by the reduction in the secondary composite outcome (TTP-related death, recurrence of TTP, or major thromboembolic event) [19]. When caplacizumab was stopped, aTTP recurred in the caplacizumab.

Arm while all recurred in the placebo arm during the 30 days after daily plasma exchange was stopped [17].

The treatment's impact on the frequency of major thromboembolic events and exacerbations in the phase II TITAN study with caplacizumab was clinically defined. The caplacizumab treatment helps to enhance longer-term results by means of reducing acute thromboembolic complications and exacerbations [16]. Caplacizumab treatment required little exchange of plasma and shorter hospitalization than placebo treatment. Most often occurring adverse event was mucocutaneous hemorrhage. In comparison to placebo, caplacizumab was associated with faster normalization of the platelet count, a decreased incidence of a composite of TTP-related deaths, and recurrence of TTP [18]. The benefits of caplacizumab were illustrated by randomized control trial on caplacizumab in adults, which portrays the reduction of time to normalize the platelet counts and a reduction in the number of TTP-related death and TTP recurrences during study treatment [18,19]. Table 1 shows the characteristics of selected studies of caplacizumab in acquired thrombotic thrombocytopenic purpura.

CONCLUSION

Caplacizumab decreased the time to normalization of the platelet count, the risk of major thromboembolic morbidities, and mortality associated with aTTP. It was efficacious and well tolerated in patients with aTTP who experienced a disease exacerbation. The combination

of caplacizumab with PEX (plasma exchange) and immunosuppressant could be an alternative therapy in recurrent relapses of aTTP.

AUTHORS CONTRIBUTION

Muthu Karuppee Kannan: Data Collection, original draft preparation. Lokesh Kumar Dhavanam Ramesh Babu: Data Collection, original draft preparation. LokeshwarVijayaganapathy: Data Collection, original draft preparation. Rubak Kumaran Mylainathan: Data Collection. Dennis Win Min Tun: Data Collection. Jayasutha Jayram: Supervision, formal analysis, review, and editing of the manuscript.

CONFLICTS OF INTEREST

The author confirms no conflict of interest.

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