Transfusion Evidence Synopsis

Caplacizumab Treatment for Acquired Thrombotic Thrombocytopenic Purpura (HERCULES trial)

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Abstract

CLINICAL QUESTION: In people with acquired thrombotic thrombocytopenic purpura (TTP) does caplacizumab decrease the time to normalisation of the platelet count and the risk of death and complications caused by thrombotic events and organ damage?

EVIDENCE FROM TRIAL: In adults with acquired TTP, caplacizumab decreased the time to normalisation of the platelet count and decreased the risk of TTP-related death, and recurrence of TTP.

Introduction

Acquired thrombotic thrombocytopenic purpura (TTP) is a rare disorder, approximately 1 new case per million people, characterised by microangiopathic anaemia, thrombocytopenia and microvascular thrombosis (Joly*, et al* 2017, Scully*, et al* 2019). It is an autoimmune disorder characterised by the presence of an antibody that inhibits activity of the von Willebrand factor (vWF) cleaving protease ADAMTS13, and leads to very low levels of ADAMTS13 (< 10%) (Scully*, et al* 2019).

Acquired TTP is twice as common in women, and its clinical course is characterised by the tendency to relapse (Joly*, et al* 2017). Most recurrences occur in first two years after the initial diagnosis (Scully*, et al* 2019). It is a life-threatening disorder that can also cause major long-term morbidity e.g. cognitive deficits (Joly*, et al* 2017, Scully*, et al* 2019).

Caplacizumab is an anti-vWF immunoglobulin that inhibits the interaction between ultra large vWF multimers and platelets, therefore preventing consumption of platelets and the development of microvascular thrombi (Peyvandi*, et al* 2016).

This Transfusion Evidence Synopsis summarises the RCT in the NEJM (Scully*, et al* 2019). This RCT assesses the use of caplacizumab for at least 30 days after daily plasma exchange has been completed (Scully*, et al* 2019). The study also assessed the potential of caplacizumab to reduce the risk of recurrence by allowing treatment to continue for up to an additional 28 days if there was evidence that the underlying autoimmune disorder was still active (e.g. low ADAMTS13 levels) (Scully*, et al* 2019).

INSERT EVIDENCE BOX ABOUT HERE

Summary of the Results of the Study

The main finding was that caplacizumab reduced the time that participants were thrombocytopenic (2.69 days (95% CI 1.89 to 2.83) versus 2.88 days (95% CI 2.68 to 3.56), P = 0.01). At any time point during the study individuals receiving caplacizumab were 1.5 times more likely to have a normal platelet count (Table 1).

There was a reduction in the secondary composite outcome (TTP-related death; recurrence of TTP, or major thromboembolic event) during study treatment (12% vs. 49%; P < 0.001), this was driven by a reduction in TTP-related deaths (0% versus 4%) and recurrence of TTP (4% versus 38%) (Table 1).

The recurrence of TTP in the caplacizumab arm usually occurred in the 4 weeks after the caplacizumab had been stopped (6 out of 9 cases), whereas all the recurrences in the placebo arm occurred during the 30 day period after daily plasma exchange had stopped (Table 1).

It was unclear whether caplacizumab reduced the time to normalisation of three organ damage markers (Table 1). It appears that caplacizumab decreased the number of days of plasma exchange and the time participants were in ITU, however it was not clear whether these differences were statistically significant (Table 1).

Bleeding-related adverse events occurred in 46 participants (65%) in the caplacizumab arm and in 35 (48%) participants in the placebo arm. Most were mild or moderate severity but there were 8 (11%) cases of serious bleeding in the caplacizumab arm and 1 (1%) case in the placebo arm.

INSERT TABLE 1 ABOUT HERE

Limitations of the Trial

This trial included 145 participants, but only 108 (75%) participants completed the trial, 1 withdrew prior to receiving any trial treatment and 36 withdrew after receiving at least 1 dose. There was an imbalance between treatment arms with 13 (18%) withdrawing in the caplacizumab arm and 23 (32%) in the placebo arm.

There were also some baseline imbalance, with more participants with an initial TTP diagnosis in the caplacizumab arm (67%) than in the placebo arm (47%).

Evidence in context

This is the largest RCT of caplacizumab in adults with acquired TTP. It showed a benefit of a caplacizumab in reducing time to normalisation of the platelet count and a reduction in the number of TTP-related deaths and TTP recurrences during study treatment. However, it can increase the risk of bleeding usually due to mucosal bleeding (epistaxis, gingival). The estimated cost of treating an episode of TTP with caplacizumab is USD 270,000 (Sanofi Genzyme 2019).

Implications for research

NICE is going to perform a single technology appraisal of caplacizumab (NICE 2018).

Implications for practice

This drug has been approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for use in adults with acquired TTP. Due to its high cost health economic assessments will need to be performed to assess its cost-effectiveness prior to its use in many countries.

Conflicts of Interest

None to declare.

References

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Table 1 Outcomes from the HERCULES trial

Outcomes	**Capacluzimab (N = 71)**	**Placebo (N = 73)**	**P value**
Time to normalization of the platelet count of capacluzimab versus placebo (95% CI)	Rate ratio 1.55 (1.09 to 2.19)		0.01
Proportion of participants with: TTP-related death, a recurrence of TTP, or at least one major thromboembolic event during study drug treatment	9 (12%)	36 (49%)	< 0.001
Recurrence of TTP during study (including 4 week follow-up)	9 (12%)	28 (38%)	< 0.001
Refractory TTP	0	3 (4%)	0.06
Median number of days to normalisation of organ damage markers (95% CI)	2.86 (1.93 to 3.86)	3.36 (1.88 to 7.71)	Not reported
Median number of days of plasma exchange (range)	5 (1 to 35)	7 (3 to 46)	Not reported
Median number of days in intensive care (range)	3 (1 to 10)	5 (1 to 47)	Not reported

Evidence Box

Study design: Double-blind, superiority, randomised controlled trial

Study years: November 2015 to April 2017

Countries: Australia, Belgium, Canada, Czech Republic, France, Germany, Hungary, Israel, Italy, Netherlands, Spain, Switzerland, Turkey, UK, USA

Setting: adults requiring daily plasma exchange for clinically diagnosed acquired TTP

No. of patients: 145 randomised (144 received at least 1 dose of Caplacizumab or placebo), 36 discontinued trial regimen (13 in the caplacizumab group and 23 in the placebo group).

Mean age (range): 46 (18 to 79)

Female: 100 (69%)

ADAMTS 13 activity: < 10% 123 (85%); ≥10% 20 (14%); missing 2 (1%)

Inclusion criteria: Adults (≥ 18 years) with a clinical diagnosis of acquired TTP (initial or recurrent), has thrombocytopenia and evidence of red blood cell fragmentation (e.g., schistocytes) and has already received 1 plasma exchange

Exclusion criteria: Platelet count ≥100×10^9/L; atypical haemolytic uraemic syndrome; known other causes of thrombocytopenia; congenital TTP; pregnant or breast-feeding; clinically significant active bleeding or high risk of bleeding (excluding thrombocytopenia); therapeutic anticoagulation that cannot be stopped; malignant hypertension; life-expectancy < 6 months due to non-TTP associated condition

Comparison: Patients were randomly assigned to receive parenteral caplacizumab or placebo, in addition to standard-of-care treatment for TTP (plasma exchange, steroids, and immunosuppression). Treatment continued for 30 days after completion of daily plasma exchange, and could be extended for a further 28 days if persistent severe ADAMTS 13 deficiency.

Primary outcome: Time to platelet count response defined as initial platelet count ≥ 150×10^9/L with subsequent stop of daily PE within 5 days

Key secondary outcomes: Proportion of participants with: TTP-related death, a recurrence of TTP, or at least one major thromboembolic event during study drug treatment; recurrence of TTP during study (including 4 week follow-up); refractory TTP (absence of platelet count doubling after 4 days of standard treatment, and LDH > upper limit normal. Time to normalisation of three organ damage markers (LDH, serum creatinine, cardiac troponin I).