Editorial Commentary

How should caplacizumab be used for treatment of immune thrombotic thrombocytopenic purpura?

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In past 30 years, therapeutic plasma exchange (TPE) has been the cornerstone for managing acquired or immune thrombotic thrombocytopenic purpura (iTTP) (1). Such a therapeutic modality in conjunction with other adjunctive therapies has significantly reduced the mortality rate to less than 5–20% (2-4). However, approximately 50% of patients who recover from the acute episode may experience the disease recurrence (e.g., exacerbation and/or relapses) (2,5,6). The off-label use of rituximab, a monoclonal antibody against CD20 on B cells, during acute episode or preventatively, has significantly reduced the rate of disease relapse (7,8). However, there is still unmet need for how to address acute ongoing microvascular thrombosis, which results in organ damage while waiting for the disappearance of autoantibodies against ADAMTS13, a plasma metalloprotease that cleaves von Willebrand factor (VWF) (9) and the normalization of plasma ADAMTS13 activity.

Caplacizumab, a nanobody against VWF (10) that binds the A1 domain of VWF (11) and inhibits the adhesion of activated platelets to endothelium-derived ultra large VWF (12,13). Thus, caplacizumab can effectively block the downstream thrombus formation, resulting from exaggerated platelet-VWF interaction due to lack of VWF proteolysis by plasma ADAMTS13. In 2019, the US Food and Drug Administration (FDA) approved caplacizumab for the treatment of adult patients with acquired TTP (i.e., mostly iTTP) in combination with TPE and other immunosuppressive therapies based on the promising results of phase II and III clinical trials (12,13). One year later, the International Society on Thrombosis and Haemostasis (ISTH) guidelines conditionally recommended the use of caplacizumab for all iTTP patients experiencing the first acute episode or subsequent relapsing events on top of TPE and other immunosuppressive therapies (14,15) (*Figure 1*). This triple therapy has been proposed to be the standard of care for iTTP today (16,17). Such a combined therapy has accelerated the normalization of platelet counts, reduced TTP-related complications (such as death and thromboembolic events), shortened the intensive unit and hospital stay, and reduced the duration of TPE (13,16). Most importantly, it has significantly reduced the rates of disease exacerbation during acute episode and the mortality rate of iTTP (13,16-19).

However, there is still a question whether caplacizumab should only be reserved for severe or critically ill patients or for those who fail the initial TPE. In another word, should caplacizumab be prescribed upfront to all patients with acute iTTP? The answer is “yes”. However, patients who are allergic, or experience intracranial hemorrhage are contraindicated for caplacizumab. The provider’s hesitancy for not using caplacizumab upfront is primarily resulted from the lack of access to the drug such as in the developing countries and the concern of potentially added costs, even in the wealthy country like USA (20). It was estimated that an additional quarter million dollars may be spent for prescribing caplacizumab for each course of treatment of iTTP (20,21). However, this extra cost may still be worthwhile considering a potential fatality being prevented.

In fact, each patient with acute iTTP should be

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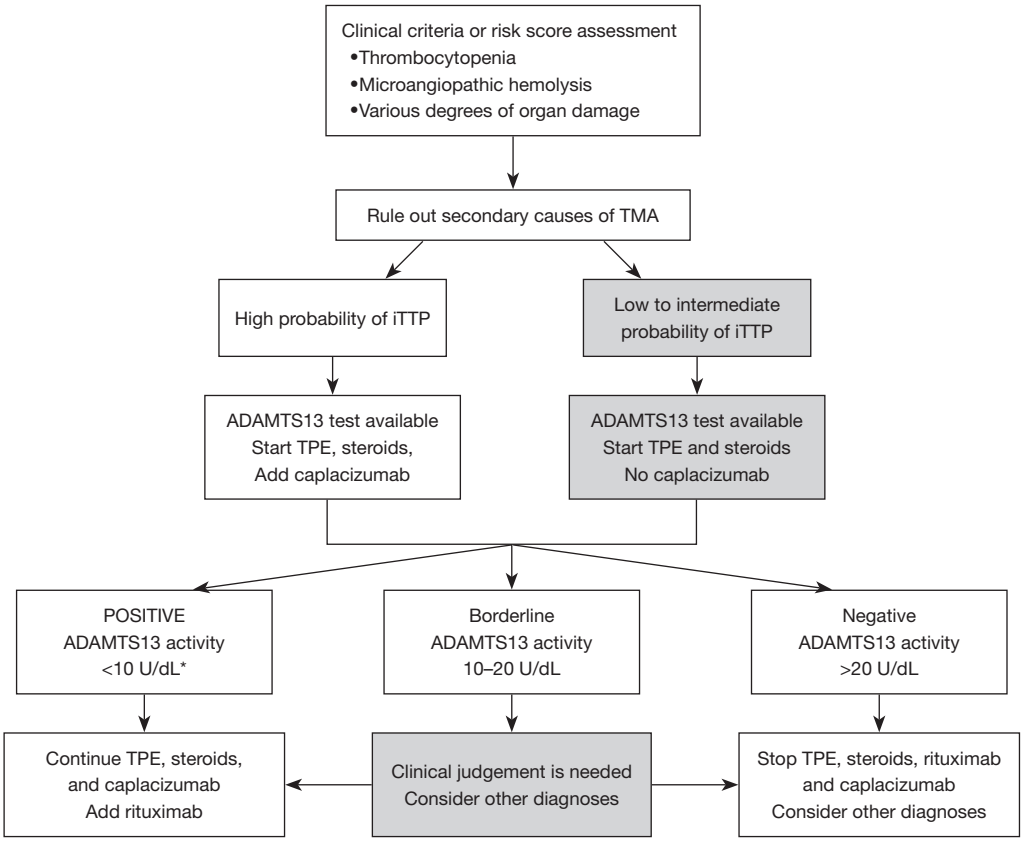

Figure 1 Schematic diagram demonstrates the process for the diagnosis and management of iTTP. When a patient presents with severe thrombocytopenia with platelet count <30×10^9/L, creatine <2.26 mg/dL in the presence of hemolysis and schistocytes, but no history of malignancy and/or hematopoietic progenitor cell transplantation or known drugs that causes TMA, the likelihood of iTTP is very high (based on French Score). This patient will be benefited from ordering an ADAMTS13 test, immediate TPE and corticosteroids, and early caplacizumab. Otherwise, if the clinical probability of iTTP is low to intermediate, ADAMTS13 test should be ordered prior to TPE and corticosteroid, but no caplacizumab. Use ADAMTS13 activity result to guide further therapies as shown in the bottom of the diagram. This figure is adapted from Zheng *et al*. (15). *, in most initial iTTP cases, plasma ADAMTS13 activity is less than 5 U/dL (or 5% of normal) or undetectable. Normal ADATMS13 activity is 50–150 U/dL. Those with a relapsed episode may have higher ADAMTS13 activity. TMA, thrombotic microangiopathy; iTTP, immune thrombotic thrombocytopenic purpura; TPE, therapeutic plasma exchange.

considered "critically ill" as the patient may suddenly demise, resulting from ongoing thrombosis and damage in the major organs (i.e., heart, brain, pancreas, and adrenal glands, etc.). Cardiac arrhythmia appears to be the primary cause of sudden death in iTTP (22,23). Thus, an intensive care unit (ICU) monitoring is necessary and early administration of caplacizumab to stop the ongoing thrombosis during the acute events may reduce not only the in-hospital mortality rate, but also potential long-term complications, such as cognitive decline, depression, and major cardiovascular events recovering from acute iTTP. When everything is considered such as the costs of ICU and hospital stay, TPE, plasma products, the iTTP-related death, and the potential long-term sequelae, the addition of caplacizumab to daily TPE and immunosuppressives (e.g., corticosteroids and rituximab) is found to be more cost-effective than a dual therapy (e.g., TPE and immunosuppressives), and allows the better utilization of the scanty healthcare resources (e.g., TPE, ICU and hospital stay, etc.) (13,16).

Another question is how to use and when to stop caplacizumab. Typically, a patient with high likelihood of iTTP based on clinical criteria or risk score assessment or a confirmed iTTP should receive an intravenous loading

dose of caplacizumab (10 mg) prior to the first round of TPE therapy; a subsequent dose (10 mg) should be injected subcutaneously daily right following the completion of each TPE. Caplacizumab treatment should continue for 30 days after the last round of TPE and may be extended for another 28 days if a patient still has low plasma ADAMTS13 activity (<10 IU/dL or 10% of normal) (13). More recently, it has been demonstrated that caplacizumab therapy can be safely discontinued when platelet counts and serum lactate dehydrogenase (LDH) levels are normalized, or plasma ADAMTS13 activity ≥20 U/dL (or 20% of normal) (13,14), consistent with the new definition of clinical remission or partial ADAMTS13 remission for safe discontinuation of caplacizumab therapy (24).

Future studies should be considered to determine whether the use of caplacizumab, corticosteroids, and rituximab without TPE will be sufficient to manage acute iTTP. Very limited clinical experience has already shown the efficacy and safety of managing iTTP with caplacizumab and immunosuppressives but without TPE (25,26); additionally, how recombinant ADAMTS13, which may come to clinic soon, will fit into the overall treatment scheme of iTTP remains to be determined.

In conclusion, caplacizumab in conjunction with TPE and other immunosuppressive therapies (e.g., corticosteroids and rituximab or other drugs), the triple therapy, should be considered upfront for all adult patients with high probability of iTTP or confirmed diagnosis of iTTP to reduce the mortality and potential long-term sequalae resulting from acute iTTP.

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Footnote

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