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Opinion Article

# Caplacizumab in Acute Immune Thrombotic Thrombocytopenic Purpura

**Paulus Anthony***

*Department of Thrombosis, Dublin City University, Dublin, Ireland*

## DESCRIPTION

Acute Thrombotic Thrombocytopenic Purpura (TTP) is a rare but life-threatening disorder characterized by the formation of small blood clots throughout the body, leading to a low platelet count (thrombocytopenia) and organ damage. The management of acute immune Thrombotic Thrombocytopenic Purpura (iTTP) has evolved significantly with the introduction of caplacizumab, a novel therapeutic agent that targets Von Willebrand Factor (VWF) to prevent platelet aggregation.

However, recent findings suggest that caplacizumab therapy may be associated with complications, including delayed recovery of ADAMTS13 activity, which is crucial for normalizing platelet function and preventing thrombus formation. This article explores the implications of caplacizumab therapy in the context of acute TTP, focusing on its effects on ADAMTS13 recovery and the potential for acute thrombotic events post-therapy.

### Acute TTP and caplacizumab

TTP is primarily caused by a deficiency of ADAMTS13, a von Willebrand factor-cleaving protease, leading to the accumulation of large VWF multimers that promote excessive platelet adhesion and aggregation. The clinical presentation includes microangiopathic hemolytic anemia, thrombocytopenia, neurological symptoms, renal impairment, and fever. Traditionally, the cornerstone of treatment has been Therapeutic Plasma Exchange (TPE), which removes the large VWF multimers and replenishes ADAMTS13.

Caplacizumab, a nanobody that inhibits the interaction between VWF and platelets, was approved by the FDA in 2019 for use in conjunction with TPE and immunosuppressive therapies. Clinical trials demonstrated that caplacizumab significantly reduces the time to platelet normalization, decreases the need for TPE, and lowers the incidence of exacerbations and relapses in patients with iTTP. However, the introduction of this therapy has raised concerns regarding the timing and completeness of ADAMTS13 recovery.

### ADAMTS13 recovery post-caplacizumab therapy

Recent studies, particularly from the Spanish Registry of Thrombotic Thrombocytopenic Purpura, have provided insights into the recovery of ADAMTS13 activity following caplacizumab therapy. It was observed that while caplacizumab effectively shortened the duration of TPE, it was associated with a delay in the restoration of ADAMTS13 activity after the cessation of TPE. Specifically, episodes where caplacizumab was initiated within three days of diagnosis showed a significantly longer time to achieve ADAMTS13 activity levels of ≥ 20% compared to those treated later or those not treated with caplacizumab. This delay in ADAMTS13 recovery could be attributed to the shorter duration of TPE in early caplacizumab-treated episodes. While the overall time to reach ADAMTS13 activity levels was similar between caplacizumab-treated and non-treated groups, the timing of caplacizumab administration appears to influence recovery dynamics. These findings suggest that while caplacizumab is beneficial in managing acute episodes of TTP, careful consideration must be given to its timing in relation to TPE to optimize patient outcomes.

### Acute thrombotic events after caplacizumab therapy

The interplay between caplacizumab therapy and the risk of acute thrombotic events is important to understanding the safety profile of this treatment. Although caplacizumab has been shown to reduce the incidence of thrombotic events during treatment, there is emerging evidence that patients may experience thrombotic complications after therapy has concluded. The mechanism behind this phenomenon may relate to the transient inhibition of VWF activity and the subsequent rebound in platelet activity once caplacizumab is withdrawn. Studies have indicated that patients who have undergone caplacizumab therapy may be at risk for thrombotic events due to the potential for rapid changes in platelet aggregation dynamics. This risk underscores the importance of monitoring patients closely after the discontinuation of caplacizumab, particularly in those with residual low ADAMTS13 activity or other risk factors for thrombosis.

**Correspondence to:** Paulus Anthony, Department of Thrombosis, Dublin City University, Dublin, Ireland, E-mail: paulus@anthony.ir

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## CONCLUSION

Caplacizumab has transformed the management of acute iTTP by providing rapid control of platelet aggregation and reducing the need for extensive plasma exchange. However, the complexities surrounding ADAMTS13 recovery and the potential for acute thrombotic events following therapy necessitate a nuanced approach to treatment. Ongoing research is essential to delineate the optimal timing of caplacizumab administration and to establish protocols for monitoring and managing patients after therapy. As the understanding of TTP evolves, so too must the strategies employed to ensure the best possible outcomes for patients facing this challenging condition. In summary, while caplacizumab represents a significant advancement in the treatment of acute TTP, clinicians must remain vigilant regarding its implications for ADAMTS13 recovery and the risk of post-therapy thrombotic events. Further studies will be pivotal in refining treatment protocols and enhancing patient safety in the management of this complex disorder.