Caplacizumab Improves iTTP Outcomes in Real-World Settings

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> Immune-mediated thrombotic thrombocytopenic purpura (iTTP) remains a rare, life-threatening haematological emergency requiring rapid diagnosis and treatment to prevent severe organ damage and death. While plasma exchange (PEX) and immunosuppression form the cornerstone of therapy, real-world evidence presented at EHA 2026 highlights the sustained impact of caplacizumab on improving patient outcomes, particularly in reducing acute phase complications and long-term sequelae.1

KEY TAKEAWAYS

- The Pivot: Caplacizumab, a targeted anti-VWF nanobody, has transitioned from trial settings to real-world clinical practice, demonstrating consistent benefits.
- The Data: Real-world cohorts show a reduction in refractory iTTP cases and lower mortality rates compared to historical controls not receiving caplacizumab.
- The Action: Clinicians should consider early initiation of caplacizumab in conjunction with PEX and immunosuppression for all iTTP patients, given its established safety profile and efficacy.

Immune-mediated thrombotic thrombocytopenic purpura (iTTP) is characterised by severe ADAMTS13 deficiency, leading to the formation of ultra-large von Willebrand factor (VWF) multimers and subsequent microvascular thrombosis. This pathophysiology results in microangiopathic haemolytic anaemia, thrombocytopenia, and organ ischaemia, with neurological and renal involvement being common.1 Historically, treatment relied on daily plasma exchange (PEX) combined with corticosteroids, often supplemented by rituximab. Despite these interventions, mortality rates remained substantial, and a significant proportion of patients experienced refractory disease or relapse.2 The introduction of caplacizumab, an anti-VWF nanobody, represented a targeted therapeutic advance designed to inhibit VWF-platelet interaction, thereby preventing microthrombi formation.3 iTTP is a rare but life-threatening disorder, with an estimated incidence of 1.5 to 6 cases per million adults per year. The acute phase of iTTP requires urgent diagnosis and initiation of treatment to prevent severe organ damage and death. The underlying autoimmune process involves autoantibodies against ADAMTS13, a metalloprotease responsible for cleaving large VWF multimers. This deficiency leads to an accumulation of uncleaved VWF, which spontaneously binds to platelets, forming microthrombi that occlude small blood vessels.1

Real-World Evidence on Caplacizumab in iTTP

Recent presentations at EHA 2026 provided crucial real-world insights into the effectiveness and safety of caplacizumab in diverse clinical settings, moving beyond the controlled environment of pivotal trials. One large retrospective

cohort study, encompassing 350 patients with acute iTTP across 20 European centres, evaluated outcomes following the integration of caplacizumab into standard care.4 Patients received caplacizumab in addition to PEX and immunosuppression (corticosteroids, with or without rituximab). The primary endpoints included time to platelet count normalisation, incidence of refractory disease, and mortality during the acute phase. The study population included both newly diagnosed patients and those experiencing a relapse, reflecting the heterogeneity of iTTP presentations in clinical practice. Data collection involved retrospective review of patient medical records, ensuring a comprehensive capture of clinical characteristics, treatment regimens, and outcomes. The centres involved were a mix of academic and community hospitals, further enhancing the generalisability of the findings.4

The study reported a median time to platelet count normalisation (platelets ≥150 × 109/L) of 3 days (IQR 2-5 days) in the caplacizumab-treated group.4 This compares favourably to historical cohorts where platelet normalisation often took 5-7 days or longer.2 The incidence of refractory iTTP, defined as persistent thrombocytopenia after 7 days of PEX or relapse during PEX, was significantly lower in the caplacizumab cohort at 8% (95% CI 5-11%) compared to historical rates of 20-30% in patients not receiving caplacizumab.4,5

Furthermore, acute phase mortality (within 30 days of diagnosis) in the caplacizumab-treated group was 4.5% (95% CI 2.5-7.0%).4 This represents a substantial reduction from historical mortality rates, which have been reported between 10-20% prior to the widespread adoption of caplacizumab.2,5 The study also noted a lower incidence of major adverse cardiovascular events (MACE) and severe neurological events during the acute phase, although specific statistical comparisons were not provided for these secondary outcomes.4

Another case-based series, drawing from a national registry of 85 patients in the UK, corroborated these findings.6 This series highlighted the successful management of patients with severe presentations, including those with significant neurological compromise at baseline. The registry data indicated that 92% of patients achieved a complete response (platelet count ≥150 × 109/L and cessation of PEX) within 7 days of caplacizumab initiation.6 The most frequently reported adverse events were mild to moderate bleeding, predominantly epistaxis and gingival bleeding, consistent with the known mechanism of action of caplacizumab. Severe bleeding events requiring transfusion were rare, occurring in less than 2% of patients.6

These real-world data collectively reinforce the efficacy and safety profile established in randomised controlled trials such as HERCULES.3 The consistent reduction in time to platelet response, lower rates of refractory disease, and decreased acute phase mortality observed across different populations and healthcare systems underscore the clinical utility of caplacizumab as a frontline therapy for iTTP. Limitations of these real-world studies include their observational nature and the potential for selection bias, as well as variations in concomitant immunosuppressive regimens. The retrospective design of the European cohort study, for instance, means that treatment decisions were not randomised, and unmeasured confounders could influence outcomes. Similarly, the UK registry, while comprehensive, may not fully capture all nuances of individual patient management. However, the large sample sizes and multi-centre designs provide a robust complement to existing trial data, strengthening the evidence base for current treatment guidelines.4,6

CLINICAL IMPLICATIONS

The real-world data presented at EHA 2026 on caplacizumab in iTTP are not merely confirmatory; they solidify the drug's position as an indispensable component of acute iTTP management. For the practising

haematologist, this means that early initiation of caplacizumab should be the default, not an option reserved for refractory cases. The observed reduction in refractory disease and acute mortality is compelling, suggesting that delaying its use is a missed opportunity to improve patient outcomes and potentially reduce the burden of long-term complications. It is a rare instance where real-world application so closely mirrors trial results, providing a strong mandate for consistent prescribing.

From a patient perspective, the implications are profound. A faster resolution of thrombocytopenia and a lower risk of acute complications translate directly into reduced hospital stays, fewer PEX procedures, and a decreased likelihood of irreversible organ damage, particularly neurological sequelae. While the cost of caplacizumab is significant, the economic burden of prolonged hospitalisation, intensive care, and managing chronic iTTP complications or relapses likely outweighs the upfront drug cost. Payers and healthcare systems should recognise this broader economic benefit, moving beyond a narrow focus on drug acquisition costs to consider the total cost of care.

For the pharmaceutical industry, the continued positive real-world performance of caplacizumab (Sanofi) reinforces the value of targeted therapies in rare diseases. It also sets a high bar for any future treatments entering the iTTP landscape. The challenge now lies in ensuring equitable access globally, as the benefits are clear, but implementation varies. Further research should focus on optimising the duration of caplacizumab therapy and its role in preventing long-term relapse, building on this strong foundation of acute phase efficacy.

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