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Real-World Insights on the Management of Immune-Mediated Thrombotic Thrombocytopenic Purpura (iTTP) With Caplacizumab

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Abstract:

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Short title: Real-world use of caplacizumab

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Immune-mediated thrombotic thrombocytopenic purpura (iTTP), also known as acquired TTP, is a life-threatening rare blood disorder caused by autoantibody-mediated severe deficiency of a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13 (ADAMTS13).[1] ADAMTS13 cleaves ultra-large von Willebrand factor (VWF) multimers into smaller multimers, preventing spontaneous platelet binding. ADAMTS13 deficiency leads to accumulation of ultra-large VWF multimers and subsequent microthrombi formation, resulting in thrombotic microangiopathy (TMA).[1]

Therapeutic plasma exchange (TPE) and immunosuppressive therapy are the mainstay treatments for adult patients with iTTP, with International Society on Thrombosis and Haemostasis (ISTH) guidelines recommending the addition of caplacizumab.[2] Caplacizumab is a VWF-directed antibody fragment that prevents the binding of platelets to ultra-large VWF multimers.[2,3] Clinical trials and European real-world studies support the efficacy and safety of caplacizumab for patients with iTTP, showing that caplacizumab treatment is well tolerated and associated with rapid platelet recovery.[4-10] Caplacizumab was approved for use in the European Union in 2018,[11] and has been commercialized and reimbursed in Belgium since September 2019.[12] A recent Belgian real-world evidence (RWE) study compared the outcomes of secondary TMA versus other TMAs (including TTP), but was conducted prior to the availability of caplacizumab and reported high mortality rates (28%) in TTP.[13] Our objective was to report real-world data on iTTP management, caplacizumab use, healthcare resource utilisation (HCRU), and the overall outcomes and safety of caplacizumab treatment.

We conducted a retrospective analysis of hospital chart data from adult patients (≥18 years old) with iTTP who were hospitalized and treated with caplacizumab in 13 Belgian hospitals. Hospitals were selected based on having ≥2 patients treated during the first 2 years of caplacizumab reimbursement (ie, by September 2021) and were equally distributed across the country. Retrospective medical data were collected (September 1, 2019 to January 15, 2022). Patients were included if they received caplacizumab treatment that was initiated and ended within the study period. No exclusion criteria were applied. Patient demographics, treatment characteristics, HCRU, efficacy, and safety outcomes are presented. Continuous variables were described as mean (standard deviation [SD]) and categorical variables were analyzed as unadjusted rates. Analyses were performed in 2 subgroups to identify differences in disease characteristics and management for first diagnosed episodes and relapse episodes.

Thirty-nine iTTP episodes (25 first diagnoses, 14 relapse episodes) were identified in 33 patients who were hospitalized and treated with caplacizumab. Most patients (81.8%) experienced 1 episode, and none experienced >2 episodes (**Table 1**). Most patients were admitted to hospital from home (first diagnoses: 13 [52.0%]; relapse episodes: 14 [100.0%]). Of the remaining 12 patients with first diagnoses, 10 (40.0%) were referred from hospitals without iTTP expertise, 1 (4%) was referred from hospital consultation and 1 (4%) was referred from a rehabilitation center. Intensive care unit stay was required for 60% of first diagnosed episodes and 28.6% of relapse episodes (duration data are shown in **Table 1)**.

Caplacizumab was initiated quickly after hospital admission for both subgroups (**Figure 1A**). Mean (SD) interval between diagnosis confirmation (ADAMTS13 activity-testing) and caplacizumab initiation was 0.4 (5.0) days and −0.7 (1.6) days for first diagnosed and relapse episodes, respectively. Treatment started the same day as TPE in 74.4% of all episodes. Mean (SD) number of caplacizumab doses per episode was 39.2 (14.7) for first diagnosed episodes and 31.9 (8.4) for relapse episodes (**Figure 1B**). Five patients needed >60 doses, including 2 patients who developed an exacerbation. Mean (SD) caplacizumab treatment duration was 39.6 (15.3) days and 32.7 (10.1) days in first diagnosed and relapse episodes, respectively (**Table 1**). All patients were treated with caplacizumab, TPE and immunosuppressive therapy. Mean (SD) time to TPE initiation after hospital admission was 2.3 (4.6) days in patients with first diagnosed episodes and 0.4 (0.5) days in patients with relapse episodes. Mean (SD) TPE duration was similar for both subgroups. The most common corticosteroid therapy was methylprednisolone, which was often dosed in 1 mg/kg per day tapered over 4 weeks. Rituximab therapy was used for 24 (96%) first diagnoses versus 9 (64.3%) relapse episodes; the most frequently (24/33 [72.7%]) used dosing scheme was 375 mg/m² on Days 1/8/15/22.

Mean (SD) time from caplacizumab initiation to sustained platelet count was 4.6 (3.3) days for first diagnosed episodes and 6.0 (5.9) days for relapse episodes. Exacerbations (2/39 [5.1%] episodes) occurred after caplacizumab was interrupted due to absence of ongoing disease symptoms. One patient did not have ADAMTS13 testing at the time of interruption, and the other had ADAMTS13 activity level <10%, suggesting the underlying cause of disease was still present. Of the 6 patients who developed a relapse (6/39 [15.4%] episodes), 3 patients experienced relapse ~1 week after caplacizumab termination. The reason for caplacizumab termination in these 3 patients was platelet count normalization for ≥30 days after TPE termination and symptom resolution. ADAMTS13 activity was <10% for all, suggesting that the underlying cause of disease was unresolved. No patients were refractory to treatment or passed away (**Table 1**).

Adverse events occurred in 6 patients (24.0%) with first diagnosed episodes and 3 patients (21.4%) with relapse episodes. Bleeding events were reported in 3/25 (12.0%) first diagnosis and 2/14 (14.3%) relapse episodes, respectively (**Table 1**). Two bleeding events, jugular catheterization and small intestine bleeding (both caplacizumab-related) were reported as serious adverse events; these were addressed by pausing treatment for 1 day and by discontinuing treatment, respectively. Thromboembolic events occurred in 7 patients (28.0%) with first diagnoses and 1 patient (7.1%) with relapse episodes. Of these, 5/7 (71.4%) events in the first diagnosis subgroup and 1/1 (100%) event in the relapse subgroup were considered complications of iTTP. None of the thromboembolic events were regarded as a complication of caplacizumab.

Our study shows that caplacizumab was initiated soon after hospital admission and diagnosis, alongside TPE and immunosuppressive therapy as per international recommendation,[2] resulting in rapid recovery of platelet count and a brief (<1 week) TPE duration, in line with results reported in HERCULES.[10] While the practice of ADAMTS13-testing at diagnosis is well established, this study shows that additional ADAMTS13-testing should be used to optimize treatment as it can guide timing of treatment discontinuation.[2] Suppressed ADAMTS13 activity (<10%) in patients who experienced relapses was also reported in TITAN and HERCULES.[9,10] The authors feel that the observed exacerbations and relapses might have been avoided if treatment was prolonged until ADAMTS13-activity normalization. While the new outcome definitions list partial remission as ADAMTS13 ≥20% but < lower limit of normal[14], the exact/best threshold to distinguish risk of relapse is uncertain. The proportion of patients with a bleeding event was lower than that observed in clinical trials (65%/21% in HERCULES/post-HERCULES respectively)[10,15] but was in line with or lower than other RWE studies; these included 13/90 (14.4%) patients with major bleeding/clinically relevant non-major bleeding,[5] and 16/77 (20%) patients with bleeding events.[7] Limitations are linked to the rarity of iTTP, resulting in the small number of patients with available data, together with decentralized care for patients with iTTP across different hospitals. Additionally, due to the retrospective nature of this study, under-recording may have occurred in hospital charts and data may not have been reported immediately (patients with iTTP are often hospitalized as emergency cases).

In conclusion, these findings on caplacizumab treatment in Belgian hospitals are in line with other published RWE[4-8] and support results from clinical trials.[9,10]

Institutional Review Board Approval: The hospital chart review was approved by all Ethics Committees of local hospitals before start of the study.

Data Sharing Statement: The data that support the finds of this study are available from IQVIA. Restrictions apply to the availability of these data, which were used under license for this study, Data are available from the author(s) with the permission of IQVIA.

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Tables and Figures

Table 1. Patient demographics, treatment characteristics, healthcare resource utilization outcomes, and efficacy and safety outcomes for patients with iTTP who had a first diagnosis or relapse episode

	First diagnoses (N=25)	**Relapse episodes (N=14)**
Gender, n (%)		
Male	14 (56.0)	4 (28.6)
Female	11 (44.0)	10 (71.4)
Time (days) between hospital admission and start of daily TPE, mean (SD)	2.3 (4.6)	0.4 (0.5)
Duration (days) of daily TPE, mean (SD)	6.1 (1.8)	5.9 (2.0)
Time (days) between TPE initiation and caplacizumab initiation, mean (SD)	0.4 (1.0)	0.0 (0.4)
Corticosteroid use, n (%)		
Yes	25 (100.0)	14 (100.0)
Rituximab use, n (%)		
Yes	24 (96.0)	9 (64.3)
Time (days) from hospitalization and request to check ADAMTS13 activity		
n	25	13
Number of days, mean (SD)	1.2 (2.3)	−0.2 (2.1)
Time (days) from ADAMTS13 result to caplacizumab initiation		
n	24	11
Number of days, mean (SD)	0.4 (5.0)[a]	−0.7 (1.6)[a]
Caplacizumab treatment duration (days)		
Mean (SD)	39.6 (15.3)	32.7 (10.1)
Median (Q1, Q3)	37.0 (33.0, 46.0)	33.5 (28.0, 36.8)
Time (days) from initiation of caplacizumab to sustained platelet count		
n	25	13
Number of days, mean (SD)	4.6 (3.3)	6.0 (5.9)
Duration (days) of hospital stay		
n	25	13
Number of days, mean (SD)	16.0 (10.3)	9.1 (2.9)
Duration (days) of intensive care unit stay		
n	15	4
Number of days, mean (SD)	6.2 (4.0)	3.8 (1.0)
Proportion of patients with an exacerbation, n (%)		
Yes	2 (8.0)	0
Proportion of patients with a relapse, n (%)		
Yes	4 (16.0)	2 (14.3)
Proportion of patients with refractory disease, n (%)		
Yes	0	0
Mortality, n (%)		
Yes	0	0
Proportion of patients with a TEE,[b] n (%)		

Yes	7 (28.0)[c]	1 (7.1)[d]
Proportion of patients with an adverse event, n (%)	6 (24.0)	3 (21.4)
Related to caplacizumab	4 (16.0)	1 (7.1)
Proportion of patients with a bleeding event, n (%)	3 (12.0)	2 (14.3)
Related to caplacizumab	3 (12.0)	1 (7.1)

Clinical response was defined as sustained platelet count ≥150x10^9/L and LDH <1.5x ULN. Clinical remission was defined as platelet count remains ≥150x10^9/L and LDH <1.5xULN for ≥30 days after stopping TPE. Exacerbation was defined as a platelet count reduction to <150x10^9/L and LDH increase within 30 days of stopping TPE, after a clinical response. Relapse was defined as platelet count reduction to <150x10^9/L after a clinical remission. Refractory disease was defined by the lack of doubling of platelet count after 4 days of treatment and an LDH level that remained above ULN.[14,16] ADAMTS13, a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13; iTTP, immune-mediated thrombotic thrombocytopenic purpura; LDH, lactate dehydrogenase; Q1/3, quartile 1/3; SD, standard deviation; TEE, thrombo-embolic event; TPE, therapeutic plasma exchange; ULN, upper limit of normal.

[a]In 4 patients caplacizumab treatment was started 1 day before ADAMTS13 test results were available. In 5 patients treatment was started 3 to 8 days before. [b]For patients with a first diagnosis, there were on average 2.6 (4.6) days between the reporting of a TEE and the start of caplacizumab. The TEE reported in the relapse subgroup was reported more than 2 months after the start of caplacizumab. The majority of patients showed several cardiovascular risk factors probably explaining the thrombotic events. Most of these events were considered as a complication of iTTP and none were considered as a complication of caplacizumab treatment. [c]Lung embolism, cerebral thrombosis, myocardial ischemia, jugular vein thrombosis, renal infarction, splenic infarction, and renal vein thrombosis. [d]Deep vein thrombosis in legs and lung embolism.

Figure 1. (**A**) Mean (SD) number of days between hospital admission and initiation of caplacizumab treatment (**B**) Mean (SD) number of doses of caplacizumab per episode

SD, standard deviation.

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Figure 1