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Original Article

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Abstract

European real-world data indicate that front-line treatment with caplacizumab is associated with improved clinical outcomes compared with delayed caplacizumab treatment. The objective of the study was to describe the characteristics, treatment patterns, and outcomes in hospitalized patients with an immune-mediated thrombotic thrombocytopenic purpura (iTTP) episode treated with front-line versus delayed caplacizumab in the US. This retrospective cohort analysis of a US hospital database included adult patients (≥18 years) with an acute iTTP episode (a diagnosis of thrombotic microangiopathy and ≥1 therapeutic plasma exchange [TPE] procedure) from January 21, 2019, to February 28, 2021. Unadjusted baseline characteristics, treatment patterns, healthcare resource utilization, and costs were compared between patients who received front-line versus delayed (<2 vs ≥2 days after TPE initiation) caplacizumab treatment. Out of 39 patients, 16 (41.0%) received front-line and 23 (59.0%) received delayed treatment with caplacizumab. Baseline characteristics and symptoms were similar between the two groups. Patients who received front-line caplacizumab treatment had significantly fewer TPE administrations (median: 5.0 vs 12.0); and a significantly shorter hospital stay (median: 9.0 days vs 16.0 days) than patients receiving delayed caplacizumab therapy. Both of these were significantly lower in comparison of means (t-test $P < .01$). Median inpatient costs (inclusive of caplacizumab costs) were 54% higher in the delayed treated patients than in the front-line treated patients (median: $112 711 vs $73 318). TPE-specific cost was lower in the front-line treated cohort (median: $6 989 vs $10 917). In conclusion, front-line treatment with caplacizumab had shorter hospitalizations, lower healthcare resource utilization, and lower costs than delayed caplacizumab treatment after TPE therapy.

Keywords

caplacizumab, healthcare resource utilization, hospital costs, immune thrombotic thrombocytopenic purpura, real-world evidence

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Introduction

Acquired thrombotic thrombocytopenic purpura, also known as immune-mediated thrombotic thrombocytopenic purpura (iTTP), is a rare, life-threatening, immune-mediated hematologic disease, which is characterized by severe thrombocytopenic, hemolytic anemia, and organ damage of varying severity caused by microthrombi.[1] The estimated global incidence of iTTP is approximately one–two cases per 1 million people/

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year.[2] In iTTP, inhibitory antibodies cause a severe deficiency of ADAMTS13, resulting in the accumulation of ultra-large von Willebrand factor (VWF). The onset of symptoms in iTTP is typically acute, with a mortality rate of approximately 90% if left untreated.[3]

Historically, treatment of acute iTTP episodes with therapeutic plasma exchange (TPE) in combination with immunosuppression improved survival rates and patient outcomes.[4] However, this treatment regimen is still associated with 7%-25% mortality, with most deaths occurring within the acute phase.[5,6] Furthermore, 10%-42% of patients with iTTP are refractory to this treatment option.[7] Exacerbations of iTTP symptoms occur in 30%-50% of patients during or after treatment with TPE.[8,9]

Caplacizumab is a bivalent, humanized Nanobody®, which targets the A1 domain of VWF, thereby preventing the binding of platelets to ultra-large VWF multimers and inhibiting microthrombi formation.[10,11] Based on the efficacy and safety demonstrated in the Phase 2 TITAN and Phase 3 HERCULES trials, caplacizumab, in conjunction with TPE and immunosuppression, is indicated for the treatment of acute iTTP episodes.[12–15] Caplacizumab was approved by the US FDA in February 2019 for the treatment of adult patients with aTTP in combination with plasma exchange and immunosuppression. The current US prescribing information recommends the administration of caplacizumab upon the initiation of TPE with subsequent treatment once daily following TPE and for 30 days beyond the last TPE. If after initial treatment course, sign(s) of persistent underlying disease such as suppressed ADAMTS13 activity levels remain present, treatment may be extended for a maximum of 28 days.[16] The 2020 International Society of Thrombosis and Haemostasis (ISTH) guidelines for the diagnosis and management of iTTP conditionally recommend that caplacizumab be included in the front-line treatment regimen, alongside TPE and immunosuppression, for patients with a high probability of iTTP.[16] Furthermore, the ISTH panel noted that the benefit with caplacizumab is greatest when initiated front-line during an iTTP episode.[16] European Renal Best Practice Working Group endorsed the ISTH guidelines and emphasized the importance of front-line caplacizumab treatment.[17]

Real-world evidence from two studies in Spain and Germany confirmed that front-line treatment with caplacizumab alongside TPE and immunosuppression as in the FDA label and clinical guidelines was associated with improved clinical outcomes compared with delayed start of caplacizumab until after TPE initiation. These two studies found that front-line use of caplacizumab alongside initiation of TPE and immunosuppression was associated with shorter time to clinical response, significantly shorter time to platelet normalization, significantly lower rates of exacerbations, significantly lower rates of refractoriness, significantly fewer TPE treatments, and significantly shorter hospitalization duration as opposed to delayed start.[18,19]

In this analysis, we conducted a retrospective, observational study of patients with an acute iTTP episode in the US, treated with caplacizumab using a large US hospital database. We compared the demographic and clinical characteristics, treatment patterns, and healthcare resource utilization (HCRU) of hospitalized patients treated with front-line caplacizumab alongside TPE and immunosuppressants versus those who received delayed caplacizumab at least 2 days after the start of TPE. This analysis focused on the acute portion of treatment in the inpatient setting.

Methods

Study Design and Data Source

This was a retrospective, observational study of adult patients who experienced an acute inpatient iTTP episode and whose data were captured within the Premier Healthcare Database (PHD) from January 2019 to February 2021. PHD is a US hospital-based, service-level, all-payer electronic healthcare database with information on inpatient discharges. The hospitals were geographically diverse non-profit, non-governmental, and community and teaching hospitals. PHD captures data on both hospital costs and charges (charge master data) throughout a patient's inpatient stay. PHD additionally captures data on patient information, diagnoses, procedures (including timing, number, and cost), medications given inpatient (including cost of medications), patient vitals, and in some instances laboratory results and other clinical scores. This database includes >119 million inpatient admission visits. Data from outpatient visits to emergency departments, ambulatory surgery centers, and alternate sites of care may exist in the database only if these sites were within the same hospital as the original inpatient stay. Completeness of follow-up data post discharge is unknown and therefore not used in this analysis.

Study Population

Patients were included in the study if they had an iTTP episode hospitalization during the patient identification period from January 21, 2019, to February 28, 2021. The full study period was from January 1, 2018, to April 15, 2021. While caplacizumab was approved in the US in February 2019, the patient identification period began earlier to account for adjustments performed on the reporting of dates in the PHD to protect patient privacy.

An iTTP episode was defined as an inpatient hospital encounter with thrombotic microangiopathy (TMA; ICD-9-CM = 446.6 and ICD-10-CM = M31.1) and ≥1 TPE procedure (ICD-10-PCS = 6A550Z3,6A551Z3 and PHD standard charge master codes (360360003422015, 360360365140000, 36051036 5140000, 360820365200001, 980980365140000, 360360 365200020, 360450365140000, 360761365140000, 9809800 03422015, 360490365200000), within the same index hospitalization. Based on a previously validated algorithm, patients were excluded if they were <18 years on the index date, or had a diagnosis related to conditions that mimic iTTP during the index hospitalization (hemolytic uremic syndrome, systemic infection, Rocky Mountain spotted fever, aspergillosis infection, Escherichia coli infection, or hypertensive crisis), or had a diagnosis in the 180 days prior to and during the index iTTP hospitalization of organ/stem cell transplant, malignancy, or systemic lupus erythematosus.[20]

The analysis cohorts consisted of patients who had an iTTP episode, were admitted for an inpatient stay and were either (1) treated with caplacizumab front line defined as within fewer than 2 calendar days from TPE initiation or (2) received delayed caplacizumab defined as 2 or more calendar days post TPE initiation. All patients also received immunosuppressants.

As the database used in the study is fully de-identified and compliant with the Health Insurance Portability and Accountability Act of 1996 regulations, this study does not require institutional review board review.

Outcomes and Analyses

The index date was defined as the date of first TPE procedure during hospitalization for the first qualifying acute iTTP inpatient episode. The index iTTP episode was defined as the first iTTP episode recorded during the patient identification period where caplacizumab was administered, even if the patient had a prior iTTP episode without caplacizumab during the patient identification period. Patients were followed from the index date to the end of the follow-up, defined as time until censoring with patients censored at death, end of patient data, or end of the study period. End of patient data were defined as the last recorded data for the patient. Patient baseline clinical characteristics were assessed in the 180-day baseline period prior to the index date.

Treatment patterns, iTTP-specific outcomes, HCRU, and costs were assessed among patients receiving front-line and delayed treatment. Treatment pattern outcomes included duration of treatment, number of administrations, time to initiation of TPE and caplacizumab; concomitant treatment (use of systemic corticosteroids and/or rituximab), and time between TPE and caplacizumab treatment initiation. Mortality in the inpatient phase was also reported. HCRU outcomes analyzed were length of inpatient hospitalization during index iTTP episode, number, and duration of TPE administrations, proportion of patients requiring an intensive care unit (ICU) visit, and length of stay in the ICU.

Outcomes were analyzed descriptively within each analysis group and cohort, including mean, standard deviation (SD), median, and interquartile range (IQR) values for continuous variables and outcomes measures, and frequency and percentages for categorical variables and outcomes measures. Time-to-event and continuous count outcomes were reported using incidence rates per 1000 person-years. For all outcomes, missing data were quantified in terms of the number of unique patients with missing data and patients with missing data were assigned to unknown categories. Unadjusted bivariate analyses were conducted for comparisons between the analysis groups including t-test of means for continuous variables and Pearson's chi-squared test for categorical variables

Data management and statistical analyses within this study were conducted using the Aetion Evidence Platform™ (Version 4.3).

Results

Patient Characteristics

Among the patient encounters in the PHD, 633 individual patient encounters were recorded with ≥1 iTTP episode (inpatient hospitalization with a TMA diagnosis and ≥1 TPE procedure during the same inpatient stay). Among these, 594 patients were excluded due to age, (<18 years), having a diagnosis related to conditions that mimic iTTP or not receiving caplacizumab in the inpatient setting. Ultimately, 39 patients with an iTTP episode received caplacizumab in the inpatient setting (Figure 1).

Of the 39 patients who received caplacizumab, 16 (41%) patients received front-line treatment (starting <2 days after TPE initiation) and 23 (59%) patients received delayed treatment (starting ≥2 days after TPE initiation) (Table 1). Median (IQR) age in the front-line and delayed cohorts was 46.5 (34.0-63.5) and 45.0 (37.0-59.0) years, respectively. Most patients were female (front-line: 12 [75.0%]; delayed: 18 [78.3%]). The most common patient race was Black (front-line: 6 [37.5%]; delayed: 14 [60.9%]), followed by White (front-line: 6 [37.5%]; delayed: 8 [34.8%]). Three patients in each cohort (front-line: 18.8%; delayed: 13.0%) had a history of iTTP episode. Most patients had a history of cardiac condition (front-line: 13 [81.3%]; delayed: 16 [69.6%]), and some had a history of neurologic condition (front-line: 6 [37.5%]; delayed: 5 [21.7%]). None of the demographic differences were statistically significant.

iTTP Treatment Patterns

Median (IQR) time from admission to TPE initiation was 1.0 (0.0-1.0) day in both the front-line and delayed introduction of caplacizumab groups (Table 2). Patients in the front-line group had a significantly shorter median duration of TPE treatment (front-line: 4.0 (3.0-6.8); delayed: 11.0 (7.0-13.0) days) and received fewer TPE administrations (5.0 (3.0-7.0) versus 12.0 (8.0-14.0)) compared with the delayed cohort (Table 2).

Median (IQR) time from admission to caplacizumab treatment was 0.5 (0.0-1.0) days in the front-line cohort and 8.0 (4.0-13.0) days in the delayed cohort (Table 2). Patients in the front-line cohort received a median (IQR) of 8.0 (3.0-9.5) administrations of caplacizumab and were treated with caplacizumab for a median (IQR) duration of 7.0 (3.0-8.0) days during their index hospitalization. Patients in the delayed cohort had a median (IQR) of 6.0 (3.0-7.0) administrations of caplacizumab over a median (IQR) treatment period of 5.0 (3.0-6.0) days during their index hospitalization.

Rituximab was administered in 50.0% (n = 8/16) patients in the front-line cohort and 69.6% (n = 16/23) patients in the delayed cohort. All patients received concomitant systemic corticosteroid treatment (Table 2).

Clinical Outcomes

One (4.3%) patient in the delayed cohort died 18 days after their iTTP index admission; no patient who received front-line caplacizumab treatment died during the iTTP hospitalization.

Healthcare Resource Utilization

Median (IQR) length of stay of index iTTP episode hospitalization was significantly shorter for patients who received front-

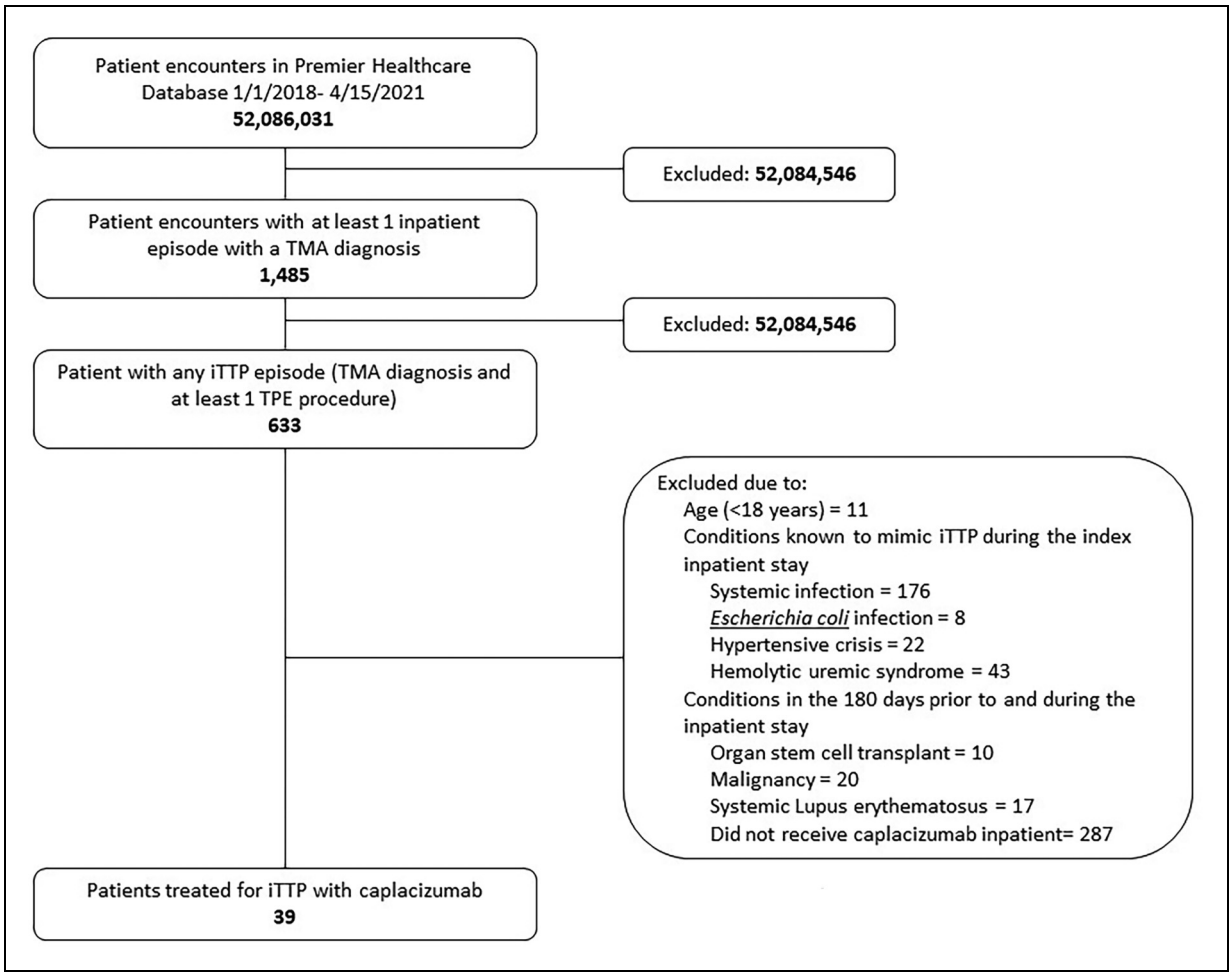

Figure 1. Patient selection. Abbreviations: ICD, international classification of diseases; iTTP, immune-mediated thrombotic thrombocytopenic purpura; TMA, thrombotic microangiopathy; TPE, therapeutic plasma exchange.

line treatment (9.0 (8.0-12.5) days) than delayed treatment (16.0 [11.0-22.0] days; comparison of means, t-test, $P < .01$) (Table 2). Overall, five (31.3%) patients and nine (39.1%) patients in the front-line and delayed cohorts, respectively, had an ICU admission during index hospitalization. The period of ICU stay was similar between the two cohorts. Post discharge, one patient from each cohort had a re-hospitalization within 30 days of the index TTP episode. Five (31.3%) and 12 (52.2%) patients from the front-line and delayed cohorts, respectively, had outpatient visits with the same treating hospital within 30 days of follow-up. One patient from the delayed cohort and none from the front-line cohort had ER visits in 30 days of post-index TPE episode (Figure 2).

Costs

Median total inpatient costs (inclusive of cost of caplacizumab, TPE, hospitalization, and any other drug) were 54% higher in patients who received delayed treatment compared to those who received front-line treatment (median (IQR): $112 711 (69 336-167 424) versus $73 318 (63 433-99 914); comparison of means, t-test, $P = .13$). Costs and the number of administrations of TPE were significantly lower ($P < .01$) in patients who received front-line treatment while the costs and number of administrations of caplacizumab were higher ($P = .11$) in patients who received front-line treatment (Tables 2 and 3 and Figure 3).

Discussion

This retrospective analysis of front-line versus delayed caplacizumab use in patients hospitalized with iTTP is the first known review of US real-world treatment patterns for caplacizumab. While caplacizumab is approved in the US for the treatment of all patients with iTTP alongside initiation of TPE and immunosuppressants, previous literature shows that certain patients may receive caplacizumab in a delayed manner.[21,22] This analysis similarly found that, after the caplacizumab approval until February 2021, a large proportion of patients in the US received delayed caplacizumab treatment. Patients with delayed start of caplacizumab treatment had longer duration of hospital stay by approximately 7 days, higher TPE burden, and 40% higher mean total cost of care (inclusive of caplacizumab cost) than

Table 1. Patient Demographics and Clinical Characteristics.

Characteristics	Patients receiving caplacizumab <2 days from the start of TPE (n = 16)	Patients receiving caplacizumab ≥2 days from the start of TPE (n = 23)	*P*-value
Age at index date, years			
Median (IQR)	46.5 (34.0-63.5)	45.0 (37.0-59.0)	-
Mean (SD)	49.1 (16.8)	46.9 (13.1)	.66
Sex, n (%)			
Female	12 (75.0)	18 (78.3)	1.00
Race, n (%)			
Asian	1 (6.3)	0 (0.0)	.85
Black	6 (37.5)	14 (60.9)	.27
Other/Unknown	3 (18.8)	1 (4.3)	.36
White	6 (37.5)	8 (34.8)	1
US Census Region, n (%)			
Midwest	3 (18.8)	4 (17.4)	1.00
Northeast	1 (6.3)	3 (13.0)	.88
South	11 (68.8)	13 (56.5)	.66
West	1 (6.3)	3 (13.0)	.88
History of iTTP episode, n (%)	3 (18.8)	3 (13.0)	.97
French Severity Score, n (%)			
n available (%)	2 (12.5)	6 (26.1)	.53
Low risk (0-1)	0 (0)	6 (26.1)	.08
Intermediate risk (2)	2 (12.5)	0 (0)	.32
High risk (3-4)	0 (0)	0 (0)	-
ADAMTS13 activity (%)			
n available (%)[a]	1 (6.3)	2 (8.7)	1.00
≤10%	1 (6.3)	2 (8.7)	1.00
Cerebral involvement, n (%)	8 (50.0)	1 (4.3)	<.01
LDH (U/L)			
n available (%)	2 (12.5)	6 (26.1)	.53
Median (IQR)	461.5 (377.0, 546.0)	881.5 (584.0, 1222.0)	-
Mean (SD)	461.50 (119.50)	907.17 (353.24)	<.01
High (>280 U/L),	2 (12.5)	6 (26.1)	.53
Serum creatinine (mg/dL)			
n available (%)	3 (18.8)	6 (26.1)	.88
Median (IQR)	0.8 (0.6, 3.5)	1.2 (1.0, 1.7)	-
History of cardiac conditions; n (%)			
Any	13 (81.3%)	16 (69.6%)	.65
Chronic rheumatic heart disease	1 (6.3%)	0 (0.0%)	.85
Essential hypertension	9 (56.3%)	8 (34.8%)	.32
Other hypertensive disease	4 (25.0%)	5 (21.7%)	1.00
Ischemic heart disease	3 (18.8%)	8 (34.8%)	.46
Other heart disease	6 (37.5%)	5 (21.7%)	.48
History of neurologic conditions; n (%)			
Any	6 (37.5%)	5 (21.7%)	.48
Systemic atrophies	1 (6.3%)	0 (0.0%)	.85
Epilepsy/migraine/headache	2 (12.5%)	1 (4.3%)	.74
Neuropathies and myoneural conditions	1 (6.3%)	0 (0.0%)	.85
Other disease of the nervous system	3 (18.8%)	5 (21.7%)	1.00

Abbreviations: IQR, interquartile range; iTTP, immune-mediated thrombotic thrombocytopenic purpura; LDH, lactic acid dehydrogenase; SD, standard deviation; TPE, therapeutic plasma exchange.

French severity score involved evaluation of 3 parameters cerebral involvement (yes = 1, no = 0), LDH (>10xULN = 1, < 10xULN = 0), and age (>60 years = 2; > 40 and <60 years = 1; < 40 years = 0). The bivariate tests used in this analysis were t-test of means for continuous variables and Pearson's chi-squared test for categorical variables.

[a]Missingness of ADAMTS13 test results is likely due to database restrictions when testing is conducted by independent labs whose data is not integrated into the premier dataset. This should not be interpreted as the prevalence of testing.

Table 2. iTTP Treatment Patterns and HCRU Outcomes.

Outcomes	Patients receiving caplacizumab <2 day from the start of TPE (n = 16)	Patients receiving caplacizumab ≥2 day from the start of TPE (n = 23)	*P*-value
TPE treatment patterns			
Time from iTTP inpatient episode admission to TPE, days			
Mean (SD)	0.6 (0.5)	0.8 (1.3)	.46
Median (IQR)	1.0 (0.0-1.0)	1.0 (0.0-1.0)	-
Duration of TPE treatment, days			
Mean (SD)	4.8 (2.9)	11.5 (6.4)	<.01
Median (IQR)	4.0 (3.0-6.8)	11.0 (7.0-13.0)	-
Number of TPE administrations			
Mean (SD)	5.3 (3.2)	12.4 (6.4)	<.01
Median (IQR)	5.0 (3.0-7.0)	12.00 (8.00-14.00)	-
Caplacizumab treatment patterns			
Time from iTTP inpatient episode admission to caplacizumab treatment, days			
Mean (SD)	0.6 (0.7)	10.1 (7.1)	<.01
Median (IQR)	0.5 (0.0-1.0)	8.0 (4.0-13.0)	-
Duration of caplacizumab treatment during the inpatient stay, days[a]			
Mean (SD)	7.3 (5.5)	5.0 (2.8)	.14
Median (IQR)	7.0 (3.0-8.0)	5.0 (3.0-6.0)	-
Number of caplacizumab administrations during the inpatient stay[a]			
Mean (SD)	7.7 (5.8)	5.1 (2.8)	.12
Median (IQR)	8.0 (3.0-9.5)	6.00 (3.0-7.0)	-
Time between TPE and caplacizumab initiation, days			
Mean (SD)	0.3 (0.5)	9.3 (6.5)	<.01
Median (IQR)	0.0 (0.0-0.8)	7.0 (3.0-13.0)	-
Hospitalization treatment patterns			
Length of Stay (LOS) (days) of index iTTP Episode, mean (SD)			
Mean (SD)	10.9 (6.0)	17.3 (8.1)	<.01
Median (IQR)	9.0 [8.0, 12.5]	16.0 [11.0, 22.0]	-
ICU Visit during index hospitalization, n (%)	5 (31.3)	9 (39.1)	.87
Length of Stay (LOS) (days) of ICU Visit (when ICU visit occurred), mean (SD)			
Mean (SD)	2.0 (0.7)	2.4 (1.1)	.14
Median (IQR)	2.0 [1.5, 2.5]	2.0 [1.5, 3.5]	-
Concomitant immunosuppressive treatment patterns, n (%)			
Any concomitant immunosuppressive treatment	16 (100.0)	23 (100.0)	-
Systemic corticosteroids	16 (100.0)	23 (100.0)	-
Rituximab	8 (50.0)	16 (69.6)	.37
Other clinical outcomes, n (%)			
Death during index iTTP episode	0 (0.0)	1 (2.6)	.40

Abbreviations: ICU, intensive care unit; IQR, interquartile range; iTTP, immune-mediated thrombotic thrombocytopenic purpura; LOS, length of stay; SD, standard deviation; TPE, therapeutic plasma exchange.

The bivariate tests used in this analysis were t-test of means for continuous variables and Pearson's chi-squared test for categorical variables.

[a]Only inpatient caplacizumab doses and duration of treatment is captured. Postdischarge caplacizumab scripts are not included in this analysis as they are typically managed by outpatient pharmacy, a separate analysis of claims data would be necessary to quantify.

patients who received caplacizumab front-line alongside initiation of TPE and immunosuppressants.

The results of this analysis are consistent with previously published conclusions from Spanish and German real-world studies[18,19] and suggestions from ISTH guidelines which state that caplacizumab benefit is greatest when given earlier.[23] Similarly to previous publications, adverse outcomes were likely a consequence of delayed initiation of caplacizumab. We did not assess the reasons for delayed caplacizumab treatment. A previous small, US-based real-world study of caplacizumab for aTTP ascribed delays in administration of the drug to prior authorization requirements and delays in laboratory testing for ADAMTS13 activity.[24] Another factor guiding selection of delayed caplacizumab could be internal protocols or decisions to treat with caplacizumab at time of clinical worsening. While it has been suggested that caplacizumab use could

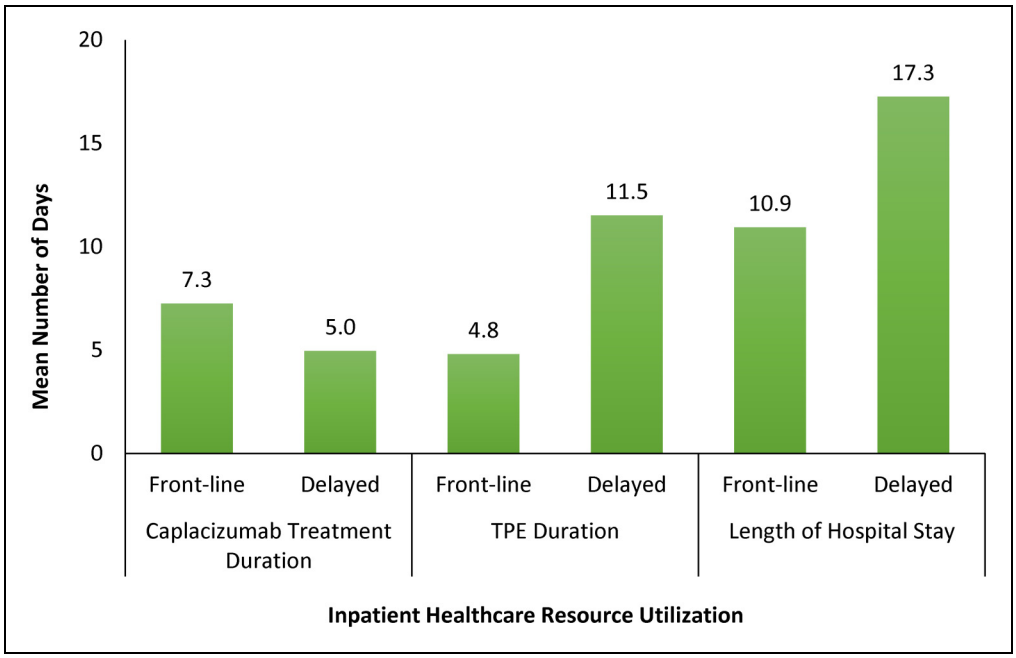

Figure 2. Duration of inpatient healthcare resource utilization.

be reserved for specific patients, no reliable strategy exists to stratify patients and to predict poor outcomes such as refractoriness, exacerbations, or select patients who may be more severe at baseline.[25,26] As such, front-line treatment with caplacizumab in all patients is recommended. Increasing provider awareness and patient access to early initiation of caplacizumab may improve clinical outcomes and reduce costs for patients hospitalized for acute iTTP episodes. These results are related to the US inpatient setting and should not be interpreted as a reflection of the entirety of the cost of TTP.

While this study did not have sufficient sample size to apply methods that address confounding bias in the association between timing of caplacizumab administration and study outcomes, there were no significant differences in the observed demographics between study cohorts, including history or presentation with cardiovascular and neurological disorders or the observed severity scales. This suggests that the cohorts who received front-line and delayed caplacizumab therapy were similar at baseline. That said, a greater proportion of patients in the delayed group were of Black race than the front-line group (60.9% vs 37.5%); however, 19% of patients in the front-line caplacizumab group were of unknown race making this difference difficult to interpret.

This study has several limitations. Information regarding ADAMTS13 results were only available in select patients, likely due to data missingness in the premier database whereby test results were not captured. However, the cohort inclusion and exclusion criteria were designed to leverage available information to increase the likelihood of identifying a population of patients with iTTP. As mentioned previously, more rigorous comparative analyses could not be conducted other than unadjusted bivariate comparisons due to limited sample size. Additional research is needed in larger populations to further define associations. This analysis was based on a small sample size. Given that TTP is an ultra-orphan disease, sample size may be limited by the rarity of disease. Further, the sample size of the present analysis may also be attributable to the segmented nature of US healthcare data as well as scope and representativeness of the Premier analytic dataset. The complexity and rigor of inclusion/exclusion criteria to identify TTP as well as the extent of use of caplacizumab during the study period may further be contributing to decreased patient counts. Additionally, existing EMR databases may have data missingness in the inpatient setting thereby some patients treated with caplacizumab, and plasma exchange may not have been captured in the dataset. Despite these limitations, this study leveraged chargemaster data in addition to procedure and diagnosis codes allowing for capture of on as TTP related treatments during the hospitalization. In this analysis, two days or more was selected as the cutoff threshold in defining the delayed start of caplacizumab based on previously published data and the HERCULES study design.[27,28] However, various cutoffs including 48 h and three days have been used in other studies.[19]

Due to the nature of the database, the current analysis is reflective of the inpatient HCRUs, costs, and treatment patterns as experienced during the acute phase of treatment and observed in a hospital database. Additional treatment patterns and clinical outcomes including exacerbations, refractoriness, safety, or complications cannot be summarized from this dataset. For real-world clinical outcomes data, reference should be made to registry or chart-based analyses such as Volker et al 2023.[19] Costs of continued caplacizumab use beyond the inpatient duration are not summarized here as it is

Table 3. iTTP Hospitalization Costs.

Outcomes	Patients receiving caplacizumab <2 day from the start of TPE (n = 16)	Patients receiving caplacizumab ≥2 day from the start of TPE (n = 23)	*P*-value
Total inpatient cost (inclusive of hospitalization, ICU, TPE, Caplacizumab, and other medication costs)			
n (%)	16 (100.0%)	23 (100.0%)	
Mean (SD)	89 579 (65 968)	125 036 (77 937)	.13
Median (IQR)	73 318 [63 433, 99 914]	112 711 [69 336, 167 424]	-
TPE cost (subset of inpatient costs)			
n (%)	14 (87.5%)	23 (100.0%)	
Mean (SD)	6 829 (3477)	16 004.5 (15 091)	<.01
Median (IQR)	6 989 [3 906, 9 185]	10 917 [5 219, 21 859]	-
Caplacizumab cost (subset of inpatient costs)			
n (%)	14 (87.5%)	21 (91.3%)	
Mean (SD)	57 057 (37 772)	37 727 (32 468)	.11
Median (IQR)	48 082 [36 440, 73 321]	26 323 [12 760, 56 239]	-

Abbreviations: ICU, intensive care unit; IQR, interquartile range; iTTP, immune-mediated thrombotic thrombocytopenic purpura; SD, standard deviation; TPE, therapeutic plasma exchange.
The bivariate tests used in this analysis were t-test of means for continuous variables and Pearson's chi-squared test for categorical variables.

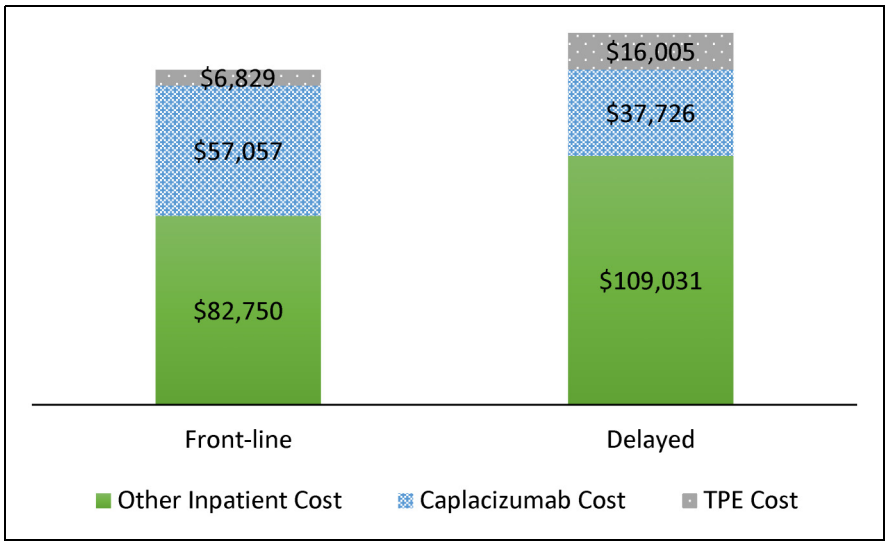

Figure 3. Mean total inpatient care costs. TPE, therapeutic plasma exchange.

typically covered by the patient's pharmacy benefits outside of the hospital and would require separate analysis of insurance claims. Other data sources including patient charts would also be needed to investigate the longer-term outcomes of patients treated with caplacizumab in the United States (US). A recently presented analysis of the cost effectiveness of caplacizumab in the US was presented which summarizes the estimated total costs and benefits of treating TTP in the US over a lifetime. The results found that caplacizumab was cost effective when using the independently reviewed NICE economic model with an expected lifetime incremental cost of $242 200 (accounting for the cost of treating relapses) and an incremental benefit of 1.75 QALYs.[29] While patient demographics and clinical presentations at baseline were similar, any observable or unobservable covariate leading to the choice of using caplacizumab in a delayed manner as well as hospital expertise in treating iTTP or experience with caplacizumab could not be controlled for, including use of caplacizumab after the patient has become refractory to other treatments. Also, laboratory measurements were available in only a minority of patients but presented when available. Lastly, the study period of January 2019 through March 2021 spans the COVID-19 pandemic. It is unclear what effect COVID-19 had on the HCRU patterns of patients with iTTP episodes or on their identification for inclusion in this study.

Conclusions

Evidence from this real-world study suggests that patients with iTTP who received front-line caplacizumab treatment fewer than two days from TPE initiation experienced improved

inpatient outcomes and lower costs compared with patients who received delayed treatment initiation.

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Authors Contributions

A.A., S.S., J.L., and A.R. conceived and designed the study. S.S., J.L., and A.R. assisted in data acquisition and analyses. All authors contributed to data analysis, critically revised the article, and agreed to be accountable for all aspects of the work.

Data Sharing

Qualified researchers may request access to patient-level data and related study documents, which may include clinical study report, study protocol with any amendments, statistical analysis plan, and dataset specifications. Patient-level data are anonymized. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: https://vivli.org/

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: A.A., M.M., and H.O. are employees of Sanofi and hold stocks or stock options in the company. A.M. is an employee of Sanofi. S.S., J.L., and A.R. are employees of Aetion Inc. and hold stocks or stock options in the company. F.L. was an employee of Sanofi when the study was conducted.

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