Received: 19 January 2023 | Revised: 27 July 2023 | Accepted: 8 August 2023

https://doi.org/10.1016/j.rpth.2023.102185

RESEARCH LETTER

Caplacizumab use for immune thrombotic thrombocytopenic purpura: the Milan thrombotic thrombocytopenic purpura registry

Essentials

- Data on caplacizumab use for thrombotic thrombocytopenic purpura (TTP) in Italy are missing.
- Twenty-six Italian patients were treated with caplacizumab for an acute immune TTP episode.
- Caplacizumab was effective in treating acute TTP in the Italian real-world clinical setting.
- Two major bleeds leading to drug discontinuation were observed.

1 | INTRODUCTION

The standard treatment of acute immune-mediated thrombotic thrombocytopenic purpura (iTTP) has consisted of daily therapeutic plasma exchange (TPE) and immunosuppressive therapy for many decades. The humanized bivalent nanobody caplacizumab has changed this therapeutic paradigm [1]. Randomized clinical trials (RCTs) showed that caplacizumab significantly reduces time to platelet count normalization, refractoriness, exacerbation rates, number of TPE, and length of hospitalization [2–4]. The safety profile was reported to be favorable, with an increase in mild-to-moderate mucocutaneous bleeds as the main finding and a 9.5% excess of serious bleeds compared with placebo [2–4]. Based on this evidence, current guidelines from the *International Society on Thrombosis and Haemostasis* conditionally recommend the early use of caplacizumab to treat acute iTTP, in combination with TPE and corticosteroids [1].

After drug approval by regulatory agencies, data from real-world clinical settings have been published, showing data consistent with those of RCTs [5–8]. However, data on patients with iTTP treated with caplacizumab in Italy are missing. This study aims to describe the efficacy and safety of caplacizumab in an Italian cohort of patients with iTTP from a real-world clinical setting.

2 | METHODS

In this retrospective study, we included all patients from the Milan TTP registry (www.ttpdatabase.org) receiving caplacizumab treatment for an acute iTTP episode between September 2018 and August 2021. Data related to age, sex, ethnicity, clinical manifestations, laboratory parameters, and treatments were collected. As endpoints, death, clinical response, clinical exacerbation, clinical and ADAMTS-13 remission, episode length, and caplacizumab-related adverse events leading to drug discontinuation were recorded. An extensive description of study methods is reported in the Supplementary Methods.

3 | RESULTS AND DISCUSSION

Twenty-six patients from 12 Italian centers were included (Table 1). All patients were treated with TPE, corticosteroids, and caplacizumab, except 1 presenting with a relatively mild thrombocytopenia (113,000/μL), who was treated only with corticosteroids and caplacizumab. Rituximab was used in 67% of patients. Caplacizumab was started at a median of one day after TPE initiation. However, in 32% of patients, caplacizumab was administered ≥7 days after TPE initiation to treat a refractory TTP or an exacerbation. All patients achieved clinical remission, with one patient (4.3%) experiencing a clinical exacerbation 11 days after stopping caplacizumab (Table 2).

Our data are aligned with the RCTs integrated analysis, where 5.6% and 0% rates of exacerbation and mortality in the interventional arm were reported, respectively [4]. In our study, the median time to platelet count normalization after caplacizumab start was 4 days, with a median of 8 TPE days, both slightly higher than those reported in the RCTs integrated analysis (2.8 and 5 days, respectively) [4]. However, when considering only the 15 patients treated upfront with

Presented in abstract form at the 30th Congress of the International Society on Thrombosis and Haemostasis (ISTH), London, England, U.K., July 9-13, 2022, and at the XXVII National Congress of the Società Italiana per lo Studio dell'Emostasi e della Trombosi (SISET), Perugia, Italy, November 2-5, 2022.

TABLE 1 Main patient characteristics, episode clinical manifestations, and laboratory parameters.

Variables	*N* = 26
First TTP episode, *n* (%)	15 (57.7)
Follow-up, (d) , median (IQR)	279 (121-339)
Age, (y), median (IQR)	53 (47.3-60.4)
Female, *n* (%)	20 (76.9)
White ethnicity, *n* (%)	24 (92.3)
Platelet count/μL, median (IQR)	14,000 (10,250-18,750)
Hemoglobin, g/dL, median (IQR)[a]	9 (7.8-10.8)
Creatinine, mg/dL, median (IQR)[b]	1.08 (0.89-1.31)
LDH, IU/L, median (IQR)[c]	1243 (490-1919)
Total bilirubin, mg/dL, median (IQR)[b]	2.2 (1.6-3.5)
Indirect bilirubin, mg/dL, median (IQR)[d]	1.6 (1.3-2.4)
Systemic signs/symptoms, *n* (%)	22 (84.6)
Neurologic signs/symptoms, *n* (%)	15 (57.7)
Hemorrhagic signs/symptoms, *n* (%)	12 (46.2)
Cardiovascular signs/symptoms, *n* (%)	5 (19.2)
Renal signs/symptoms, *n* (%)	4 (15.4)

The median follow-up period was defined from the date of initiation of caplacizumab to the last documented follow-up. All clinical manifestations and laboratory parameters were recorded at the time of the acute TTP episode onset. Laboratory examinations were performed before plasma infusion or TPE. Clinical manifestations were categorized as follows:

- systemic signs/symptoms: fatigue, fever, abdominal pain, headache, vomiting, jaundice (defined as total bilirubin levels ≥2.5 mg/dL);
- neurologic signs/symptoms: ischemic stroke, transient ischemic attack, epileptic seizures, coma, personality disorders, focal neurologic signs;
- hemorrhagic signs/symptoms: skin bleeding (purpura, bruising), mucosal bleeds (including epistaxis), hematuria, meno-metrorrhagia, gastrointestinal hemorrhages;
- cardiovascular signs/symptoms: acute coronary syndrome, myocardial infarction, electrocardiographic ischemic changes;
- renal signs/symptoms: acute renal failure, anuria, need for dialysis, hemoglobinuria, proteinuria, oliguria.

LDH, lactate dehydrogenase.
[a]Available in 25 patients;
[b]available in 23 patients;
[c]available in 24 patients;
[d]available in 19 patients.

caplacizumab (within 24 hours after TPE initiation), these figures were 3 and 6 days, similar to RCTs findings.

Compared with published data from our historical cohort of 302 patients with acute iTTP treated between 2002 and 2015 [9], we observed lower rates of mortality (0% vs 5%) and clinical exacerbation (4.3% vs 15%), and a slightly lower median number of TPE needed to attain clinical response (7 [IQR, 6-14] vs 9 [IQR, 6-14]). In the 15 patients treated upfront with caplacizumab, this figure seemed to be lower, especially for first iTTP events (6 [IQR, 4-6] vs 11 [IQR, 7–18] in our historical data) [9]. However, we cannot draw any solid conclusion regarding the efficacy of caplacizumab from the comparison of these 2 studies due to methodological limitations. These limits include changes in disease management and endpoint definitions over the past 20 years, as well as the small sample size of the present study, which would not allow us to adjust for differences in patient characteristics between the 2 groups.

Since caplacizumab approval, real-world data on caplacizumab post-marketing surveillance in relatively large cohorts of patients (60-90) from Germany, France, the United Kingdom and Spain have been published [5–8]. In these studies, similarly to the present findings, time to platelet count normalization (3-5 days), number of TPE procedures (4-7) and TPE days (5-9), rate of clinical exacerbation (2%-5%) and mortality (1%-6%), were more favorable in patients treated with caplacizumab (triple regimen) than in the historical cohorts [5–7].

In this study, caplacizumab remained effective even when its initiation was delayed by ≥7 days from TPE initiation (time to platelet count normalization: 4 days [IQR, 3-4]). However, patients with delayed caplacizumab initiation, compared with non-delayed, required a higher number of TPE to achieve clinical response (median difference: 9 [IQR, 7-14]) and hospitalization days (median difference: 12 [IQR, -5 to 19]) (Supplementary Table). The delay in starting caplacizumab, used to treat refractoriness or exacerbation in about one third of our cases, which may partly explain the higher median number of TPE and hospitalization days we observed (8 and 18 days, respectively), in line with the German cohort (9 and 18 days, respectively), and at variance with the French (5 and 13 days, respectively) and United Kingdom cohorts (7 and 12 days, respectively).

The median time to ADAMTS-13 remission (partial or total) after caplacizumab initiation was 33 days (IQR, 15-49), in line with that observed by Coppo et al. [6] (28 days; IQR, 14-42).

In our study, one patient was treated with a TPE-free approach, which resulted to be effective, in line with a previous case series [10]. The platelet count normalization was achieved after 3 days and partial ADAMTS-13 remission after 14 days, 7 days after rituximab initiation [10].

As concerns safety, we observed a prevalence of 7.7% of patients with major bleeds (2/26), slightly higher than that reported in previous real-world studies (1%-5%). A 56 year-old woman showed an episode of hemoptysis 12 days after starting upfront caplacizumab, requiring blood transfusion, i.v. factor VIII or von Willebrand factor concentrate and an emergency transcatheter arterial embolization (she was actively bleeding from the main right bronchus). A 66-year-old man had a gastrointestinal bleeding episode requiring red blood cell transfusion, and leading to discontinuation of caplacizumab (started upfront) after 15 days. It is worth noticing that in both cases, there were predisposing conditions and concomitant treatment with heparin and/or antiplatelet therapy. The first patient presented with a severe TTP episode triggered by SARS-CoV2 pneumonia, complicated with disseminated intravascular coagulation and multiorgan failure syndrome. Moreover, the bleeding episode occurred during daily treatment with 100 mg aspirin (started because of the evidence of ischemic brain lesions) and antithrombotic prophylaxis with 4,000 International Units (IU) enoxaparin. The second patient, ie, the case treated with a TPE-free approach, was on secondary

TABLE 2 Caplacizumab-related features and clinical endpoints.

Variables	N = 26
Time to receive the first dose of caplacizumab after TPE start, (d) median (IQR)[a]	1 (0-8)
Length of caplacizumab treatment after the end of daily TPE, (d) median (IQR)[b,i]	26 (18-30)
Time to first normalization of platelet count after caplacizumab start, (d) median (IQR)[b]	4 (3-4)
Time to clinical response after caplacizumab start, (d) median (IQR)	6 (5-7)
Total no. of TPE procedures to achieve clinical response, median (IQR)	7 (6-14)
Total days of TPE to achieve clinical response, median (IQR)[b]	8 (6-14.8)
Total length of hospital stay, (d) median (IQR)[c]	18 (9-29)
ICU admission, *n* (%)	5 (19.2)
ICU stay, (d) median (IQR)	13 (8-15)
Clinical response, *n* (%)	26 (100)
Acute clinical exacerbation after caplacizumab start, *n* (%)[d,j]	1 (4.3)
Clinical remission, *n* (%)	26 (100)
Partial ADAMTS-13 remission in total observational time, *n* (%)[e]	22 (91.7)
Total ADAMTS-13 remission in total observational time, *n* (%)[e]	19 (79.2)
Partial ADAMTS-13 remission within 30 d after caplacizumab stop, *n* (%)[f]	17 (81.0)
Total ADAMTS-13 remission within 30 d after caplacizumab stop, *n* (%)[f]	13 (56.5)
ADAMTS-13 activity level at caplacizumab stop[f]	
<20 IU/dL, *n* (%)[g]	6 (27.3)
20 IU/dL<ADAMTS-13<45 IU/dL, *n* (%)	7 (31.8)
≥45 IU/dL, *n* (%)	9 (40.9)
Caplacizumab-related adverse events leading to drug discontinuation	2 (7.7)
Caplacizumab-related major bleeding episodes[h]	2 (7.7)

For the patient treated with a TPE-free approach, the time to receive the first dose of caplacizumab has been considered since episode onset. For patients admitted also to ICU, as total length of hospital stay we considered the total number of days (both in ICU and not in ICU).

ICU, intensive care unit; TPE, therapeutic plasma exchange.

[a]Available in 25 patients;
[b]available in 22 patients;
[c]available in 21 patients;
[d]available in 23 patients;
[e]available in 24 patients;
[f]these proportions became 77% (partial) and 57% (total) in the 15 patients treated with caplacizumab upfront;
[g]undetectable in 3 patients (8 IU/dL, 10 IU/dL and 11 IU/dL);
[h]defined based on the ISTH criteria employed for non-surgical patients; more details are reported in the Supporting information.
[i]The ADAMTS13 response allowed to discontinue caplacizumab before 30 days after the end of daily TPE in about 70% of cases. Adverse drug reactions and drug cost-related issues may explain the early discontinuation in the other cases.
[j]The patient who exacerbated had started caplacizumab 59 days after TPE initiation for a refractory disease and, at caplacizumab stop, ADAMTS13 activity was still undetectable.

cardiovascular prevention with daily treatment with 100 mg of aspirin, had duodenal arteriovenous malformation, cecal angiodysplasias, duodenal ulcer, and chronic gastritis. No other adverse events leading to drug discontinuation were observed.

Our study has limitations. First, the limited sample size and the retrospective nature of the study. Patients were treated in different centers (9 in Milan, 17 in other 11 centers), leading to heterogeneity in treatment regimens. The different times to receive caplacizumab after episode onset limit the comparability of data with those from RCTs. On the other hand, this allowed us to evaluate differences in caplacizumab efficacy between patients treated upfront and those treated because of refractoriness to TPE and immunosuppressors.

In conclusion, our results confirm caplacizumab efficacy in treating acute iTTP in the Italian real-world setting (ie, time to platelet count normalization, exacerbation rate, number of TPE procedures, and days). However, further post-marketing surveillance studies are

needed to look for less common adverse drug reactions, particularly in patients with additional risk factors of bleeding.

ACKNOWLEDGMENTS

The authors gratefully acknowledge Professor P.M. Mannucci for his critical revision.

FUNDING

The study was partially supported by the Italian Ministry of Health - Bando Ricerca Corrente (RC2022). The Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico is member of the European Reference Network (ERN) EuroBloodNet.

AUTHOR CONTRIBUTIONS

P. Agosti, I. Mancini, and F. Peyvandi designed the study. P. Agosti, P. De Leo, M. Capecchi, S. Gattillo, S.M. Trisolini, E. Rinaldi, G.M. Podda, L. Prezioso, P. Salutari, L. Facchini, D. Caramazza, and G. Tolomelli collected data. P. Agosti analysed the data. P. Agosti wrote the manuscript. P. Agosti, P. De Leo, M. Capecchi, B. Ferrari, I. Mancini, S. Gattillo, S.M. Trisolini, E. Rinaldi, G.M. Podda, L. Prezioso, P. Salutari, L. Facchini, D. Caramazza, G. Tolomelli, A. Artoni and F. Peyvandi interpreted the data and carefully revised the manuscript.

RELATIONSHIP DISCLOSURES

I.M. received honoraria for participating as a speaker at educational meetings organized by Instrumentation Laboratory and Sanofi; F.P. has received honoraria for participating as a speaker in education meetings organized by Grifols and Roche, and she is a member of scientific advisory boards of Biomarin, Roche, Sanofi, Sobi, and Takeda. The other authors do not have any conflict of interests to disclose.

DATA AVAILABILITY

For original, deidentified data, please contact the corresponding author.

Pasquale Agosti[1]
Pasqualina De Leo[2]
Marco Capecchi[3]
Barbara Ferrari[2]
Ilaria Mancini[1]
Salvatore Gattillo[4]
Silvia Maria Trisolini[5]
Erminia Rinaldi[6]
Gian Marco Podda[7]
Lucia Prezioso[8]
Prassede Salutari[9]
Luca Facchini[10]
Domenica Caramazza[11]
Giulia Tolomelli[12]
Andrea Artoni[2]
Flora Peyvandi[1,2]

[1]*Department of Pathophysiology and Transplantation, and Fondazione Luigi Villa, Università degli Studi di Milano, Milan, Italy*
[2]*Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Milan, Italy*
[3]*Clinica Moncucco, Hematology Service, Lugano, Switzerland*
[4]*Immuno-Hematology and Transfusion Medicine Unit, San Raffaele Hospital, Milan, Italy*
[5]*Hematology, Department of Translational and Precision Medicine, "Sapienza" University of Rome, Rome, Italy*
[6]*Hematology Unit, A. Perrino Hospital, Brindisi, Italy*
[7]*U.O.C. Medicina II, ASST Santi Paolo e Carlo, Dipartimento di Scienze della Salute, Università degli Studi di Milano, Milan, Italy*
[8]*Haematology and BMT Unit, Azienda Ospedaliero-Universitaria di Parma, Parma, Italy*
[9]*Ospedale Civile "Spirito Santo", Pescara, Italy*
[10]*Hematology Unit, Azienda USL-IRCCS di Reggio Emilia, Viale Umberto I n, 50 42123 Reggio Emilia, Italy*
[11]*Hematology, University Hospital "Ospedale di Circolo e Fondazione Macchi" - ASST Sette Laghi, Viale L. Borri 57, 21100, Varese, Italy*
[12]*Unit of Hematology, Rimini Hospital "Infermi", Rimini, Italy*

Handling Editor: Dr Suely Rezende

Correspondence
Flora Peyvandi, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center; Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Via Pace 9, 20122, Milan, Italy.
Email: flora.peyvandi@unimi.it

TWITTER

Pasquale Agosti @Pasquale_Agosti

REFERENCES

[1] Zheng XL, Vesely SK, Cataland SR, Coppo P, Geldziler B, Iorio A, et al. ISTH guidelines for treatment of thrombotic thrombocytopenic purpura. *J Thromb Haemost*. 2020;18:2496–502.
[2] Peyvandi F, Scully M, Kremer Hovinga JA, Cataland S, Knöbl P, Wu H, et al. Caplacizumab for acquired thrombotic thrombocytopenic purpura. *N Engl J Med*. 2016;374:511–22.
[3] Scully M, Cataland SR, Peyvandi F, Coppo P, Knöbl P, Kremer Hovinga JA, et al. Caplacizumab treatment for acquired thrombotic thrombocytopenic purpura. *N Engl J Med*. 2019;380:335–46.
[4] Peyvandi F, Cataland S, Scully M, Coppo P, Knoebl P, Kremer Hovinga JA, et al. Caplacizumab prevents refractoriness and mortality in acquired thrombotic thrombocytopenic purpura: integrated analysis. *Blood Adv*. 2021;5:2137–41.
[5] Pascual Izquierdo MC, Mingot-Castellano ME, Kerguelen Fuentes AE, García-Arroba Peinado J, Cid J, Jiménez M, et al. Real-world effectiveness of caplacizumab vs standard of care in immune thrombotic thrombocytopenic purpura. *Blood Adv*. 2022:bloodadvances.2022008028.
[6] Coppo P, Bubenheim M, Azoulay E, Galicier L, Malot S, Bigé N, et al. A regimen with caplacizumab, immunosuppression, and plasma

exchange prevents unfavorable outcomes in immune-mediated TTP. *Blood*. 2021;137:733–42.

[7] Dutt T, Shaw RJ, Stubbs M, Yong J, Bailiff B, Cranfield T, et al. Real-world experience with caplacizumab in the management of acute TTP. *Blood*. 2021;137:1731–40.

[8] Völker LA, Kaufeld J, Miesbach W, Brähler S, Reinhardt M, Kühne L, et al. Real-world data confirm the effectiveness of caplacizumab in acquired thrombotic thrombocytopenic purpura. *Blood Adv*. 2020;4:3085–92.

[9] Mancini I, Pontiggia S, Palla R, Artoni A, Valsecchi C, Ferrari B, et al. Clinical and laboratory features of patients with acquired thrombotic thrombocytopenic purpura: fourteen years of the Milan TTP registry. *Thromb Haemost*. 2019;119:695–704.

[10] Völker LA, Brinkkoetter PT, Knöbl PN, Krstic M, Kaufeld J, Menne J, et al. Treatment of acquired thrombotic thrombocytopenic purpura without plasma exchange in selected patients under caplacizumab. *J Thromb Haemost*. 2020;18:3061–6.