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Letter to the Editors-in-Chief

Safety and efficacy of caplacizumab retreatment in a real-life monocentric cohort of patients with immune-mediated thrombotic thrombocytopenic purpura

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To the Editor,

Immune-mediated thrombotic thrombocytopenic purpura (iTTP) is an acute life-threatening disease characterized by the association of thrombocytopenia, microangiopathic hemolytic anemia, organ involvement and ADAMTS-13 protease deficiency [1]. The standard of care for iTTP has historically been based on therapeutic plasma exchange (TPE) and immune suppression. More recently, the treatment with caplacizumab has led to a significantly faster iTTP recovery. This is a nanobody that targets the interaction between platelet's glycoprotein 1b and the ultra-large A1 domain of von Willebrand factor (VWF). When administered as a first-line treatment, caplacizumab has been shown to be generally safe: the most common reported adverse event (AE) is represented by mucocutaneous bleeding [2]. iTTP shows an additional 30–50 % disease relapse risk after the first onset, but limited efficacy and safety data are available in patients treated with a second course of caplacizumab. Indeed, to the best of our knowledge, besides an anecdotical case report [3], only the post-Hercules study showed safety data on 9 patients retreated with caplacizumab for iTTP recurrence or relapse, 44 % of whom reported serious AEs [4].

Aiming to analyze data coming from a real-life monocentric cohort, we considered 24 consecutive iTTP patients treated with caplacizumab from August 2020 to February 2023 at the Hematology Unit, Ospedale Businco Cagliari; 7 of these (29.1 %) underwent a second course of caplacizumab (Table 1). All retreated patients (80.7 % were female) experienced a relapse defined as recurrent thrombocytopenia requiring initiation of TPE >30 days after the last TPE, confirmed by severe ADAMTS-13 deficiency [5]. Relapses occurred after a mean of 17.6 months (range 6–27) from the previous iTTP resolution. In 2020 and 2021, we administered caplacizumab daily until double consecutive confirmation of ≥10 % ADAMTS-13 activity; subsequently, we administered the drug for at least 30 days, even in presence of ≥10 % ADAMTS-13 activity. Indeed, in 2020 and 2021 we followed up our patients according to the ISTH guidelines published in 2021, scenario "C": ADAMST-13 activity measurement available with a delay (after 72 h but <7 days) and adopted a cautious approach. Since 2022 we have been experimenting the scenario "A": ADAMST-13 activity measurement available within 72 h [1] and prolonged treatment with caplacizumab according to the Italian Society of Hematology recommendation [6]. Four out 7 relapsed patients (57 %) were treated with caplacizumab <30 days in the first iTTP occurrence.

The mean platelets (PLT) count at relapse was significantly higher than the previous iTTP episodes (32 × 10^3/μL, range 9–68, vs 12, range 5–30; p = 0.01), probably because the patients were more aware of the potential risk of relapse; moreover, they underwent regular clinical follow-up. The hospitalization during the second course of caplacizumab ranged from 6 to 8 days, with a mean of 7 TPE (range 5–7) before achieving complete recovery of PLT and LDH (Fig. 1). These data were similar to those reported during the first course of caplacizumab (p = 0.56 and 0.40, respectively). The second course of caplacizumab was administered for a mean of 24 days, similarly to the mean duration of treatment in the previous iTTP occurrence (p = 0.55). In 6 out of 7 patients (85.7 %), a concomitant treatment with rituximab was associated: due to regulatory provisions it is not available in first line treatment in Italy. Overall, 4 non-serious bleeding AEs (16.7 %) were recorded in the cohort of patients treated with a first course of caplacizumab (2 cases of metrorrhagia, one upper arm hematoma and one cutaneous bleeding after insulin puncture). This rate was significantly lower if compared to the bleeding rate reported by the post-Hercules study [4] but similar to the 20–30 % reported by real-life cohorts [7,8].

No bleeding events were recorded in the cohort of retreated patients, probably due to the small number of cases. A serious cardiovascular AE was reported in a patient at iTTP onset, concomitant at the beginning of the first treatment with caplacizumab (transitory cerebral ischemic stroke): echocardiography revealed a patent ductus arteriosus and the AE was not related to caplacizumab. After iTTP relapse occurred 12 months after the previous episode, the patient was retreated with caplacizumab without further complications. The mean follow-up of retreated patients was 9.1 months (range 1–23).

In the post-Hercules study, 9 patients received repeated administration of caplacizumab. All patients were reported to achieve complete resolution of iTTP recurrence or relapse. Regarding safety, during repeat administration of caplacizumab, 7 patients (78 %) experienced treatment-emergent bleeding events, with 2 serious events (hematuria

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Table 1
Characteristics of patients with iTTP underwent a first and second course of caplacizumab.

	First course of caplacizumab (n = 24)	Second course of caplacizumab (n = 7)	p value
Sex female, no. (%)	18 (75)	7 (85.7)	0.81
Age at treatment, median years (range)	44.2 (22–75)	36 (26–59)	0.15
Hemoglobin g/dL, mean (range)	11 (4.7–10.7)	12 (10–13.7)	0.22
Platelet $\times 10^3/\mu L$, mean (range)	12 (5–30)	32 (9–68)	**0.01**
Creatinine mg/dL, mean (range)	1 (0.4–2.72)	0.8 (0.5–1.6)	**0.03**
LDH mU/mL, mean (range)	1.354 (516–3.491)	839 (353–2.292)	0.24
TPE, mean no. (range)	6 (2–15)	6 (5–7)	0.40
Caplacizumab doses, mean no. (range)	24 (11–36)	24 (6–30)	0.55
Days of hospitalization, mean no. (range)	8 (5–17)	7 (6–8)	0.56
Previous iTTP relapse, mean no. (range)	2 (0–15)	1 (1–8)	0.43
Follow-up, mean months (range)	16.5 (1–33)	9.1 (1–23)	**0.05**
Bleeding adverse event, no. (%)	4 (16.7)	0 (0)	
Cardiovascular adverse event, no. (%)	1 (4.1)	0 (0)	

Legend: TPE = therapeutic plasma exchange; iTTP = immune-mediated thrombotic thrombocytopenic purpura.
p value in bold = statistical significance

and gastrointestinal hemorrhage) [4]. However, data on caplacizumab treatment duration and days of hospitalization in this specific cohort of retreated patients were not shown. In our real-life monocentric cohort of 7 patients who underwent a second course of caplacizumab, we did not observe AEs, in particular bleeding or cardiovascular AEs. Moreover, the duration of the hospitalization and days of TPE were similar to those recorded during the previous iTTP event treated with the first course of caplacizumab (Fig. 1). Days of hospitalization and TPE in the retreated group were significantly lower when compared to a historical internal cohort of 68 patients with iTTP treated only with immunosuppression and TPE, without caplacizumab (7, range 6–8, vs 16, range 7–46, p = 0.02 and 6, range 5–7, vs 11, range 7–26, p = 0.01, respectively).

This study has several limitations due to its retrospective nature, the small number of patients and the short follow-up. Nevertheless, these data stemming from the real life further support the evidence that repeated use of caplacizumab has a safe profile and is effective in providing a rapid resolution of iTTP episodes, similar to that observed during the first treatment.

Declaration of competing interest

The authors declare no conflict of interest.

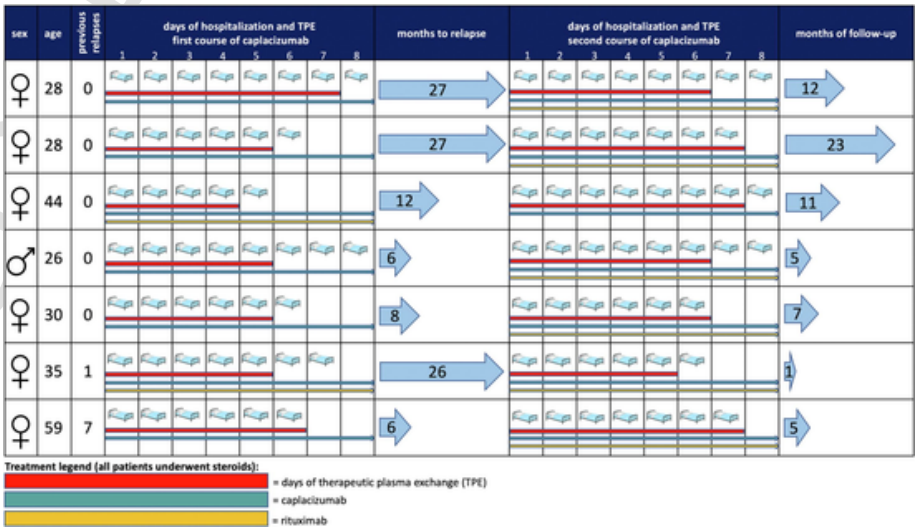

Fig. 1. Duration of hospitalization and treatment of 7 patients with iTTP underwent a first and second course of caplacizumab.
TPE = therapeutic plasma exchange; iTTP = Immune-mediated thrombotic thrombocytopenic purpura.

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