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Received: 10 November 2024 | Accepted: 28 January 2025

DOI: 10.1002/hem3.70109

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Caplacizumab treatment in elderly patients with iTTP: Experience from the Spanish TTP Registry

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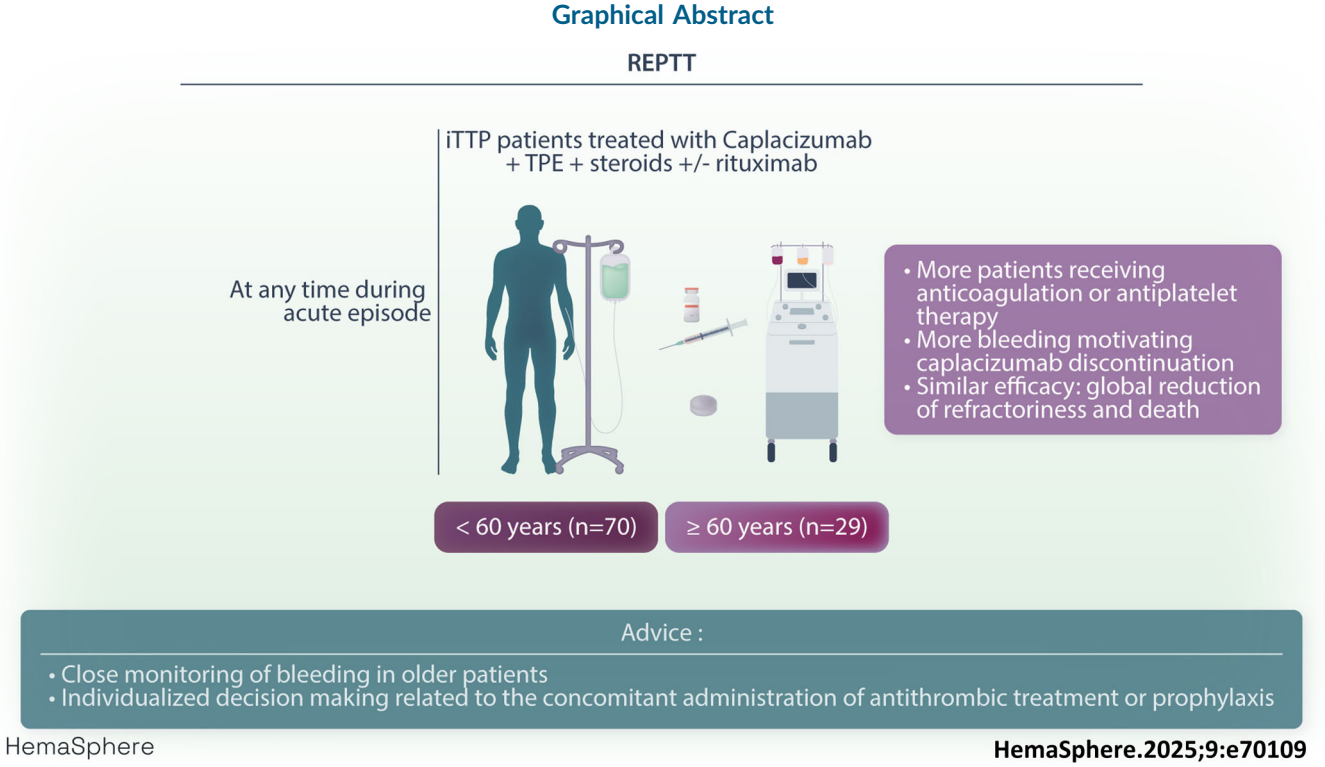
Graphical Abstract



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Abstract

Immune thrombotic thrombocytopenic purpura (iTTP) typically affects middle-aged individuals, although it sometimes appears in older patients. Caplacizumab is approved for the treatment of iTTP, but information on the safety and efficacy of this drug in elderly patients is not available. We aimed to analyze the management and outcomes of iTTP patients registered in the Spanish TTP Registry and receiving caplacizumab at any time during the acute episode, focusing on patients ≥60 years ($n = 29$) and comparing them with patients <60 years ($n = 70$). Severe bleeding motivated caplacizumab's initiation delay in one patient ≥60 years. Patients receiving anticoagulation or antiplatelet therapy at diagnosis were more common in older patients (10% vs. 1%; $p = 0.074$), as well as the occurrence of bleeding motivating caplacizumab discontinuation (17% vs. 1%, respectively; $p = 0.008$). Caplacizumab seemed to be efficient in the treatment of iTTP in older patients, reducing refractoriness and death to 3% and exacerbation to 10%, similar to younger patients. The higher risk of bleeding in this older population warrants the need for close monitoring during treatment and to further explore the best management of thrombotic and bleeding risk.

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INTRODUCTION

Immune thrombotic thrombocytopenic purpura (iTTP) is a potentially life-threatening disorder characterized by severe ADAMTS13 deficiency, which promotes the presence of ultra large von Willebrand factor (vWF) multimers in the blood stream. Under these circumstances, additional inflammatory or shear conditions lead to the formation of platelet-rich thrombi in small vessels and consequently produce organ ischemia.[1] iTTP is classified as a rare disorder due to its low frequency (1–6 cases per year, per million people).[2] Typically, it affects middle-aged women and the incidence in elderly patients is low. More specifically, patients over 60 years represent the last quartile of the age distribution in iTTP.[3]

Caplacizumab is a nanobody that targets the vWF–platelet interaction and inhibits microvascular thrombosis.[4] It has been approved for patients with acute iTTP episodes after demonstrating benefits in reducing mortality, minimizing major thromboembolic events, and accelerating clinical response in two randomized phase II and phase III trials comparing treatment of iTTP with or without caplacizumab.[5,6] Although the age range in these two trials reached 72 and 77 years, respectively, the number of patients over 60 years of age was not specified, and there are no data on safety and efficacy in this subgroup of patients. Subsequent real-world series did not include any patients over 60 years[7] or included very few[8,9] with no specific details on the management and outcome of this population. Some registries from different countries have greatly contributed to improving our understanding of the clinical course of iTTP in elderly patients,[10–12] but none of them included patients who underwent treatment with caplacizumab. Besides, even though several post hoc data analyses have been published in recent years, none has focused on the use of caplacizumab in the elderly patient population.[13–16]

We recently reported our preliminary experience in the Spanish TTP Registry (REPTT, Registro Español de Púrpura Trombocitopénica Trombótica), analyzing diagnostic parameters and clinical outcomes of 44 patients aged over 60 years, and included 14 patients who had received treatment with caplacizumab.[17] We have expanded our analyses to include more recent data, focusing on older patients treated with caplacizumab to gain insight into its use in a broader series of patients.

MATERIALS AND METHODS

Data were obtained from the REPTT. The characteristics and information regarding REPTT have been published previously.[17] Briefly, REPTT is a database including demographic, clinical, and laboratory data, as well as details on treatment and clinical progress of patients diagnosed with TTP. This information is introduced by clinicians into a customized web-based form. Revision of data, requests for additional information when needed, and confirmation of diagnosis are centralized to a technical committee. The Registry complies with Spanish and European legislation on confidentiality of medical data, having been approved by the Spanish General Registry of Data Protection (registration code: 2161102476) and the Committee of Ethics in Medical Research of the Autonomous Community of Galicia (registration code: 2010/155).

Population

Adult patients over 18 years of age were eligible for the study if they met the following criteria: (i) confirmation of iTTP diagnosis by determination of ADAMTS13 activity below 20%, along with the presence of anti-ADAMTS13 autoantibodies, normalization of ADAMTS13 after treatment, or absence of ADAMTS13 mutations; (ii) having received caplacizumab at any time during the acute episode; (iii) availability of essential data regarding caplacizumab treatment, including the date and reason of initiation, termination, discontinuation, and outcome of the acute episode. For the analysis, the study population was divided into two groups: the older group (≥60 years) and the younger group (<60 years).

Outcome definitions

Outcome definitions are based on the revised criteria published by the International Working Group in 2021.[18] Specifically: (i) clinical response is defined as sustained normalization of platelet count ($>150 \times 10^9$/L) and lactate dehydrogenase (LDH) <1.5 times the upper limit of normal, with absence of clinical evidence of new or progressive ischemic organ injury; (ii) clinical exacerbation is defined as a decrease in platelet count $<150 \times 10^9$/L with or without clinical evidence of new or progressive ischemic organ injury, within 30 days of stopping plasma exchange therapy (PEX) or anti-VWF therapy; (iii) clinical remission is defined as sustained clinical response with either (1) no PEX and no anti-VWF therapy in the past 30 days or (2) attainment of ADAMTS13 remission (partial or complete), whichever occurs first; (iv) relapse is defined as a decrease in platelet count to $<150 \times 10^9$/L with or without clinical evidence of new ischemic organ injury, after attainment of clinical remission and new confirmation of severe ADAMTS13 deficiency.

Statistical analysis

All results are given as median (range) or mean with 95% confidence interval (CI) when appropriate. Comparisons between both patient groups were tested for statistical significance using the Mann–Whitney *U* test or chi-squared test. Overall survival (OS) was defined as the time interval from the day of diagnosis of the first episode of iTTP until death from any cause with survivors censored at the last follow-up. OS was plotted according to the Kaplan–Meier product-limit method with comparisons made by the log-rank test. Differences were considered statistically significant when p values were <0.05 in a two-tailed test. Statistical analyses were performed using EZR software, based on R commander (R Commander Version 2.6-1).[19]

Data sharing statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

RESULTS

Patients' characteristics

From November 2018 to April 2023, a total of 175 acute iTTP episodes were included in the REPTT. Of these, 99 patients from 39 centers received caplacizumab during the acute episode, comprising our study cohort. Twenty-nine patients were ≥60 years (older group) and 70 were <60 years (younger group). Ninety were first episodes and 9 were relapses (eight in the younger group and one in the older group; $p = 0.276$).

The age distribution at onset ranged from 19 to 84 years of age, with median incidence occurring at 48 years of age. Five patients were under the age of 25, while 10 were aged over 70. Females accounted for 74% of the patients (77% vs. 69% in Groups 1 and 2, respectively; p = n.s.). Obesity, defined as a body mass index ≥30, was highly prevalent in our series (31.25%) and more frequent in the younger group (39% vs. 13%; $p = 0.033$).

At the time of onset, leukocyte and platelet blood counts were similar in both groups. Hemoglobin determination was lower in the younger group (median count 7.8 vs. 9.2 g/dL in the older group), and renal

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dysfunction (serum creatinine above UNL) was more frequent in the older group (24% vs. 38%), although these differences were not statistically significant. Serum bilirubin levels were significantly higher in the younger group (1.96 vs. 2.70 mg/dL; $p = 0.031$). LDH levels were similar in both groups.

Bleeding symptoms at onset occurred in a similar proportion of patients (57% in the older group vs. 58% in the younger group). There were no significant differences in the number of patients presenting with neurological involvement (64% in the older group vs. 65% in the younger group). Although the proportion of patients with cardiac involvement at diagnosis was higher among elderly patients (17% vs. 10%), the difference did not reach statistical significance. Table 1 shows the most relevant characteristics of patients at diagnosis according to each age group.

Treatment

As this is a registry study, treatment was administered as directed by the corresponding physician. Every patient included in the study received frontline treatment with PEX and steroids. Additional immunosuppressive treatment with rituximab was administered to 81% patients in the older group and 86% patients in the younger group ($p = 0.771$).

Caplacizumab was administered to all patients during the acute episode. Initiation of caplacizumab therapy occurred following a median of 3.5 days of diagnosis (ranging from 0 to 26) in patients <60 years and 5 days (0–23) in patients ≥60 years ($p = 0.384$). Caplacizumab was used at onset as frontline therapy in 16 patients and was introduced following an exacerbation ($n = 5$) or due to refractoriness ($n = 8$) in the cohort of patients ≥60 years, and this occurred in a similar proportion of patients <60 years (49, 10, and 11, respectively; $p = 0.284$). This information is detailed in Table 2. Notably, one patient in each group started caplacizumab after achieving clinical response due to a new decrease in platelet count, although exacerbation was later ruled out upon confirmation of normal ADAMTS13 activity, and these findings were attributed to rituximab-induced thrombocytopenia and infectious thrombocytopenia.

TABLE 1 Main characteristics of patients treated with caplacizumab according to age groups.

Characteristics	Age <60 *n* = 70	Age ≥60 *n* = 29	*p*
Age (years), median (range)	42 (19–59)	66 (60–84)	
Female sex, *n* (%)	54 (77)	20 (69)	0.449
Weight (kg), median (range)[a]	78 (46–118)	66 (44–124)	**0.004**
BMI (kg/m^2)[b]	28.8 (18.9–42.6)	24.9 (17.4–38.3)	**0.008**
Obesity (BMI > 30), *n* (%)[b]	22 (39)	3 (13)	**0.033**
CBC, median (range)			
Leukocytes, 10^9/L	8.7 (3.2–22.8)	7.1 (3.8–29)	0.259
Hemoglobin, g/dL	7.8 (4.8–14.6)	9.2 (4.2–12.5)	0.462
Platelets, 10^9/L	12 (3–112)	10 (1–57)	0.517
LDH (UI/L), median (range)	899 (237–7334)	1117 (464–3280)	0.922
LDH (fold UNL), median (range)	4 (1 to >10)	4 (2–10)	0.659
Creatinine (mg/dL), median (range)	0.92 (0.54–6.20)	1.07 (0.61–2.78)	0.808
Creatinine ≥2 mg/dL, *n* (%)	3 (4.2)	2 (6.9)	0.628
Creatinine >UNL, *n* (%)	17 (24)	11 (38)	0.221
Serum bilirubin (mg/dL), median (range)[c]	1.96 (0.6–9.1)	2.70 (0.8–15.9)	**0.031**
ADAMTS13 activity (%), median (range)[d]	0 (0–17)	0 (0–19)	0.742
Neurological involvement, *n* (%)	45 (64)	19 (65)	1
Cardiac involvement, *n* (%)	7 (10)	5 (17)	0.326
Bleeding symptoms, *n* (%)	40 (57)	17 (58)	1
Temperature ≥38°C, *n* (%)	5 (7)	3 (10)	0.689
Treatment			
Plasma exchange	70 (100)	29 (100)	1
Corticoids	70 (100)	29 (100)	1
Caplacizumab	70 (100)	29 (100)	1
Rituximab	57 (81)	25 (86)	0.771

Note: Neurological symptoms ranged from headache to coma. Cardiac involvement ranged from chest pain to myocardial infarction. Bleeding ranged from petechie to intracranial bleeding. Bold value indicates statistically significant *p* value.

Abbreviations: BMI, body mass index; CBC, complete blood count; LDH, lactate dehydrogenase; UNL, upper normal limit.

[a]Available data in 94 patients.

[b]Available data in 80 patients.

[c]Available data in 97 patients.

[d]Two patients (one in each group) had a reported ADAMTS13 activity at diagnosis between >10% and <20%. Both were diagnosed with iTTP by the corresponding physician, as the clinical picture was judged to be typical.

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TABLE 2 Details of caplacizumab treatment in our series, including time of initiation, days until treatment initiation, and duration of treatment.

Caplacizumab treatment	Time of initiation			Days until initiation			Days of treatment		
	Age <60 *n* (%)	Age ≥60 *n* (%)	*p*	Age <60 Median (IQR)	Age ≥60 Median (IQR)	*p*	Age <60 Median (IQR)	Age ≥60 Median (IQR)	*p*
At diagnosis	49 (70)	16 (55)		2.5 (0.8–4.3)	2 (1–4)	0.745	34 (23–35)	34 (26–39)	0.758
At exacerbation	10 (14)	5 (17)	0.284	13 (12–14)	10 (8–13)	0.098	33 (30–38)	37 (32–38)	0.586
At refractoriness	11 (16)	8 (28)		9.5 (6.3–11.3)	11 (9–17)	0.144	36 (23–37)	48 (37–77)	0.111

Abbreviation: IQR, interquartile range.

In one patient in the older group, therapy with caplacizumab was delayed due to initial hemorrhagic symptoms (severe hematuria that required transfusion support with red blood cells), while this was not reported in the younger group. Notably, we evaluated the time to caplacizumab initiation in relation to the presence of bleeding at diagnosis and found no relationship either in the general cohort (median of 4 days for patients without bleeding vs. 3.5 days for patients with bleeding symptoms at diagnosis; $p = 0.729$), nor in the subgroup of patients that started caplacizumab as frontline therapy (2.8 vs. 3.2, respectively; $p = 0.667$).

Four patients were receiving anticoagulation (direct anticoagulants, $n = 2$; vitamin K antagonists, $n = 1$) or antiplatelet therapy (inhibitor of P2Y12 receptor, $n = 1$) at the time of TTP diagnosis due to atrial fibrillation ($n = 2$), previous myocardial infarction ($n = 2$), or ictus ($n = 1$; one patient with these two last conditions). Specifically, one belonged to the younger group and three to the older group (1.4% vs. 10.3%, respectively; $p = 0.074$) (Table 3). In the four cases, these drugs were discontinued at diagnosis or before the initiation of caplacizumab. In one of these patients, this treatment resulted in a delay in the administration of caplacizumab.

Bleeding motivating transient caplacizumab discontinuation occurred in five patients >60 years (17.2%) (subarachnoid hemorrhage [one patient with two episodes], hematuria and peri catheter hemorrhage [one patient], abdominal hematoma, gastrointestinal, and gingival hemorrhage [one each]), while only one patient <60 years (1.4%) developed three episodes of caplacizumab-related rectal bleeding ($p = 0.008$) (Table 3). No other side-effects were reported.

The duration of treatment with caplacizumab was similar in patients ≥60 and <60 years (median of 34 [range, 1–77] and 35 days [range, 1–188], respectively; $p = 0.270$), as well as across different subgroups based on the timing of caplacizumab initiation (Table 2).

Response to treatment and OS

Refractoriness was observed in 11 (15.7%) patients in the younger group and in 8 (27.5%) patients in the older group, but only one of them (from the older group) occurred after caplacizumab initiation. This patient was diagnosed 2 days after hospital admission and developed severe encephalopathy requiring mechanical ventilation after the first PEX. Caplacizumab was initiated 1 day later and a total of eight daily doses were administered, despite which the patient developed multiorgan failure and died due to refractory disease on day 11 after diagnosis. Death was considered secondary to iTTP refractoriness and not caplacizumab-related.

Clinical remission rate was similar in both groups (100% in the <60 group and 97% in the ≥60 group). Once caplacizumab was initiated, 10 exacerbation episodes were registered (four in the older

TABLE 3 Bleeding events and anticoagulation or antiplatelet therapy during caplacizumab treatment.

Caplacizumab bleeding risk and occurrence	Age <60 *n* (%)	Age ≥60 *n* (%)	*p*
Patients under anticoagulation/antiplatelet therapy at diagnosis	1 (1.4)	3 (10.3)	0.074
Bleeding that motivates caplacizumab delay	0 (0)	1 (3.4)	0.293
Bleeding that does not motivate caplacizumab delay[a]	25 (35.7)	12 (41.4)	0.823
Bleeding while on caplacizumab that motivates treatment cessation	1 (1.4)	5 (17.2)	**0.008**

Note: Bold value indicates statistically significant *p* value.

[a]At the time of caplacizumab initiation.

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group and six in the younger group) (Table 4). Of note, these exacerbations were mainly due to caplacizumab discontinuation (6 out of 10), because of administrative problems ($n = 2$), serious bleeding ($n = 2$), or planned discontinuation ($n = 2$), but also occurred in 4 out of 10 cases while under caplacizumab treatment. In these four cases, treatment with PEX was restarted and caplacizumab maintained, while additional immunosuppression was given, achieving a new clinical response. Two patients suffered two exacerbations: (i) one patient in the older group who suffered an exacerbation while receiving caplacizumab and subsequently a new exacerbation due to discontinuation of caplacizumab because of severe epistaxis, and (ii) another patient in the younger group suffered two exacerbations and initiated caplazicumab following the second episode. In addition, four more patients discontinued caplacizumab treatment intermittently due to administrative problems ($n = 1$, from the younger group) or due to severe bleeding ($n = 3$, from the older group), but they did not suffer exacerbation.

Median follow-up of surviving patients was 8 months. OS of the whole series was 99% (96.6% vs. 100% in the older and younger group, respectively; $p = 0.120$) (Figure 1), as only one patient ≥60 years died due to refractory disease. Final outcomes are detailed in Table 4.

TABLE 4 Clinical outcomes of patients according to age groups.

Outcomes	Age <60 *n* (%)	Age ≥60 *n* (%)	*p*
Clinical remission	70 (100)	28 (96.6)	0.293
Exacerbation			
Before initiation of caplacizumab	11 (15.7)[a]	5 (17.2)	0.966
After initiation of caplacizumab	6 (8.5)	3 (10.3)	0.719
Due to caplacizumab cessation	3	3[b]	
While on caplacizumab	3	1[b]	
Refractoriness	11 (15.7)	9 (31)	0.102
Before initiation of caplacizumab	11	8	
After initiation of caplacizumab	0	1	
Early death	0 (0)	1 (3.4)	0.293

[a]One case of exacerbation before caplacizumab start, which finally was refractory, and at this moment caplacizumab was started.

[b]One patient suffered two exacerbations after initiation of caplacizumab: one while on caplacizumab treatment and another due to treatment discontinuation.

DISCUSSION

Our study has assessed the efficacy and safety of caplacizumab for the treatment of an acute episode of iTTP on 99 patients from the REPTT, particularly focusing in patients ≥60 years old.

Although caplacizumab is approved as frontline therapy for acute iTTP episodes, the real-world scenario has proven to be different to that of clinical trials. Caplacizumab was approved by the Spanish Health Authorities in August 2018, for patients diagnosed with iTTP who "show inadequate initial response to standard therapy or those who suffer recurrences."[20] This fact justifies the selection bias in our series, in which high risk patients, such as those with exacerbation and refractoriness, are overrepresented (34%). This circumstance has been observed in previous studies.[8] Most patients in our cohort (91%) presented with a first iTTP episode, especially in the elderly group. This finding contrasts with that described in caplacizumab's clinical trials, where a lower (~60%) first episode rate is reported,[5,6] and

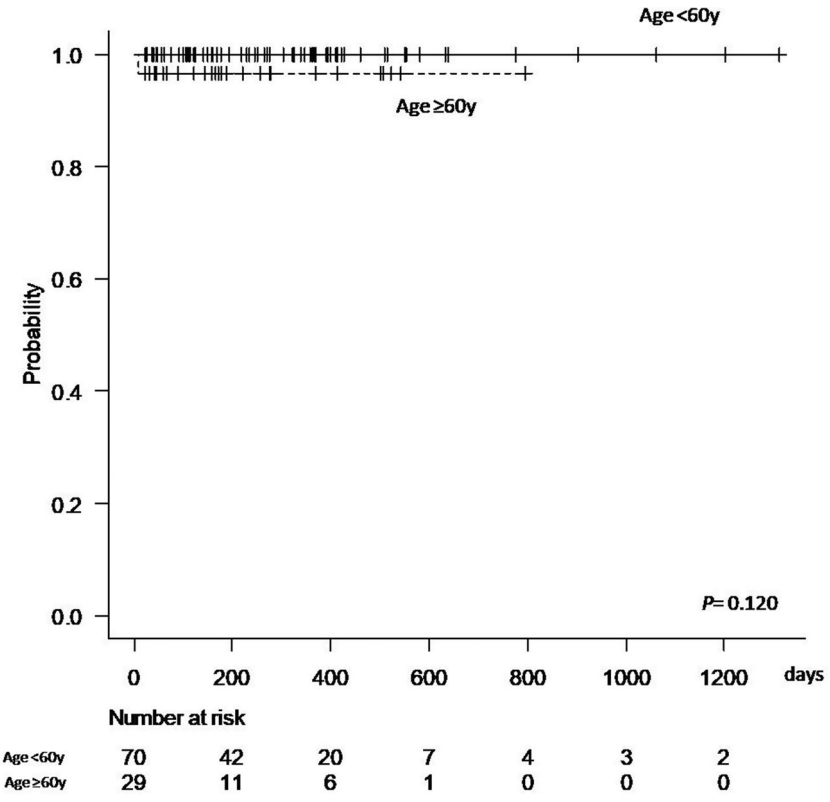

FIGURE 1 Overall survival of patients according to age group.

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highlights the presence of high-risk features in our series, as initial TTP episodes are generally more severe at presentation compared to recurrent episodes.[21]

In our series, 29% of patients were ≥60 years, a proportion much higher than the majority of studies.[3,16,22–24] Organ ischemia and extended treatment duration may affect older patients more significantly than younger ones, potentially influencing clinicians to be more inclined to initiate caplacizumab in older patients.

Among baseline characteristics, we observed a trend toward a higher proportion of renal and cardiac involvement in older patients, when compared to the control group. This is consistent with our previously reported results[17] and others.[10–12] On the contrary, we did not find a higher proportion of neurologic involvement, as other study groups did.[10,11]

Treatment with PEX and steroids was administered to every patient, and the addition of rituximab was very frequent in both age groups (>80%), compared to our own previous report and others.[11,17] Although rituximab is not approved for the treatment of iTTP, current guidelines and cost-effectiveness studies support its use in the frontline,[25–27] and our series compiles patients from the most recent years (>2018).

Caplacizumab confers an intrinsic hemorrhagic risk.[5] Bleeding events are usually mild but can be potentially life-threatening. Therefore, in the case of active bleeding (or bleeding risk), initiation of caplacizumab should be withheld, as stated in the product information.[28] Patients with active bleeding or with risk factors for bleeding (other than thrombocytopenia) were excluded from clinical trials,[5,6] and we acknowledge the possible selection bias in our series, as these high-bleeding risk patients might have not been offered caplacizumab and were not included in this study. In our series, the proportion of patients with hemorrhagic symptoms at diagnosis was similar in both cohorts (57%–58%), and patients with or without bleeding started caplacizumab within a similar timeframe. Of note, thrombocytopenia resolves faster with the use of caplacizumab, and it is reasonable to proceed with caplacizumab initiation even in patients with mild bleeding symptoms. In our study, only in one patient (1%) ≥60 years with severe hematuria caplacizumab administration was delayed 3 days. In one post-commercialization study, 4 out of 139 (2.8%) patients did not start caplacizumab treatment due to risk of bleeding ($n = 1$) or active bleeding ($n = 3$), but the age of these patients was not reported.[7] This information cannot be found in other post-commercialization studies.[8,9,29]

In our study, most patients receiving antiplatelet or anticoagulant drugs were older. Similarly, Prevel et al. showed 34% and 10% of older patients receiving antiplatelet therapy or anticoagulants (compared to 5% and 1%, in younger ones).[12] Patients receiving anticoagulants or antiplatelet drugs were excluded from pivotal trials,[5,6] and caplacizumab's product information underlines the additional bleeding risk of the drug if used concomitantly with antiplatelets or anticoagulants.[28] Therefore, in our series, the four patients under these drugs discontinued treatment to allow initiation of caplacizumab without complications.

Mild hemorrhagic symptoms during caplacizumab treatment that did not motivate an intervention (such as caplacizumab discontinuation) were not systematically reported to our registry and have not been assessed. However, bleeding symptoms causing caplacizumab discontinuation were found in 17% and 1% of older and younger patients, highlighting the need of a closer monitoring of bleeding side-effects while under treatment with caplacizumab in this population. The reintroduction of antiplatelet or anticoagulant drugs when platelets rise $>50 \times 10^9$/L was recommended in some guidelines before the availability of caplacizumab.[30] When caplacizumab is used, this practice remains controversial, as the thrombotic mechanism is targeted by the drug; however, some authors still support the administration of prophylaxis with low molecular weight heparin, as there is still some risk of thrombosis despite the use of caplacizumab (7.4% in the integrated analysis of caplacizumab clinical trials), especially if hospitalized/immobilized.[7,28,31] In Titan and Hercules trials, patients could receive aspirin and heparin or other anticoagulants at the discretion of the investigator, although a threshold of $>100 \times 10^9$ platelets/L was recommended.[5] In a more recent real-world study including 26 patients, the two only patients suffering serious bleeding events related to caplacizumab were under heparin and/or antiplatelet drug concomitantly.[29] In the UK Registry, four out of five patients who developed venous thromboembolism while on caplacizumab discontinued the drug to start anticoagulation.[9] Our finding adds information for this concern, as both older age and concomitant anticoagulant/antiplatelet treatment increase the bleeding risk of caplacizumab. In our opinion, the addition of pharmacologic thrombotic prophylaxis while on caplacizumab should be carefully decided after a risk–benefit analysis, especially in older population. Finally, to reduce the risk of caplacizumab-associated bleeding, some authors suggest administering caplacizumab every other day or monitoring vWF activity.[32,33]

Despite the use of caplacizumab, exacerbations were observed in both cohorts (8%–10%). Caplacizumab discontinuation explains 6 of the 10 exacerbations seen in our study. However, four of the exacerbations occurred while receiving daily caplacizumab. These exacerbations during caplacizumab treatment were also reported in 5% and 3% of patients in phase II and phase III clinical trials[5,6] and 0%–3% in real-world studies.[7–9,29] In our series, these patients were restarted on PEX, while maintaining daily caplacizumab and completing or intensifying immunosuppression. PEX was also restarted in patients included in Titan and Hercules trials, but the French series reported favorable outcomes without treatment intensification.[7] Therefore, it remains unknown which patients are at risk for this intra-treatment exacerbation and what the best management approach for this complication is. Of note, in two cases of our series, caplacizumab was initiated due to suspicion of exacerbation, but this was not later confirmed (ADAMTS13 activity >20%) and they were diagnosed as having drug and infection-induced thrombocytopenia. Others have reported difficulties in situations mimicking exacerbation during iTTP management (e.g., CMV infection).[34] ADAMTS13 activity reassessment and clinical context are crucial to approach differential diagnosis correctly and adopt the appropriate therapeutic strategy.

Refractoriness was overcome with the addition of caplacizumab in all the patients of both cohorts ($n = 19$). However, one patient ≥60 years did not improve the response despite the addition of caplacizumab one day after PEX initiation and he died due to multiorgan failure. Refractoriness poses a very high risk for death.[35] In a real-world series from the German group, one refractory patient (out of 60) who received additional treatment with caplacizumab from day 3 died without response 24 hours later; however, this case did not comply with the definition of refractoriness as platelet response was documented in the report and would be probably better categorized as early death.[8] In addition, the French series reported two cases (out of 90) of refractoriness, one of them dying due to massive pulmonary embolism despite receiving frontline caplacizumab.[7] Finally, the UK Registry reported five refractory cases (out of 85) leading to death (two of them in patients ≥60 years) in which caplacizumab had been started ≥2 days previously.[9] Only in two of these cases a platelet recovery was not seen (truly refractory). In our case, as in many of the refractory cases detailed before, caplacizumab was not used in the frontline, and some authors have suggested that this could be a risk factor for non-response to therapy.[8,9] However, many other patients initiated caplacizumab while already refractory

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to PEX and immunosuppression, and a clinical response was achieved in all those cases. Therefore, the reasons for the aggressive behaviour of the disease in these instances remain uncertain. We believe that starting comprehensive therapy before irreversible organ damage occurs is crucial to preventing death and complications. In this context, it is worth noting that the patient who died in our series suffered a 2-day delay in diagnosis. Diagnostic delay due to atypical presentation has already been reported in older patients,[12,36] and it is probably a key point for improving outcomes in this population.

Overall mortality during the iTTP episode has been stated to be increased in older patients (8%–37%),[10–12] although we have recently reported a lower mortality rate, similar to younger patients (2.4% and 4.5%, respectively) due to improved diagnostic and treatment strategies.[17] Despite our series contains a high proportion of high-risk patients, the mortality rate remained exceptionally low (1%). We support that this low mortality rate is due to the use of caplacizumab. Indeed, we did not document any early deaths in our series, (i.e., within the first 72 h of disease onset). We acknowledge the potential for reporting bias in a non-mandatory registry like ours; however, it is also possible that caplacizumab treatment may have mitigated this risk, making it comparable between younger and older patients. Another limitation of our study is the relatively small sample size analyzed precluding drawing definitive conclusions. However, to the best of our knowledge, this is the largest series of older patients with iTTP being treated with caplacizumab.

In conclusion, caplacizumab seems to be safe and effective in older patients with iTTP, reducing refractoriness and death to 3.4% and exacerbation to 10%. However, the risk of caplacizumab-associated bleeding in this population requires individualized decision-making related to the concomitant administration of antithrombotic treatment or prophylaxis.

AUTHOR CONTRIBUTIONS

Javier De la Rubia and Inés Gómez-Seguí designed the research and performed the analysis. All other authors collaborated with the entry of cases in the Registry and reviewed the manuscript.

CONFLICT OF INTEREST STATEMENT

I. G. S. has received honoraria from Sanofi and Takeda. M. E. M. C. received grants from Amgen and Novartis and served as an advisor or speaker for Amgen, Sanofi, Grifols, Novartis, Novo Nordisk, and Takeda. M. L., in the name of his institution, the Clínic Foundation for the Research, has received research support from Sanofi-Aventis. J. D. l. R. has participated in advisory boards for Sanofi. The remaining authors have no competing interests to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

FUNDING

The authors received no specific funding for this work.

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