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Treatment of immune-mediated thrombotic thrombocytopenic purpura without plasma exchange

Running title: Plasma-exchange free treatment of iTTP

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Authorship Contributions

MC, GG, IM and JAG collected the data. MC and GG analysed the data. MC and GG wrote the manuscript. All authors interpreted the data and carefully revised the manuscript.

Disclosure of Conflicts of Interest

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

Data sharing statement

For original data, please contact the corresponding author.

Article Summary:

- The introduction of caplacizumab in the therapeutic armamentarium of immune-mediated thrombotic thrombocytopenic purpura has opened the way for plasma-exchange free regimens in selected cases.
- In our manuscript we report three cases of patients with acute immune-mediated thrombotic thrombocytopenic purpura successfully treated with plasma exchange-free regimens.

Immune-mediated thrombotic thrombocytopenic purpura (iTTP) is an autoimmune thrombotic microangiopathy caused by inhibitory autoantibodies against the von Willebrand factor (VWF)-cleaving protease ADAMTS13, resulting in microthrombosis, thrombocytopenia and hemolytic anemia¹. According to international guidelines, standard treatment for iTTP includes therapeutic plasma exchange (TPE), immunosuppressive therapy (glucocorticoids and/or rituximab) and caplacizumab². TPE is a life-saving procedure aimed to remove anti-ADAMTS13 autoantibodies and ultra-large VWF multimers and to give donor ADAMTS13; however, it carries substantial risks related to the central venous catheter (e.g., bleeding risk and infections), the exposure to donor plasma (e.g., infusion reactions) and electrolytes disturbances. Caplacizumab is a nanobody that binds to the A1 domain of the VWF blocking its interaction with the GP1b glycoprotein on the platelets surface, halting the formation of small vessel microthrombi and the consequent consumptive anemia and thrombocytopenia. When added to standard treatment, a lower incidence of TTP-related complications, earlier platelet count normalization, a reduced number of TPE procedures, and a lower incidence of exacerbations were observed³. Given this evidence and the risks associated with TPE, the possibility of treating acute iTTP minimizing or avoiding the use of TPE is of particular interest.

Herein we report three cases of relapsed iTTP treated without TPE at our center (**Table 1, Figure**).

Written informed consent was obtained from all participating subjects.

Case 1: A 67-year-old man with a previous episode of acute iTTP, presented at the follow-up visit with neurological manifestations (confusion and aphasia). He was on aspirin due to previous non-TTP-related recurrent ischemic strokes. The laboratory exams showed mild anemia and thrombocytopenia and >1% schistocytes per high power field at the peripheral blood smear. The suspect of iTTP relapse was confirmed by evidence of severe ADAMTS13 activity deficiency (<3 IU/dL, normal range 45-138 IU/dL) and high anti-ADAMTS13 autoantibodies titer (50 U/mL, negative values <12 U/mL). A brain computed tomography

showed several recent ischemic lesions. Daily treatment with glucocorticoids and caplacizumab was started. TPE was omitted based on platelet count above $100 \times 10^3/\mu\text{L}$. A prompt improvement of the neurologic manifestations and platelet count was observed. The clinical response, defined as sustained (at least two consecutive days) platelet count normalization ($>150 \times 10^3/\mu\text{L}$) and LDH levels <1.5 ULN, without new or progressive ischemic organ damage⁴, was achieved on day 5. However, ADAMTS13 activity remained undetectable, so that on day 8 weekly 375 mg/kg rituximab was started, achieving a partial ADAMTS13 remission (20 IU/dL) on day 15. On day 16 the patient developed an episode of melena with severe anemia due to active bleeding from arteriovenous intestinal malformations and a duodenal ulcer that were promptly treated. Caplacizumab and aspirin were stopped. After a total of 6 rituximab infusions and 10 weeks of steroid treatment, ADAMTS13 became again undetectable. Therefore, a third-line immunosuppressive treatment with azathioprine was started, subsequently replaced by mycophenolate mofetil because of liver toxicity. This treatment was well tolerated and induced a complete response with normalization of ADAMTS13 activity, which was maintained at the last follow-up visit (30 months after iTTP relapse).

Case 2: A 64-year-old woman with a history of relapsing iTTP and a persistent severe ADAMTS13 deficiency despite multiple immunosuppressive therapies, was diagnosed for a new relapse when new bruising appeared and the laboratory exams showed a platelet count decrease to $85 \times 10^3/\mu\text{L}$. She was admitted to the hospital and immediately treated with glucocorticoids plus caplacizumab, without TPE because of the mild thrombocytopenia and the paucisymptomatic presentation. She achieved a clinical response on day 4 and was discharged continuing her treatment with prednisone and caplacizumab. Since ADAMTS13 activity remained undetectable and the titer of anti-ADAMTS13 autoantibodies high, on day 27 an immunosuppressive treatment with cyclosporin was started and caplacizumab was slowly discontinued. A sustained clinical response was obtained until the last control (4 months after the iTTP relapse).

Case 3: A 34-year-old man had the first acute episode of iTTP in 2022 when he was treated with TPE, glucocorticoids and caplacizumab. Caplacizumab was discontinued on day 37 (ADAMTS13 activity was undetectable) and 7 days later the patient had a clinical exacerbation which was treated with the same regimen plus rituximab. A second attempt in discontinuing caplacizumab was made on day 122, despite ADAMTS13 activity being still undetectable; nine days later the patient experienced a second clinical exacerbation, therefore caplacizumab alone was promptly restarted, with normalization of the platelet count after 3 days. Since ADAMTS13 activity remained undetectable, on day 153 an off-label immunosuppressive therapy with bortezomib was started and caplacizumab was slowly discontinued. The patient showed a progressive normalization of ADAMTS13 activity and anti-ADAMTS13 autoantibodies negativization, and caplacizumab was safely discontinued 9 months after the onset of acute iTTP.

At the last follow-up, 12 months after the iTTP event, the patient was still in clinical and complete ADAMTS-13 remission.

In the last years, few cases of acute iTTP treated without TPE have been reported. Eight different reports of iTTP in Jehovah's Witness patients showed the use of multiple immunosuppressive therapies without TPE due to their religious beliefs. All patients had a good clinical and laboratory response, although most likely slower (median time to platelet count normalization, 14 days) than they would have had with standard treatment; ADAMTS13 response was not reported⁵. Another report described a patient with relapsed iTTP treated with low-dose rituximab plus corticosteroids without TPE due to difficulties related to the COVID-19 pandemic, obtaining a complete hematological response in 6 weeks⁵.

More recently, few cases of iTTP successfully treated with immunosuppressive therapy together with caplacizumab and without TPE have been published⁶⁻⁹. One report described a patient with a first episode of iTTP successfully treated with rituximab and caplacizumab, because of the patient's request not to be hospitalized⁶. Another case of relapsing iTTP was reported in a

Jehovah's Witness patient treated with caplacizumab, steroids and rituximab: this patient as well rapidly recovered with platelet count and ADAMTS13 activity normalization⁷. The case of another patient with a first episode of iTTP treated with caplacizumab, steroids and rituximab due to an anaphylactic reaction to plasma after the first TPE has been reported, with sustained clinical and ADAMTS13 response⁸. Finally, German authors reported a case series of 7 episodes of acute iTTP treated with caplacizumab and steroids (4 with rituximab) confirming the TPE-free approach to be effective. All patients obtained a clinical remission with a median time to platelet count normalization of 3.5 days and a median time to partial ADAMTS13 remission of 25 days. The decision of omitting TPE was based on the patient's clinical presentation, on poor venous access and on patient's preference⁹.

In our three patients, considering the not severe clinical presentation and the relatively mild thrombocytopenia, we decided for a TPE-free approach. Platelet count normalization was achieved after a median of 5 days, while partial ADAMTS13 remission was obtained after 14 days in the first patient, never in the second, and after 9 months in the third. The better response observed in the first patient suggests the importance of achieving an early immunosuppression, supporting the use of caplacizumab together with an anti-CD20 monoclonal antibody upfront when using a TPE-free approach.

This case series adds evidence to previous ones on the efficacy of caplacizumab in addition to steroids in acute iTTP. According to the results of a Spanish study showing a higher efficacy in achieving the clinical response when caplacizumab is started within the first 3 days (median time to platelet count normalization 4 days [IQR, 3-5] compared to 14.5 days [IQR, 10-26.5] when delayed after 7 days)¹⁰, a sudden start of caplacizumab, especially in TPE-sparing regimens, seems to be of pivotal importance.

Even though the median time to ADAMTS13 remission is 28 days¹¹ when caplacizumab is used as frontline treatment together with steroids and TPE, also considering the absence of data on efficacy outcome in TPE-free regimens, we precautionary decided to add rituximab in the first

patient and cyclosporin in the second due to the absence of an ADAMTS13 remission, and we added bortezomib in the third patient because of the dependence on caplacizumab.

All the three reported patients showed a protracted clinical course with the necessity of many lines of immunosuppressive treatment. Even though this may be due to their previous iTTP clinical history, we cannot exclude a detrimental role of TPE omission in the frontline treatment of acute iTTP episodes on ADAMTS13 response induction and consequently on the risk of exacerbation or relapse.

Treatment with caplacizumab was well tolerated except for the first patient who showed major gastrointestinal bleeding due to gastric ulcers and concomitant treatment with anti-platelet drugs. Even though randomized controlled trials and the most recent real-world studies are reassuring on caplacizumab safety, our case series together with previous ones¹² highlights the importance of paying more attention to patients with concomitant risk factors for bleeding.

In conclusion, our case series shows the efficacy of TPE-free regimens in patients with acute iTTP. Only few case reports and retrospective series have been published on such regimens and a clinical trial on the use of caplacizumab together with immunosuppressive therapy without TPE (MAYARI study, NCT05468320) is currently recruiting. Despite the good outcome of our patients, to date TPE-free regimens should not be routinely used until most robust data from clinical trials will be published. However, currently available data reassure clinicians forced not to use TPE. Moreover, our case series highlights the importance of carefully balancing the risk/benefit ratio of continuing treatment with antiplatelet agents while on caplacizumab, especially in presence of concomitant risk factors for bleeding, in view of a comprehensive and personalized approach.

References

1. Page EE, Kremer Hovinga JA, Terrell DR, Vesely SK, George JN. Thrombotic thrombocytopenic purpura: diagnostic criteria, clinical features, and long-term outcomes from 1995 through 2015. *Blood Adv.* 2017;1(10):590-600.
2. Zheng XL, Vesely SK, Cataland SR, et al. ISTH guidelines for treatment of thrombotic thrombocytopenic purpura. *J Thromb Haemost.* 2020;18(10):2496-2502.
3. Scully M, Cataland SR, Peyvandi F, et al. Caplacizumab Treatment for Acquired Thrombotic Thrombocytopenic Purpura. *N Engl J Med.* 2019;380(4):335-346.
4. Falanga A, Chiaramonte M, De Silvestro G, et al. Guidelines for the diagnosis and treatment of thrombotic thrombocytopenic purpura. Italian Society of Hematology (SIE), March 2021 version; <https://snlg.iss.it/?cat=6> (document in italian). last access 4 January 2024.
5. Galindo-Calvillo CD, Rodríguez-Roque CS, Gómez-De León A, Tarín-Arzaga L, Gómez-Almaguer D. Treating thrombotic thrombocytopenic purpura without plasma exchange during the COVID-19 pandemic. A case report and a brief literature review. *Transfus Apher Sci.* 2021;60(3):103107.
6. Sukumar S, George JN, Cataland SR. Shared decision making, thrombotic thrombocytopenic purpura, and caplacizumab. *Am J Hematol.* 2020;95(4):E76-E77.
7. Chander DP, Loch MM, Cataland SR, George JN. Caplacizumab Therapy without Plasma Exchange for Acquired Thrombotic Thrombocytopenic Purpura. *N Engl J Med.* 2019;381(1):92-94.
8. Irani MS, Sanchez F, Friedman K. Caplacizumab for treatment of thrombotic thrombocytopenic purpura in a patient with anaphylaxis to fresh-frozen plasma. *Transfusion.* 2020;60(8):1666-1668.
9. Völker LA, Brinkkoetter PT, Knöbl PN, et al. Treatment of acquired thrombotic thrombocytopenic purpura without plasma exchange in selected patients under caplacizumab. *J Thromb Haemost.* 2020;18(11):3061-3066.

10. Pascual Izquierdo MC, Mingot-Castellano ME, Kerguelen Fuentes AE, et al. Real-world effectiveness of caplacizumab vs standard of care in immune thrombotic thrombocytopenic purpura. *Blood Adv.* 2022;6(24):6219-6227.
11. Coppo P, Bubenheim M, Azoulay E, Galicier L, et al. A regimen with caplacizumab, immunosuppression, and plasma exchange prevents unfavorable outcomes in immune-mediated TTP. *Blood.* 2021;137(6):733-742.
12. Capecchi M, Mocellin C, Abbruzzese C, Mancini I, Prati D, Peyvandi F. Dramatic presentation of acquired thrombotic thrombocytopenic purpura associated with COVID-19. *Haematologica.* 2020;105(10):e540.

	Case 1	Case 2	Case 3
Age at diagnosis	55	32	34
Sex	Male	Female	Male
Relapse of known TTP	Yes	Yes	Yes
Reason for omission of TPE	Not severe clinical presentation and relatively mild consumptive thrombocytopenia	Oligo-asymptomatic and mild consumptive thrombocytopenia	Asymptomatic and mild thrombocytopenia
Neurologic symptoms	Confusion and aphasia	None	None
Renal involvement	None	None	None
Cardiac involvement	None	None	None
Initial platelet count (x 10³/μL)	110	85	42
Initial LDH (U/L)	419	442	223
Initial ADAMTS13 activity (IU/dL)	2	0.2	0.2
Initial anti-ADAMTS13 inhibitor (U/mL)	50	> 84	>82
No. of caplacizumab doses	14	47	225
Time to platelet count normalization/clinical response (day)	5	4	5
Additional treatments	Glucocorticoids, rituximab, azathioprine, mycophenolate mofetil	Glucocorticoids, cyclosporin	Bortezomib

Table 1. Demographic, clinical and laboratory characteristics of the reported patients.

Figure legend

Figure. Graphical representation of the clinical and laboratory features of the reported patients.

Panel A shows the course of the platelet count, hemoglobin and LDH levels over time in the first patient, while **panel B** shows the course in the second patient and **panel C** in the third patient.

