# Treatment of immune-mediated thrombotic thrombocytopenic purpura without plasma exchange

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 anemia.[1] According to international guidelines, standard treatment for iTTP includes therapeutic plasma exchange (TPE), immunosuppressive therapy (glucocorticoids and/or rituximab) and caplacizumab.[2] 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 observed.[3] 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.

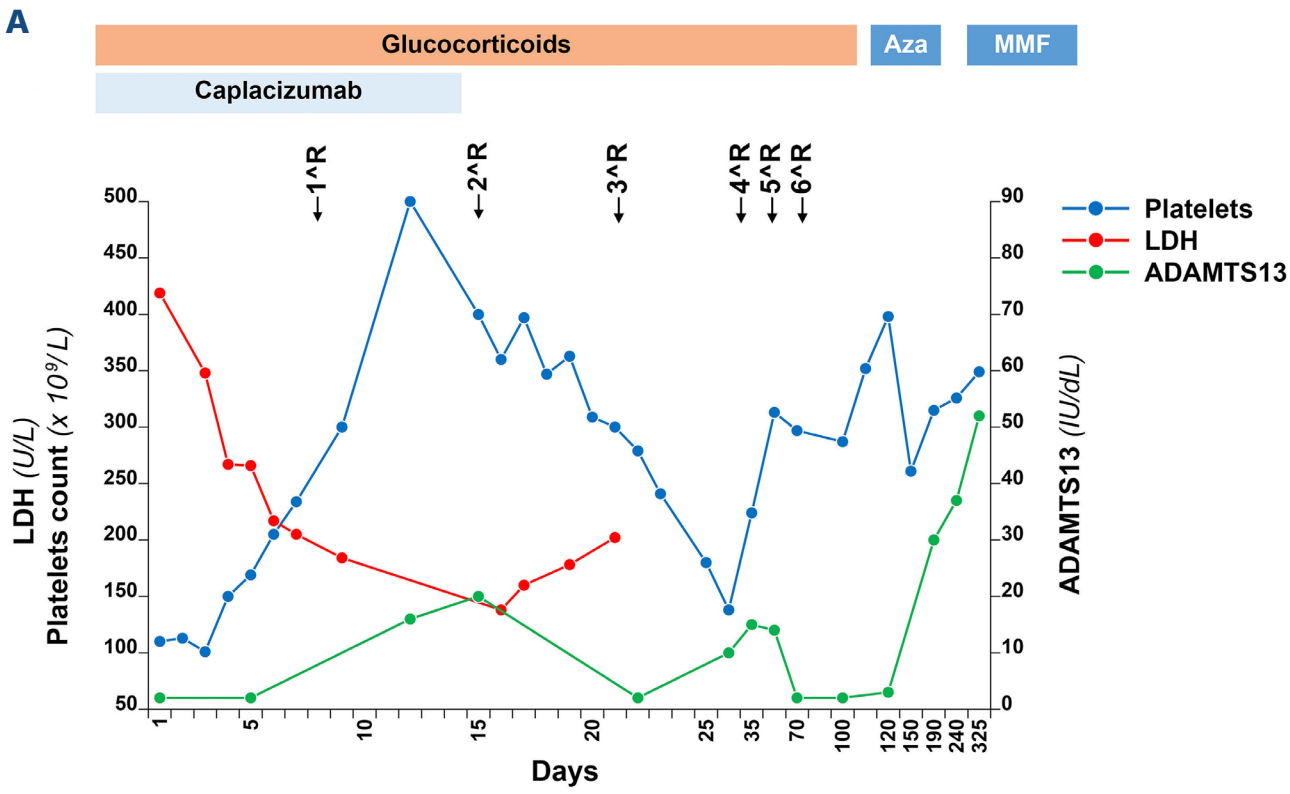
Herein we report three cases of relapsed iTTP treated without TPE at our center (Table 1; Figure 1). Written informed consent was obtained from all participating subjects.

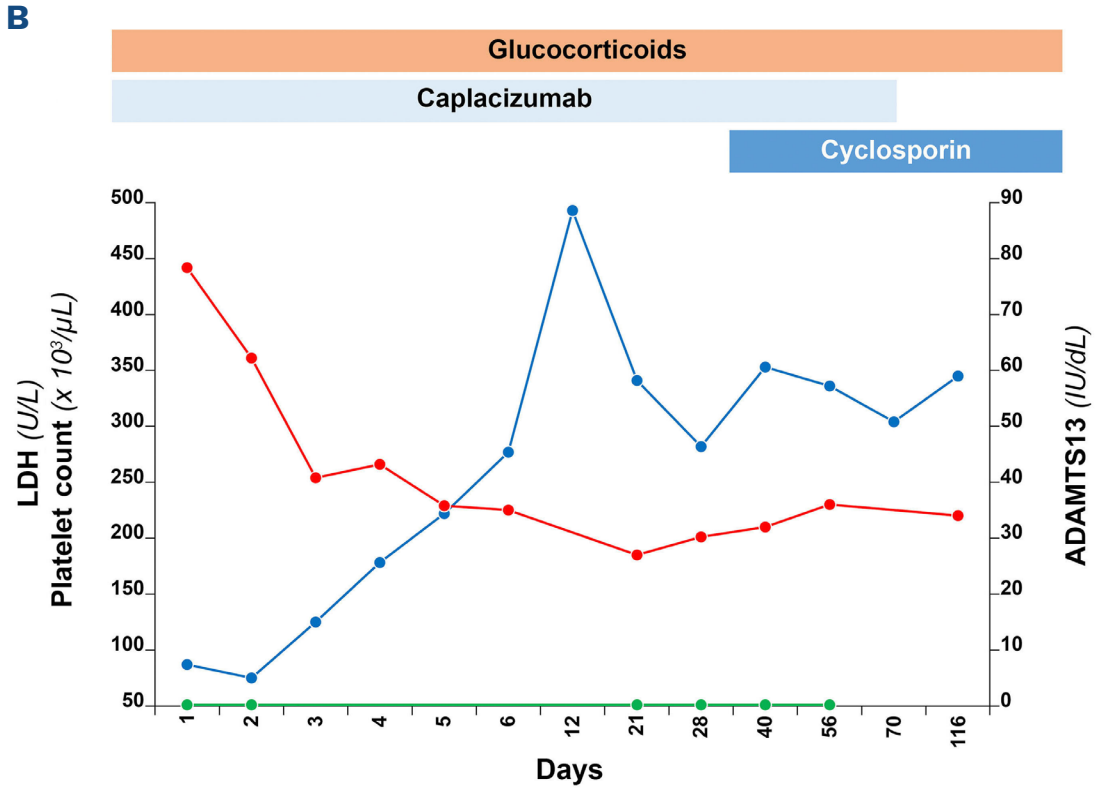
*Case 1*: A 67-year-old man with a previous episode of acute iTTP, presented at the follow-up visit with neurological manifestations (confusion and aphasia). He was on aspirin due to previous non-TTP-related recurrent ischemic strokes. The laboratory exams showed mild anemia and thrombocytopenia and >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

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

| Characteristics | Case 1 | Case 2 | Case 3 |
|---|---|---|---|
| Age in years 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$10^9$/L | 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 |
| Caplacizumab doses, N | 14 | 47 | 225 |
| Time in days to platelet count normalization/clinical response | 5 | 4 | 5 |
| Additional treatments | Glucocorticoids, rituximab, azathioprine, mycophenolate mofetil | Glucocorticoids, cyclosporin | Bortezomib |

TTP: thrombotic thrombocytopenic purpura; TPE: therapeutic plasma exchange; LDH: lactate dehydrogenase.



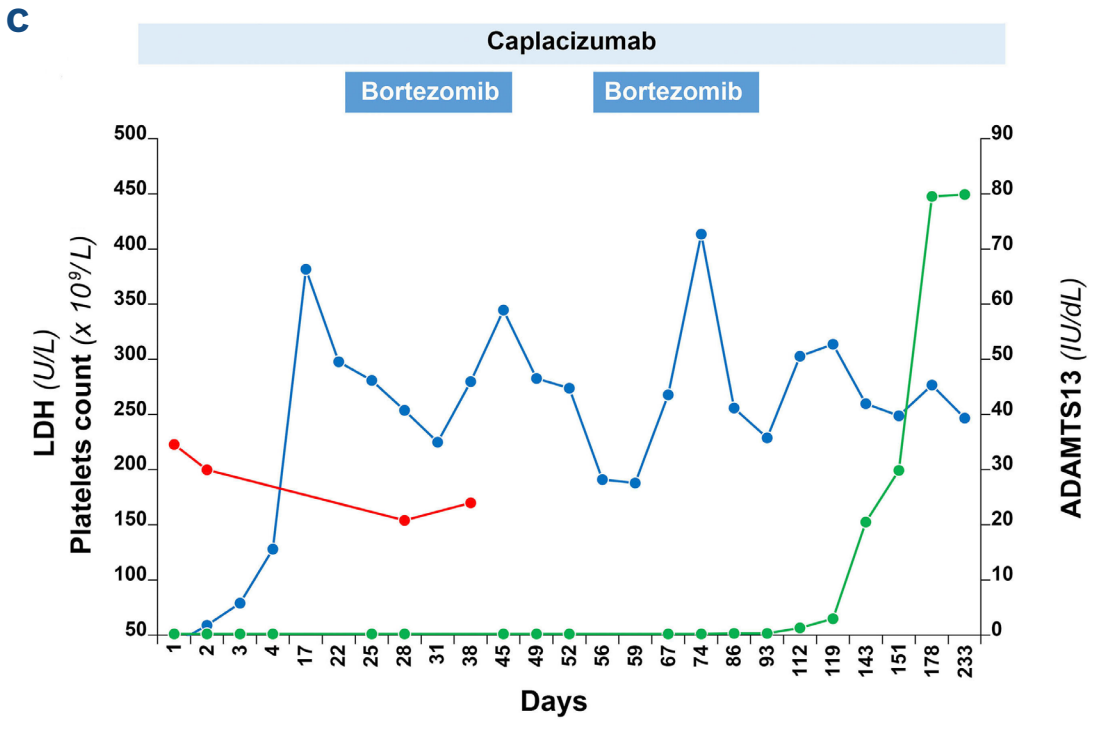




**Figure. Graphical representation of the clinical and laboratory features of the reported patients.** Panel (A) shows the course of the platelet count, hemoglobin and lactate dehydrogenase (LDH) levels over time in the first patient, while panel (B) shows the course in the second patient and panel (C) in the third patient. Aza: azacytidine; MMF: mycophenolate mofetil.

was omitted based on platelet count above 100x10$^9$/L. A prompt improvement of the neurologic manifestations and platelet count was observed. The clinical response, defined as sustained (at least 2 consecutive days) platelet count normalization (>150x10$^9$/L) and LDH levels <1.5 ULN, without new or progressive ischemic organ damage,[4] 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 six 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 85x10$^9$/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; 9 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 the negativization of anti-ADAMTS13 autoantibodies, 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 reported.[5] 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 complete hematological response in 6 weeks.[5]

More recently, few cases of iTTP successfully treated with immunosuppressive therapy together with caplacizumab and without TPE have been published.[6-9] 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 hospitalized.[6] Another case of relapsing iTTP was reported in a Jehovah's Witness patient treated with caplacizumab, steroids and rituximab: also this patient rapidly recovered with platelet count and ADAMTS13 activity normalization.[7] 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 response.[8] Finally, German authors reported a case series of seven 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 preference.[9]

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 [interquartile

range (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 days[11] 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 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 ones[12] 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 a 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, *clinicaltrials gov. Identifier: 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 anti-platelet agents while on caplacizumab, especially in the presence of concomitant risk factors for bleeding, in view of a comprehensive and personalized approach.

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**Contributions**

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

**Data-sharing statement**

For original data, please contact the corresponding author.

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