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– CASE REPORT –

Caplacizumab in the Treatment of Patients with Recurrent Thrombotic Thrombocytopenic Purpura (TTP)

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Abstract

We report two cases of recurrent thrombotic thrombocytopenic purpura, both patients without significant personal pathological antecedents, in which the evolution was favorable following the association of Caplacizumab with the classic treatment with plasmapheresis and cortisone therapy.

We studied two cases of thrombotic thrombocytopenic purpura in two young women, without comorbidities or background treatment, who relapsed after the initial treatment with corticotherapy and plasma exchange, after a period of 4 and 6 years with a different clinical picture, compared to the initial one. The difference is given by the presence/absence of neurological manifestations, both at the first presentation and at the relapse of the disease. In both exposed cases, following the association of Caplacizumab with the classic PTT treatment represented by plasmapheresis and cortisone therapy, the patients had a favorable response to therapy and a maintenance of remission at 1,3 and 2+ years after the relapse.

In conclusion, the treatment of relapsed thrombotic thrombocytopenic purpura with a humanized monoclonaal antibody targeting von Willebrand factor, combined with plasma exchange and corticosteroids, enhances the treatment of this pathology and the remission.

Keywords: *thrombotic thrombocytopenic purpura, Caplacizumab, treatment, platelets, ADAMTS 13*

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Introduction

Thrombotic thrombocytopenic purpura, an acute illness that requires rapid medical intervention, characterized by the formation of microthrombi at the microvascular level, results from a severe deficiency of the specific von Willebrand factor (VWF)-cleaving protease, ADAMTS13. ADAMTS13 deficiency is most commonly acquired due to anti-ADAMTS13 autoantibodies and measuring its activity with the use of fluorescence resonance energy transfer (FRET), significantly enhances diagnostic accuracy and patient outcome in TTP management.[1]

First-line therapy includes plasma exchange with replacement of fresh frozen plasma and immunosuppression with corticosteroids. Immunosuppression targeting ADAMTS13

autoantibodies with the humanized anti-CD20 monoclonal antibody Rituximab is frequently added to initial therapy and when available, anti-VWF therapy with Caplacizumab [2].

Caplacizumab is a crucial add-on therapy for aTTP, reducing microvascular thrombosis risk, but should be used alongside standard care, with ADAMTS13 monitoring essential to prevent relapse [3].

Caplacizumab inhibits the interaction between von Willebrand factor multimers and platelets, providing a new insight into the treatment of TTP by preventing potentially life-threatening microvascular thrombosis that occurs in the course of the disease.

In a randomized phase 3 trial, patients treated with caplacizumab showed a faster normalization of platelet counts compared to subjects who received placebo. Also, the use of caplacizumab was associated with lower relapse rates and decreased disease-related mortality [4].

Also, other randomized controlled trials have demonstrated a faster response time by adding caplacizumab to standard of care treatment [5].

Cases Presentation

The first patient, aged 41 at the time of disease relapse (2022), with evidence of an episode of TTP 6 years ago (2016), completely in remission under standard therapy (plasmapheresis and corticosteroid therapy), presents with suspicion of disease relapse.

Clinically, the patient presented only cutaneous hemorrhagic syndrome, in the form of petechial purpura located on both lower limbs and did not present neurological signs.

Biologically, mild normochromic normocytic anemia, severe thrombocytopenia, schizocytes on the peripheral blood smear, the presence of hemolysis markers (lactate dehydrogenase, increased direct and total bilirubin, reticulocytosis), low ADAMTS13 activity, as well as high titer antiADAMTS13 antibodies were detected (TABLE 1).

Parameter	Value
Hb	8,5g/dL
PLT	18000/mmc
Reticulocytes	7,78%
PBS	8 schizocytes /camp
LDH	675UI/L
DB	0,86mg/dL
TB	2.91 mg/dL
Serum creatinine	0,81 mg/dL
ADAMTS13 activity	<0,01%
Ag ADAMTS13	0.1ug/mL
Ac anti ADAMTS13	>82 U/mL

Table 1. *The biological picture of the 41-year-old patient*

Following the investigations carried out, the diagnosis of relapsed TTP was established and corticosteroid therapy was promptly initiated along with Solumedrol 500 mg per day, Acifol 5 mg 2 tablets per day, intravenous gastroprotectors, substitution with fresh frozen plasma every 8 hours. The first dose of caplacizumab 10 mg intravenously was administered prior to initiation of plasmapheresis sessions. 3 sessions of plasma exchange were performed until complete response and 2 more consolidation sessions. Therapy with Caplacizumab in a dose of 10 mg subcutaneously was performed daily, throughout the duration of plasmapheresis, then daily for 30 days after the end of plasmapheresis. The evolution was favorable and allowed initiation of antiplatelet therapy and deep vein thrombosis prophylaxis with low molecular weight heparin.

Under treatment, the evolution was favorable, with a spontaneous increase in hemoglobin and platelet count, with normalization of LDH. On subsequent reevaluations, improvement of the anemic syndrome, absence of schizocytes on the peripheral blood smear, increased platelet count, and persistence of LDH within normal limits were noted. The patient was monitored for 24 months, without signs of disease.

The second patient, aged 50 years at the time of the relapse of the disease (2023), in evidence with an episode of TTP 4 years ago (2019), completely remitted by corticotherapy and plasmapheresis, presented with severe

neurological manifestations, suspecting the disease relapses.

Clinically, with altered general condition, tachycardic, with important neurological changes, such as left deviation of the head and eyeballs, right homonymous hemianopsia, right hemiparesis, right hemibody hypotonia, positive Babinski sign on the right side, positive Hoffmann sign bilaterally, aphasia global, focal seizures- right upper limb clones with gaze capping.

Biologically, severe anemia, severe thrombocytopenia, leukocytosis with neutrophilia, schizocytes on the peripheral blood smear, the presence of positive markers of hemolysis (marked reticulocytosis, significant increase in lactate dehydrogenase, direct and total bilirubin), as well as low activity of ADAMTS13 and the presence, in high titer, of antiADAMTS13 antibodies (TABLE 2).

Parameter	Value
Hb	4,7 g/dL
Leu, Neu	↑
Reticulocytes	20.18%
PBS	Schizocytes 4-5/camp
LDH	2311 UI/L
BD	1.14 mg/dL
BT	3.52 mg/dL
Serum Creatinine	1.16 mg/dL
ADAMTS13 activity	<0.01%
Ag ADAMTS13	0.2ug/mL
Ac ADAMTS13	>85 U/mL

Table 2. The biological picture of the 50-year-old patient

A cerebral computed tomographic examination was also performed, which revealed a hypodense area at the left frontal cortico-subcortical level, suggestive of a small recent ischemic lesion, without signs of hemorrhagic transformation. Doppler ultrasound of cervico-cerebral vessels revealed early carotid atheromatosis, increased flow velocities at the level of the middle cerebral artery bilaterally, with a small systole-diastole difference.

Diagnoses of acute ischemic stroke in the left carotid territory, relapsed TTP, microangiopathic hemolytic anemia and sepsis were established.

Substitute treatment was instituted (erythrocyte concentrate, platelet concentrate and fresh frozen plasma), cortisone therapy was performed, hydration, gastroprotective, beta-blocker solutions were administered for the management of tachycardia, antiepileptics (Levetiracetam 1000 mg with subsequent dose increase to 1500 mg), antibiotic therapy with Meropenem 2g every 8 hours, Vancomycin 1g every 12 hours. 9 sessions of plasma exchange and caplacizumab therapy were performed according to current guidelines.

The evolution was favorable, with the normalization of the number of platelets, with the remission of neurological manifestations. The patient was monitored for a period of 15 months, without signs of relapse.

Discussions

TTP has various clinical presentations and the diagnosis could be difficult to confirm. The deficiency of

ADAMTS13 activity (less than 10%) is a characteristic finding of TTP. The ADAMTS13 activity should not be used to decide the initiation of the treatment due to delayed obtaining of the result. The Harvard TMA Research Collaborative Registry study showed that 73% of TTP patients had ADAMTS13 activity of more than 10%. The deficiency of ADAMTS13 activity is a key point in pathogenesis of the disease, but not the most important factor in the decision of treatment initiation [6]. The standard therapy of TTP is represented by high dose cortisone and plasmapheresis. In addition to standard therapy, caplacizumab has also been approved since 2019. This is a humanized anti von Willebrand immunoglobulin fragment, which prevents the interaction between the multimers of the von Willebrand factor and the platelets and, at the same time, their consumption by clot formation [7].

In our study, caplacizumab had a great impact on thrombocytes count after a short period of time (three days in the first case- figure 1 and x days in the second case- figure 2) from treatment initiation.

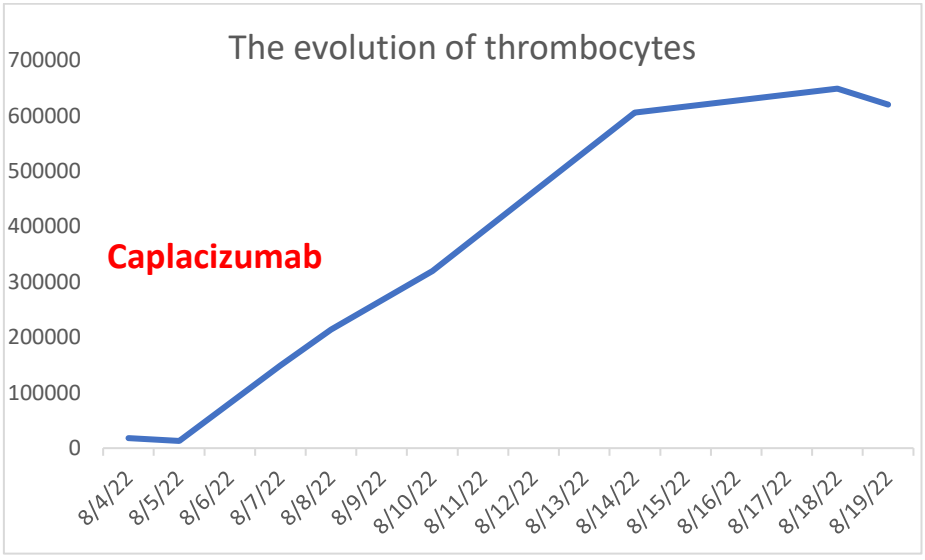

Figure 1. *The evolution of thrombocytes after initiation of caplacizumab treatment in first patient.*

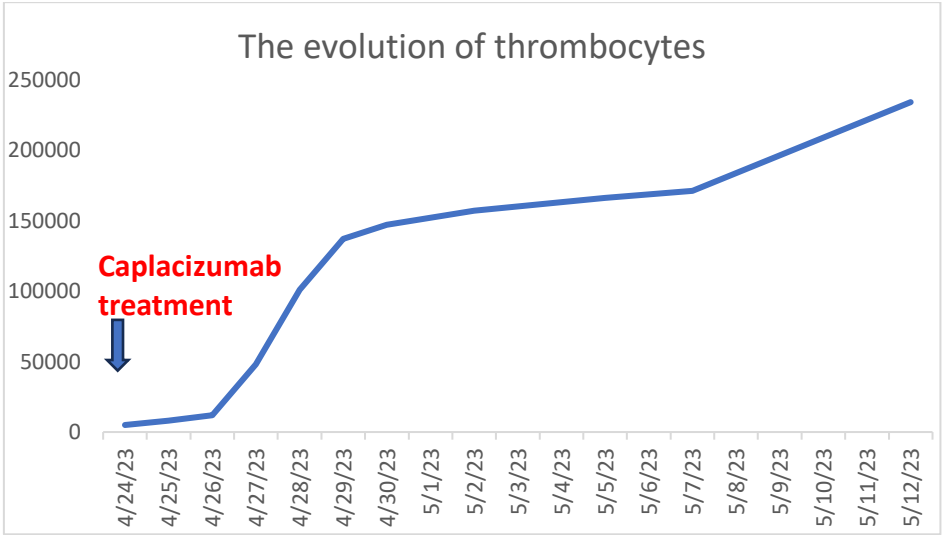

Figure 2*. The evolution of thrombocytes after initiation of caplacizumab treatment in second patient.*

In term of caplacizumab benefits, a comparative analysis of TTP episodes treated with and without caplacizumab in Germany and Austria from 2015 to May 2021, suggested that caplacizumab may lower iTTP-related mortality and refractoriness and decrease the number of daily PEX and hospital stay. The non-first-line use and the premature discontinuation of caplacizumab led to exacerbation in the caplacizumab group of studied patients, but caplacizumab was not less efficacious if it was used in the non-first-line after 72 hours [8].

The TITAN study (Treatment of Thrombotic Thrombocytopenic Purpura with Caplacizumab) is a phase 3 clinical study, conducted between 2014 and 2017, on a number of 145 patients diagnosed with TTP, to evaluate the safety and efficacy of treatment with caplacizumab, offering an option additional therapeutic for patients who do not respond well to plasmapheresis and immunosuppressive therapy and thus demonstrating the reduction of time to complete remission and the prevention relapses, as well as preventing the formation of microthrombi and severe complications of the disease [9].

Another phase 3 study in 150 patients with relapsed TTP - the HERCULES trial - shows that treatment with caplacizumab was associated with faster normalization of platelet counts, with a lower incidence of TTP-related death, with a higher incidence low rate of recurrence of TTP or thromboembolic event during the treatment period [10].

The treatment of patients with relapsed TTP is crucial and must be adapted according to the clinical experience and latest medical discoveries, considering that developments in the field can more effectively address the complexity of this rare disease. It is essential that doctors keep abreast of new treatments and therapeutic approaches to improve the prognosis and quality of life of these patients.

Conclusion

In both cases of thrombotic thrombocytopenic purpura, a favorable evolution is observed following the combination of caplacizumab treatment with PEX sessions and corticotherapy more than 1 year and 2 years after the treatment, respectively, without the recurrence of the disease, with the disappearance of the initial symptoms, whether we are talking about clinical or neurological ones.

The two cases highlight the efficacy of caplacizumab in the treatment of recurrent TTP, demonstrating a rapid and stable remission without relapses over a follow-up period of 15 and 24 months. The experience at the Colentina Clinical Hospital suggests that adding caplacizumab to the treatment regimen can be a valuable therapeutic option, significantly improving the prognosis of patients. Long-term monitoring and personalization of treatment remain essential to prevent recurrences and optimize outcomes.

Conflicts of interest

"This research did not receive any grant from agencies in the public, commercial, or not-for-profit sectors.

None of the authors has any conflict of interest.

The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national laws. Informed consent was obtained from all the patients included in the study."

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