

Rituximab and caplacizumab in the treatment of acquired thrombotic thrombocytopenic purpura: a systematic review

Rituximabe e caplacizumabe no tratamento da púrpura trombocitopênica trombótica adquirida: uma revisão sistemática

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Abstract

Objective: to critically evaluate emerging technologies for antimicrobial resistance (AMR) detection in clinical microbiology, highlighting their applications. To systematically evaluate the efficacy and safety of rituximab and caplacizumab in the treatment of acquired thrombotic thrombocytopenic purpura (aTTP), with emphasis on their effects on platelet recovery, plasma exchange requirements, hospitalization, exacerbations, relapses, and thromboembolic events. **Methods:** A systematic review of English-language studies published between 2016 and 2024 was conducted to evaluate the use of rituximab and/or caplacizumab in patients with aTTP. The literature search was performed in PubMed, ScienceDirect, and Wiley. Studies investigating the therapeutic use of rituximab and/or caplacizumab and reporting clinical outcomes in patients with aTTP were considered eligible. Duplicate records and review articles were removed, and the remaining studies were screened according to the predefined eligibility criteria. Studies unrelated to aTTP treatment or outside the scope of the review were excluded. Eligible studies underwent systematic data extraction and qualitative synthesis, focusing on platelet recovery, plasma exchange requirements, length of hospital stay, exacerbations, relapses, and thromboembolic events. **Results:** A total of 14 studies met the inclusion criteria and were included in the final systematic review. The database search initially identified 365 records, including 22 from PubMed, 174 from ScienceDirect, and 169 from Wiley. After removal of 2 duplicate records and 103 review articles, 260 studies remained for screening. Of these, 246 were excluded because they were unrelated to aTTP treatment or did not meet the predefined eligibility criteria, resulting in the 14 studies included in the final analysis. Caplacizumab, when combined with plasma exchange and immunosuppressive therapy, was associated with faster platelet recovery, fewer plasma exchange sessions, and shorter hospital stays. Rituximab, an anti-CD20 monoclonal antibody that promotes B-cell depletion and reduces anti-ADAMTS13 autoantibody production, showed clinical benefit when introduced early and in patients with refractory or relapsing disease. The combined therapeutic approach was associated with reductions in exacerbations, relapses, and thromboembolic events. **Conclusion:** Rituximab and caplacizumab represent effective therapeutic strategies for aTTP, providing complementary benefits through distinct mechanisms of action. The available evidence supports their use in contemporary therapeutic strategies for both initial treatment and the management of refractory or relapsing disease.

Keywords: acquired thrombotic thrombocytopenic purpura; caplacizumab; rituximab; systematic review; treatment.

Resumo

Objetivo: avaliar sistematicamente a eficácia e a segurança do rituximabe e do caplacizumabe no tratamento da púrpura trombocitopênica trombótica adquirida (PTTa), com ênfase nos seus efeitos sobre a recuperação plaquetária, necessidade de troca plasmática, hospitalização, exacerbações, recidivas e eventos tromboembólicos. **Métodos:** foi realizada uma revisão sistemática de estudos publicados em língua inglesa entre 2016 e 2024 para avaliar o uso de rituximabe e/ou caplacizumabe em pacientes com PTTa. A busca na literatura foi realizada nas bases PubMed, ScienceDirect e Wiley. Foram considerados elegíveis estudos que investigaram o uso terapêutico do rituximabe e/ou caplacizumabe e relataram desfechos clínicos em pacientes com PTTa. Registros duplicados e artigos de revisão foram removidos, e os estudos remanescentes foram triados de acordo com os critérios de elegibilidade previamente definidos. Foram excluídos estudos não relacionados ao tratamento da PTTa ou que estavam fora do escopo da revisão. Os estudos elegíveis foram submetidos à extração sistemática dos dados e à síntese qualitativa, com foco na recuperação plaquetária, necessidade de troca plasmática, tempo de hospitalização, exacerbações, recidivas e eventos tromboembólicos. **Resultados:** um total de 14 estudos atendeu aos critérios de inclusão e foi incluído na revisão sistemática final. A busca nas bases de dados identificou inicialmente 365 registros, sendo 22 no PubMed, 174 no ScienceDirect e 169 na Wiley. Após a remoção de 2 registros duplicados e 103 artigos de revisão, 260 estudos permaneceram para triagem. Destes, 246 foram excluídos por não estarem relacionados ao tratamento da PTTa ou por não atenderem aos critérios de elegibilidade previamente definidos, resultando nos 14 estudos incluídos na análise final. O caplacizumabe, quando associado à troca plasmática e à terapia imunossupressora, esteve relacionado à recuperação plaquetária mais rápida, menor número de sessões de troca plasmática e menor tempo de hospitalização. O rituximabe, um anticorpo monoclonal anti-CD20 que promove a depleção de células B e reduz a produção de autoanticorpos anti-ADAMTS13, demonstrou benefício clínico quando introduzido precocemente e em pacientes com doença refratária ou recidivante. A abordagem terapêutica combinada esteve associada à redução de exacerbações, recidivas e eventos tromboembólicos. **Conclusão:** O rituximabe e o caplacizumabe representam estratégias terapêuticas eficazes para a PTTa, proporcionando benefícios complementares por meio de mecanismos de ação distintos. As evidências disponíveis apoiam sua utilização nas estratégias terapêuticas contemporâneas, tanto no tratamento inicial quanto no manejo da doença refratária ou recidivante.

Palavras chave: púrpura trombocitopênica trombótica adquirida; caplacizumabe; rituximabe; revisão sistemática; tratamento.

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Conflict of interesse: There is no conflict of interest on the part of any of the authors.

Received: 2026 Ago 10; Revised: 2026 Ago 28; 2026 Sep 8; Accepted: 2026 Sep 20

INTRODUCTION

Thrombotic Thrombocytopenic Purpura (TTP) is a rare disease, with an average of 2 to 4 cases per 1,000,000 per year, and is fatal if not diagnosed and treated early¹. It affects both men and women, and is two-to-three times more common in women aged 30 to 40 years².

The syndrome was first described by Eli Moschcowitz in 1924 and is also known as Moschcowitz syndrome³. TTP can be caused by a severe hereditary deficiency in the plasma activity of the enzyme A Disintegrin and Metalloprotease with Thrombospondin motif (ADAMTS13). This deficiency is the result of genetic mutations⁴. In its acquired form, TTP occurs due to the action of autoantibodies that inhibit the plasma activity of ADAMTS13, with a positive test for anti-ADAMTS13 IgG antibodies. The ADAMTS13 enzyme is synthesized in the liver (5,6) and contains a thrombospondin type 1 motif, known as member 13.

Acquired thrombotic thrombocytopenic purpura (aTTP) accounts for more than 95% of all TTP cases. In both forms, the disease manifests acutely, with anemia, thrombocytopenia, diffuse occlusion of arterioles and capillaries within the microcirculation, tissue ischemia with potential multisystem involvement, and thrombotic microangiopathic hemolytic anemia⁷⁻⁹.

The pathophysiology of aTTP was described in 1982 by Joel Moake and collaborators who detected the presence of high molecular weight multimers of von Willebrand factor (VWF) (10). The von Willebrand factor assists the aggregation of platelets to form the thrombus, while the enzyme ADAMTS13 breaks the von Willebrand factor into smaller pieces so that the thrombi formed are not permanent and fall apart when the bleeding is resolved⁶.

VWF is synthesized in megakaryocytes/platelets and endothelial cells. In endothelial cells, newly synthesized VWF is secreted or stored in Weibel-Palade bodies, which release their contents upon stimulation of endothelial cells by the action of a variety of agonists¹¹.

After stimulation, unusually large VWF multimers "Ultra-large von Willebrand Factor" (UL-VWF) are released into the systemic circulation. Under normal circumstances, thrombosis is prevented by rapid (albeit partial) proteolytic processing of UL-VWF by metalloprotease of the ADAMTS-13¹².

ADAMTS-13 cleaves the Y842/M843 peptide bond in the A2 domain of the VWF, reducing the average size of the VWF multimers and releasing fragments of 176 kDa and 140 kDa into the circulation¹³. In the absence or deficiency of this cleavage, microthrombi are formed. The presence of ultra-large von Willebrand factor multimers indicates that patients may have an inability to cleave the glycoprotein polymer, causing

accumulation and, consequently, platelet aggregation¹⁰

Individuals affected by the disease have symptoms such as weakness, severe thrombocytopenia, the appearance of petechiae and ecchymoses, fever, and symptoms correlated with vascular ischemia (14). Without specific treatment, it reaches a mortality rate of 90% in most cases, due to systemic microvascular thrombosis, affecting cerebral vessels, cardiac, renal, and the mesenteric vascular bed^{7,14,15}.

It has clinical recurrence in 40% of cases, and due to its rarity and variety of nonspecific symptoms, it is difficult to diagnose^{16,17}.

The diagnosis is made by excluding other possible causes of thrombocytopenia, and laboratory identification is indispensable for management decisions¹⁸. The confirmatory diagnosis is given by the quantification of the plasma activity of ADAMTS13 and the detection of anti-ADAMTS13 autoantibodies (15) when the enzyme has activity less than 10%¹⁹.

The most commonly used therapy is plasma exchange, which removes VWF multimers from the circulation, followed by infusion of fresh frozen plasma (FFP), cryoprecipitated supernatant plasma (CSP), or 24-hour plasma containing the ADAMTS enzyme¹³. Plasma exchange as the primary treatment for acquired and/or hereditary PTT reduces mortality from approximately 90% to less than 20%. It should be performed between 24 and 36 hours after medical diagnosis and carried out until platelets and hemoglobin normalize²⁰.

In situations where plasma exchange is not possible, simple infusion of plasma containing ADAMPT-13 from the donor, together with the use of corticosteroid drugs to reduce antibody production, should be used until plasma exchange is possible²¹.

Studies point to two promising drugs for the treatment of aTTP, rituximab and caplacizumab, associated or not with therapeutic plasma exchange (TPE)²².

The antibody rituximab (Rituxan, MabThera, Zytux) was approved by the regulatory body, the Food and Drug Administration of the United States, in 1997 for the treatment of non-Hodgkin's lymphomas²³. Although it is not approved for the treatment of TTP, it has been used off-label since 2002 (24). Structurally, rituximab is a chimeric monoclonal antibody directed against the CD20 antigen, expressed on the surface of most B lymphocytes. It activates cell-mediated and complement-mediated cytotoxic mechanisms, resulting in cell death and inhibiting the formation of autoantibodies against ADAMTS13²⁵.

Caplacizumab, on the other hand, is a 'nanobody' that inhibits the platelet-aggregating activity of VWF in the interaction with the glycoprotein-Ib, preventing the formation of pathological microthrombi and ischemic damage to end-organs. Isolated from camel blood of the species Camelidae

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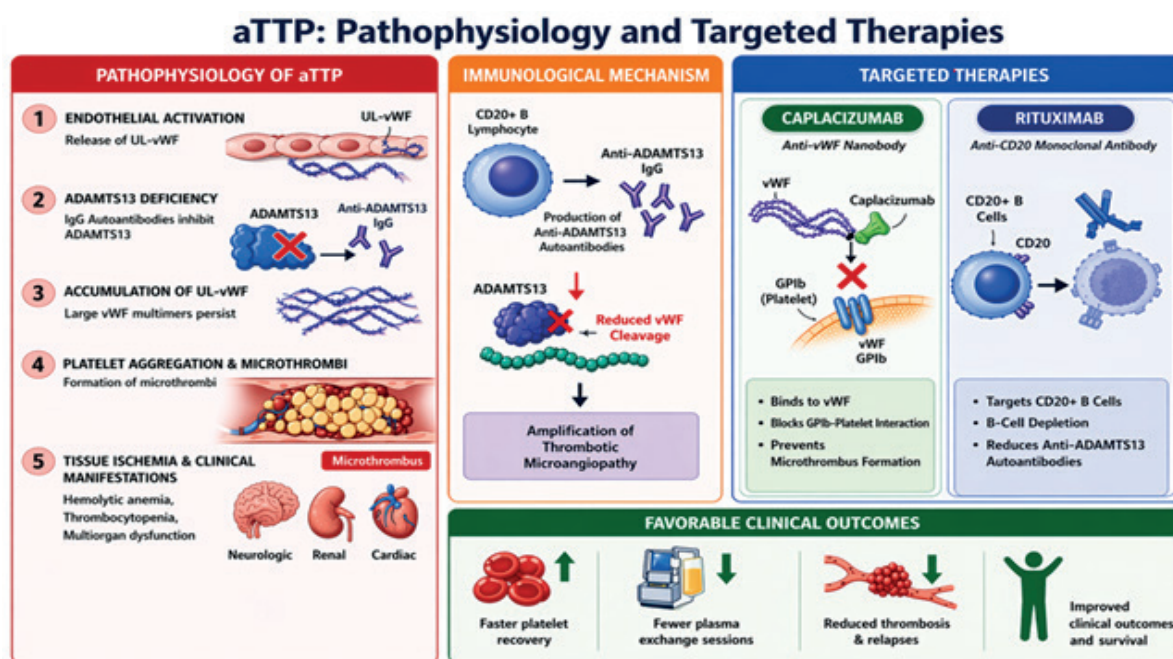
at the end of 1980²⁶, it showed the presence of a heavy chain, when compared to immunoglobulin, being a single-domain antibody and an "extensive antigen-binding repertoire", which raised the hypothesis that it could be an interesting agent in the development of therapeutic measures, diagnosis, and biochemical purposes²⁷. It is the first 'nanobody' of its class, which in clinical trials has shown marked efficacy in the treatment of PTT by reducing its complications. It was presented as a viable solution to improvements in treatment management, such as relieving the burden of care, reducing the number of sessions of TPE and using smaller plasma volumes

to achieve remission, and reducing the length of hospital stay²⁸.

This review aims to present the advances achieved with treatments for acquired thrombotic thrombocytopenic purpura using Rituximab and/or Clapacizumab, evaluating the effects of these new drugs, with a specific focus on platelet normalization,

ADAMTS13 enzyme activity, reduction of plasma exchange, and reduction of recurrent exacerbations and thromboembolic events in patients.

Figure 1. Pathophysiology and targeted therapies in acquired thrombotic thrombocytopenic purpura (aTTP). aTTP results from severe ADAMTS13 deficiency due to autoantibodies, leading to accumulation of ultra-large von Willebrand factor (UL-vWF), platelet aggregation, and microthrombus formation. Rituximab reduces anti-ADAMTS13 autoantibody production via B-cell depletion, while caplacizumab blocks vWF–platelet interaction. These therapies promote faster platelet recovery, reduce plasma exchange requirements, and improve clinical outcomes.



Note: This figure was created with the assistance of artificial intelligence (ChatGPT, GPT-5.6 Sol, OpenAI) as a supporting tool for the graphical representation of the pathophysiological mechanisms and therapeutic targets described in the manuscript. All scientific content, terminology, and visual representations were critically reviewed, verified, and approved by the authors, who take full responsibility for the accuracy and scientific integrity of the figure.

MATERIALS AND METHODS

A systematic literature review was conducted to evaluate the efficacy of rituximab and caplacizumab in the treatment of aTTP. The search was performed in the PubMed, ScienceDirect, and Wiley Online Library databases, covering publications from 2016 to 2024.

The MeSH descriptors used were: "Thrombotic Thrombocytopenic Purpura", "Rituximab", "Caplacizumab", "Therapeutics", and "Treatment Outcome". Search strategies combined these terms using Boolean operators (AND, OR), with the following filters applied: language (English), article type (original articles), and publication period (2016–2024).

Inclusion Criteria

Articles were included if they reported the use of rituximab and/or caplacizumab in patients diagnosed with aTTP; presented clinical data on efficacy, such as time to platelet count recovery, ADAMTS13 activity, number of plasma exchange sessions, and disease recurrence; were published between 2016 and 2024; and were available in English.

Exclusion Criteria

Studies were excluded if they did not directly address the treatment of acquired thrombotic thrombocytopenic purpura (aTTP) with rituximab and/or caplacizumab, did not report

relevant clinical data on therapeutic efficacy or outcomes, or consisted of review articles, editorials, letters, conference abstracts, or other publication types without original clinical data. Duplicate records were also removed during the study selection process.

Data Extraction

Extracted data included study design, number of patients, therapeutic interventions used alone or in combination, time to platelet count normalization, ADAMTS13 activity, number of therapeutic plasma exchange sessions, exacerbation and relapse rates, thromboembolic events, and overall clinical outcomes.

PICO Framework

This systematic review was conducted following the methodological principles recommended by the JBI Manual for Evidence Synthesis. The research question and eligibility criteria were structured according to the PICO framework (Population, Intervention, Comparison, and Outcomes). The review was reported in accordance with the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

The research question and eligibility criteria were structured according to the PICO framework (Population, Intervention, Comparison, and Outcomes), as presented in Table 1.

Table 1. PICO framework used to define the research question and eligibility criteria for the systematic review.

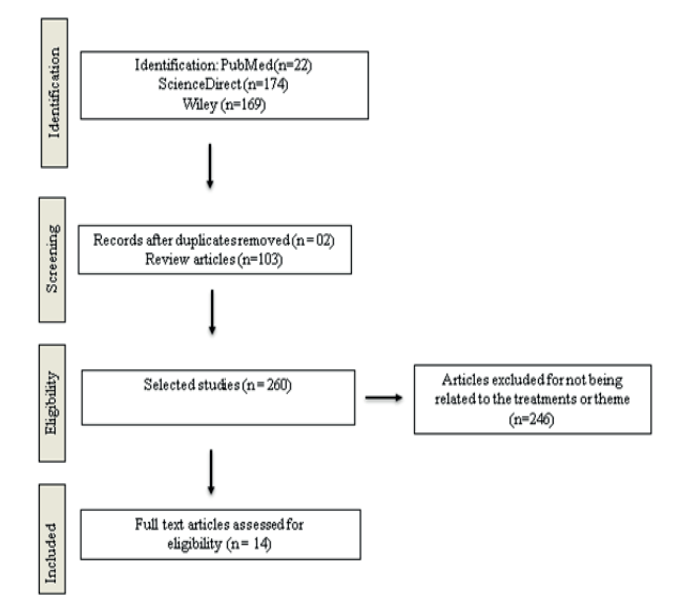
Component	Description
Population (P)	Patients diagnosed with acquired thrombotic thrombocytopenic purpura (aTTP), regardless of age, sex, or disease stage.
Intervention (I)	Rituximab and/or caplacizumab, administered alone or in combination with therapeutic plasma exchange (TPE) and immunosuppressive therapy.
Comparison (C)	Standard of care (TPE ± corticosteroids), as well as control groups, placebo, or historical comparisons when available.
Outcomes (O)	Platelet recovery time, ADAMTS13 activity, number of plasma exchange sessions, exacerbations, relapses, thromboembolic events, and overall clinical outcomes.

RESULTS AND DISCUSSION

A total of 14 studies met the inclusion criteria and were included in the final systematic review. The database search initially identified 365 records (PubMed: n = 22; ScienceDirect: n = 174; Wiley: n = 169). After the removal of 2 duplicate records and 103 review articles, 260 studies remained for screening. Of these, 246 were excluded because they were unrelated to the treatment of aTTP or did not meet the predefined eligibility criteria, resulting in 14 studies included in the final analysis, as illustrated in the study selection flowchart (Figure 1).

Figure 1. Flowchart of the study identification, screening, eligibility, and inclusion process.

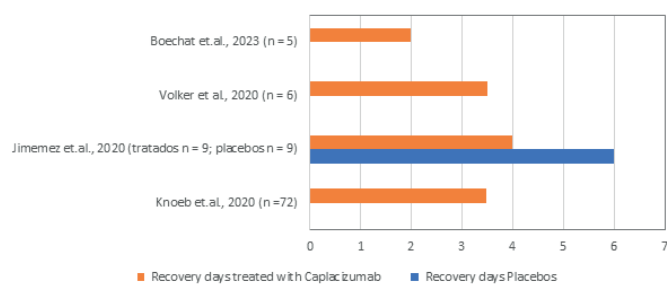
Note: n = number of records/articles.



aTTP is a fatal disease, but due to advances in treatment and rapid diagnosis, it has survival rates of up to 80%. Despite several treatment modalities, mortality increases by 20% with each episode, and survival depends on pre-existing comorbidities. In situations in which platelet elevation does not reach values above 150 x 109/L associated with persistently elevated Lactate Dehydrogenase (LDH), the treatment is considered refractory. The use of caplacizumab, associated or not with plasma exchange, together with immunosuppression, induces faster platelet recovery, reduces the number of plasma exchange sessions, exacerbations, refractoriness and embolic events, as shown by the data from the studies in Figure 2, Figure 3, Figure 4, Figure 5 and Table 2.

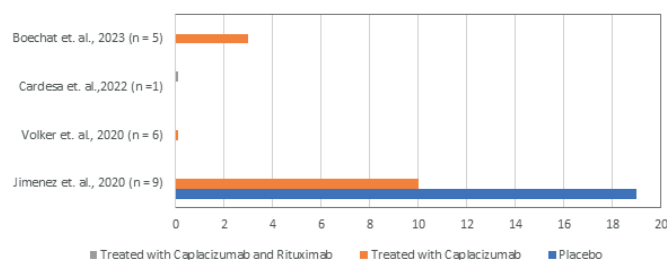
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Figure 2. Mean Platelet Recovery Time (days) in patients with acquired thrombotic thrombocytopenic purpura (aTTP). Note: n = number of patients.



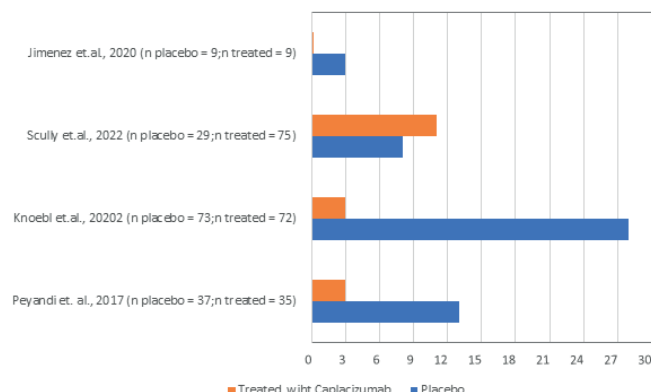
The bar chart compares the mean time to platelet count recovery among patients treated with caplacizumab versus placebo, according to data reported by Boecht et al. (2023), Volker et al. (2020), Jimenez et al. (2020), and Knoebel et al. (2020). Treatment with caplacizumab was consistently associated with a shorter platelet recovery time compared with placebo.

Figure 03. Number of plasma exchange sessions in patients with acquired thrombotic thrombocytopenic purpura (aTTP). Note: n = number of patients.



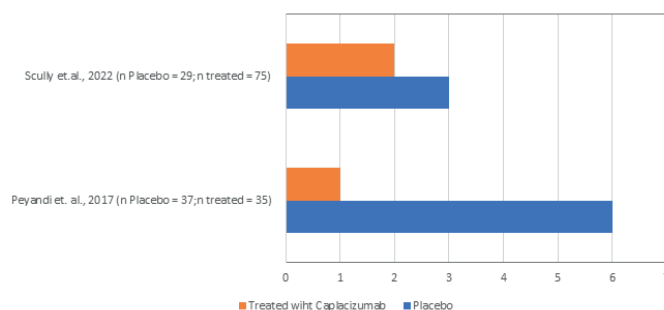
The bar chart compares the number of plasma exchange sessions required by patients treated with caplacizumab plus rituximab, caplacizumab alone, and placebo, based on data reported by Boecht et al. (2023), Cardesa et al. (2022), Volker et al. (2020), and Jimenez et al. (2020). Treatment regimens including caplacizumab were associated with a reduced need for plasma exchange sessions compared with placebo.

Figure 04. Number of clinical exacerbations in patients with acquired thrombotic thrombocytopenic purpura treated with caplacizumab versus placebo across different clinical studies. Note: n = number of patients



A consistent reduction in the number of clinical exacerbations is observed in the groups treated with caplacizumab compared with placebo.

Figure 05. Number of thromboembolic events observed in the caplacizumab and placebo groups. Note: n = number of patients



Rituximab, on the other hand, is a monoclonal antibody that promotes B-cell depletion and can be introduced at the start of treatment or in cases of refractoriness or relapse. Its administration is associated with a faster recovery of ADAMTS13 activity, as shown by the data from the studies in Table 2.

Table 2. Effects of Rituximab and Caplacizumab on ADAMTS13 Activity and Clinical Outcomes in Patients with Acquired Thrombotic Thrombocytopenic Purpura ADAMTS13 activity in patients treated with rituximab and/or caplacizumab. Note: n refers to the number of patients

Author and Year	n	Placebo	Treated	Drugs	ADAMTS13 Activity Outcome	Additional Notes
Benhamou Y et.al., 2016 ²⁸	24	0	24	Rituximab	Accelerated recovery	Rapid depletion of anti-A-DAMTS13 antibodies
Jestin M, et.al., 2018 ²⁹	92	0	92	Rituximab	Maintenance of detectable ADAMTS13 activity	Reduction in exacerbation and relapse rates
Saito, K., et al., 2024 ³⁵	30	16	14	Caplacizumab	Delayed recovery of ADAMTS13 activity	Persistence of anti-A-DAMTS13 antibodies
Doyle A. J. et. al., 2023 ³⁶	443	0	443	Rituximab	96% achieved ADAMTS13 activity >20%	Significant reduction in relapse risk
Jimenez, et.al., 2020 ³⁷	18	9	9	Caplacizumab	Persistent severe ADAMTS13 deficiency	Rituximab was required in 8 patients

TTP is a rare and severe disease characterized by the formation of microthrombi due to severe deficiency of ADAMTS activity¹³. Traditionally, standard therapy includes TPE and corticosteroids. However, recent studies have shown that new therapeutic approaches, such as the use of rituximab and caplacizumab, are highly effective in reducing the morbidity and mortality associated with TTP.

Rituximab, an anti-CD20 monoclonal antibody, has been shown to be effective in reducing TTP relapse by accelerating the recovery of ADAMTS activity¹³. Benhamou et al²⁸ demonstrated that the use of rituximab in patients with a suboptimal response to a TPE-based regimen led to a faster remission and an increase in relapse-free survival at one year. Jestin et al (29) reinforced these findings by observing that preemptive treatment with rituximab in patients in remission significantly reduced the incidence of clinical relapses while maintaining ADAMTS13 activity.

On the other hand, caplacizumab, a monoclonal antibody that inhibits the VWF factor, acts to prevent the formation of microthrombi. Studies have shown its effectiveness in accelerating platelet recovery and reducing thromboembolic events. Peyvandi et al. (30) reported that the group treated with caplacizumab had a significantly lower rate of thromboembolic events compared to the placebo group. Knoebl et al.²¹ also showed that the average time to platelet count normalization was reduced to 3.49 days with the use of caplacizumab. In addition, Völker et al.³¹ and Cardesa-Salzmann et al.³² showed that caplacizumab can be effective even without the use of plasma exchange, suggesting a significant impact on disease management.

Studies such as those by Scully et al.^{33,34} have also confirmed the safety of prolonged use of caplacizumab and the efficacy

of its reuse in disease relapses. The research by Saito et al.³⁵, however, raised concerns about a possible delay in the recovery of ADAMTS13 activity in patients treated with caplacizumab due to the reduced need for TPE, reinforcing the need for careful management of therapy.

CONCLUSION

Studies indicate that the combination of rituximab and caplacizumab, in association with therapeutic plasma exchange and immunosuppressive agents, represents a highly effective strategy for the treatment of thrombotic thrombocytopenic purpura (TTP). This approach promotes faster platelet recovery, reduces the need for plasma exchange sessions, and decreases rates of relapse, exacerbations, and ischemic events.

Due to its B-cell-depleting action, rituximab can be introduced early in the therapeutic course or used in cases of refractoriness or relapse, with consistent evidence supporting its role in reducing anti-ADAMTS13 autoantibodies. However, an individualized approach is essential to maximize clinical benefits and minimize potential adverse effects.

Furthermore, additional studies, together with the incorporation of real-world data, will be crucial to consolidate this strategy in the management of TTP.

ACKNOWLEDGMENTS

During the preparation of this manuscript, the authors utilized the artificial intelligence tool ChatGPT (OpenAI, version GPT-5.3) for the creation of illustrations and to enhance the quality of the English language. All generated content was carefully reviewed and revised by the authors, who assume full responsibility for the final content of this scientific publication.

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How to cite this article:/ Como citar este artigo

Yama JSI, Toreli JPD, Alves B, Veiga GRL, Pereira EC, Gáscon TM, Fonseca FLA. Rituximab and caplacizumab in the treatment of acquired thrombotic thrombocytopenic purpura: a systematic review. *J Health Biol Sci*. 2026; 14(1): e6618.

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