

## CASE REPORT

# Rituximab in Relapsing acquired Thrombotic Thrombocytopenic Purpura: Experience and Evidence

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## Abstract

Thrombotic Thrombocytopenic Purpura (TTP), first described in the early twentieth century, was fatal in the majority of cases until the advent of plasma therapy. Mortality has declined dramatically since the 1980s, and in the 1990s the pathophysiology was elucidated through the discovery and understanding of the central role of a deficiency of the metalloprotease ADAMTS13. The vast majority of cases occur due to an autoimmune process, with a minority of cases due to an underlying mutation. Since the turn of this century, Rituximab, a monoclonal antibody targeting CD20 expressed on B-lymphocytes, has become widely used to treat patients with a wide spectrum of autoimmune diseases, including TTP. However, Rituximab remains “off-label” in the setting of TTP. We recently encountered a patient with chronic relapsing TTP, whose clinical relapses have responded to Rituximab-based therapy without need to resort to plasmapheresis. The clinical course of this patient is described, and the literature focusing on the use of Rituximab in prophylaxis to prevent recurrent TTP is reviewed.

## Keywords

TTP, Rituximab, prophylaxis

## Introduction

Thrombotic thrombocytopenic purpura (TTP) refers to a disorder of widespread microvascular thrombosis, involving the capillaries and arterioles of multiple organs and patients typically present with thrombocytopenia, intravascular hemolysis usually characterized by schistocytosis, and frequently with fever, as well as renal dysfunction and neurologic changes such as headache, confusion, focal deficits, seizures or coma.<sup>1</sup> The first description of TTP is attributed to Eli Moschcowitz, who described a 16-year-old girl who died with clinical symptoms of fever, petechial bleeding, neurological deficits, and coma,<sup>2</sup> published in 1924. TTP is a life threatening process with an extremely high mortality if untreated. The etiology is hereditary in a minority of cases (in which case it is termed Upshaw Shulman Syndrome) but in more than ninety percent of cases, TTP is an acquired disorder.<sup>3,4</sup> In either case, the disease is the consequence of deficient activity of an enzyme, Human ADAMTS13 (A Disintegrin And Metalloproteinase with Thrombospondin type 1 motifs, member 13). ADAMTS13 is a zinc metalloprotease consisting of 1427 amino acid residues, which functions to cleave Von Willebrand factor (vWF) multimers into molecular weight complexes optimal for hemostasis. vWF complexes in the range of 20 to 40 subunits appear to be the optimal size for normal platelet aggregation and adhesion. The pathophysiology of TTP either involves a severe deficiency of ADAMTS13 due to homozygous or compound heterozygous mutations (this being the inherited form, Upshaw-Shulman Syndrome) or reduced activity of ADAMTS13 due to an inhibitory antibody – an autoimmune disorder. The absence of ADAMTS13 activity, in turn, results in the presence of ultrahigh molecular weight multimers of vWF, which then activate and aggregate platelets. This results in micro thrombi within arterioles and capillaries [op.cit].<sup>1</sup> The mainstay of treatment of acute TTP is plasma exchange (PLEX), based in part upon a pivotal prospective, and randomized clinical trial



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performed in Canada.<sup>5</sup> The standard of care at present is that PLEX should be initiated when there is a reasonably high suspicion of TTP.<sup>6</sup> Confirmation of the diagnosis is now established by the finding of an unmeasurably low (less than 10%) activity of ADAMTS13 enzyme. High dose corticosteroids are commonly used as an adjunct to PLEX, although the overall value of corticosteroids in this setting is still debated.<sup>7,8</sup> Refractory and relapsed TTP have been treated by a variety of immunomodulatory agents in recent decades, as well as by more intensive PLEX. Among the immunosuppressive agents used in the treatment of immune-mediated, acquired TTP, Rituximab, a monoclonal antibody targeting CD20 expressed on B-lymphocytes, has become the most prominent. Rituximab has been used by some centers together with PLEX in the management of the initial presentation of TTP. Rituximab has been helpful in refractory cases, but is considered by some clinicians to be over treatment at first presentation of TTP.<sup>9</sup> A patient was recently encountered with chronic, relapsing TTP who has clearly benefited from use of Rituximab to manage both hematologic relapse – manifesting with thrombocytopenia and intravascular hemolysis, and resolving with use of Rituximab but not PLEX – as well as biochemical relapse, manifesting with a profound depression of ADAMTS13 activity alone. This case clearly illustrates the value of Rituximab for the prophylaxis and management of relapsing TTP.

## Case Report

A 45-year-old man was in excellent health until 2015, when, while teaching a class at a high school, he lost the ability to speak and was taken to hospital. One week prior to that presentation, he had begun to experience intermittent fevers, accompanied profound fatigue, and by a progressively worsening petechial rash on his legs. In the emergency department, hemoglobin was 6.3 g/dL, and platelet count was and 15,000 per microliter. Further evaluation showed an elevated creatinine of 1.8 mg/dL, and elevated LDH of 991 u/L, with normal fibrinogen. Laboratory studies confirmed intravascular hemolysis, with numerous schistocytes evident in the peripheral blood smear – estimated at 8% of red cells in several fields. Polychromasia was also noted, with an elevated reticulocyte count of 4%. A clinical diagnosis of thrombotic thrombocytopenic purpura was made. He was treated in an intensive care unit with high dose corticosteroids (Solumedrol 125 mg IV daily) and daily plasma exchange (PLEX). His hospital course was complicated by hyperactive delirium, followed by tonic-clonic seizure, but without any abnormality in brain imaging. He required mechanical ventilation following the seizure activity, but demonstrated a rapid and complete clinical improvement after seven daily sessions of PLEX. ADAMTS13 activity of <1 % (Quest Diagnostics), and anti-ADAMTS13 inhibitor titer of 1 Bethesda Unit (BEU) were reported from blood specimens drawn prior to initiation of PLEX. Upon normalization of the platelet count and LDH, he was discharged from hospital on anti-seizure medications, folic acid, and tapering doses of prednisone, starting at 100 mg daily and reduced in 10 mg increments every 3 days until discontinued. The platelet count at discharge was 326,000 per microliter.

He remained clinically well for 3 months, but then developed a new petechial rash. He presented for medical evaluation and was noted to have a platelet count of 23,000 per microliter. He was immediately started on prednisone 100 mg by mouth daily, and underwent once-weekly PLEX for 4 weeks. Again, laboratory analysis prior to PLEX showed a profoundly depressed ADAMTS13 activity level, at less than 3% activity, and a detectable inhibitor. Upon completion of PLEX, he received a first course of Rituximab 375 mg/m<sup>2</sup>/dose weekly, for four weeks. He again demonstrated a complete response, and platelet count normalized, correlating with normalization of the ADAMTS13 activity, and an undetectable inhibitor.

He was then well for 2 years, but presented in 2017 with a recurrent petechial rash, and platelet count of 36,000 per microliter. He received high dose prednisone, 100 mg by mouth daily for two weeks, followed by a taper, as well as four once-weekly doses of rituximab, with an excellent response, manifest by normalization of the platelet count and the LDH, without the need for PLEX at this relapse. He continued to do well for 6 months. However, in the summer of 2018, screening laboratory studies showed ADAMTS13 activity depressed at less than 3%, along with a detectable inhibitory antibody titer of 1.1 BEU. Complete blood count and LDH, along with routine serum chemistries, remained normal. Although he continued to feel entirely well physically, a preventative approach was discussed with the patient, and he was again treated using a course of single-agent Rituximab at the same dose and schedule

as he had previously received. Corticosteroids were not administered. The ADAMTS13 activity has since normalized, with resolution of the inhibitor. He has experienced no acute toxicities associated with Rituximab therapy to date, and remains clinically well (table 1).

Table 1. TimeLine of relapses with laboratory studies and treatment in patient case described above

Date of Episode	Platelet count per microliter	Hemoglobin g/dL	ADAMTS 13 activity %	Inhibitor level Bethesda Units	Schistocytes % per high power field (average)	LDH U/L	Treatment
May 2015	15,000	5.4	<3 %	1	8%	991	PLEX and steroids
August 2015	23,000	11	<3 %	2.2	2%	253	PLEX and steroids for 4 weeks followed by Rituximab
August 2017	36,000	12.7	<3%	1.1	4%	414	Rituximab and steroids
June 2018	267,000	13.8	<3 %	1.1	0%	179	Rituximab

## Review of the Literature

Rituximab was first FDA approved in 1997 for treatment of CD20 positive follicular B cell lymphoma that relapsed after prior therapy. The most recent FDA approval of Rituximab came in the year 2018, as therapy for the autoimmune disease Pemphigus Vulgaris, and Rituximab is FDA approved for treatment of Rheumatoid Arthritis as well. Rituximab is now widely used off-label to treat a wide spectrum of immunological diseases, including immune thrombocytopenia and autoimmune hemolytic anemia, among many others. Rituximab therapy typically results in depletion of CD20 positive B-lymphocytes, and this, in turn, results in a dramatic decrease in the production of immunoglobulins, often with dramatic effect in ameliorating antibody-mediate autoimmune diseases. Case reports of the use of Rituximab for treatment of TTP began appearing in the medical literature as early as 2002.<sup>10</sup> Among the first relatively large retrospective series of patients treated for TTP using Rituximab is a report by Elliot and colleagues from the Mayo Clinic. These authors described 73 patients treated using Rituximab as part of therapy for refractory or relapsing antibody-mediated acquired TTP. In this paper, they identified four patients treated at the Mayo Clinic who met the criteria for reporting; these were patients with TTP who had anti-ADAMTS13 antibody documented in their medical record, who were refractory to PLEX, and who then received Rituximab. In that paper, the authors also described an additional 69 similar patients, identified from a systematic review of the literature to that point in time. The reports included in the analysis by Elliot and colleagues do include a prospective study by James George and colleagues from the University of Oklahoma,<sup>11</sup> and a study by Scully and colleagues.<sup>12</sup> Elliot and colleagues defined refractoriness to PLEX as failure to achieve a normal platelet count despite 7 days of PLEX, or clinical deterioration despite PLEX. The average number of doses of Rituximab administered to the 73 patients analyzed was 4 doses, and the overall complete response rate was 95%. Only four patients did not respond, and there were four instances of severe adverse reactions to Rituximab described. The median clinical relapse-free survival in this series was approximately 10 months.<sup>13</sup>

In a report by Jin and colleagues in 2008, the finding of an ADAMTS13 level below the range of 5% to 10% in patients with a prior episode of antibody-mediated acquired TTP was associated with a high risk of impending clinical relapse – within three months, in this description of the Ohio State University experience. Interestingly, in that study, the authors did not find a strong correlation between the presence of detectable anti-ADAMTS13 antibody in patients with the risk of relapse.<sup>14</sup> It should be noted that, although a variety of assays were developed in the 1990s to measure ADAMTS13 activity, at present, the most widely used is a chromogenic assay. This functional assay measures ADAMTS13 activity by a fluorescence resonance energy transfer (FRET)-based assay system using a 73 amino-acid peptide (FRET-S-VWF73) of von Willebrand factor (VWF) as substrate.<sup>15</sup> Several years after the report by Jin, Westwood and colleagues, in the year 2012, retrospectively analyzed their experience using Rituximab to treat TTP at University College Hospital in London, UK, a large TTP referral center. They examined two groups of patients treated using Rituximab over an eight-year time period: (1) those treated at clinical presentation, divided into a group treated “early” (within 3 days of diagnosis) or those treated “late” in clinical presentation

(beyond 3 days after presentation – either *de novo* or relapse); and (2) those treated prophylactically using Rituximab. Of note, steroids were administered to all patients in these cohorts. In this report, patients who received Rituximab “early”, that is, within three days of beginning PLEX, required fewer sessions of PLEX to achieve remission. Complete remission was achieved in 95% of patients (82 out of 86 subjects); the remaining four patients died. Median length of hospital stays was statistically significantly shorter for patients receiving Rituximab early. Median length of stay was 16 days for those receiving Rituximab within three days of diagnosis, as compared to a median length of stay of 23 days for those receiving Rituximab “late”. In this report, 15 patients had prior TTP and were found to have developed depressed ADAMTS13 activity levels and were then promptly treated prophylactically using Rituximab, with 17 instances of prophylactic Rituximab treatment courses. In thirteen of these episodes, ADAMTS13 activity was < 5%, and in four episodes, the ADAMTS13 activity was between 6% and 14%. 16 out of 17 of these prophylactic treatment episodes resulted in normalization of the ADAMTS13 activity within three months.<sup>16</sup>

A subsequent retrospective report by the French Thrombotic Micro angiopathies Reference Centre, published in the year 2014, examined the outcome among 48 patients with acquired TTP who were noted to have persistent, profound depression of the ADAMTS13 activity level while still in clinical remission. In this study population, 30 patients with persistently low ADAMTS13 activity received pre-emptive Rituximab therapy, and 18 patients did not. The relapse rate at 17 months follow up was zero among the thirty patients who received Rituximab. The relapse rate was statistically significantly higher, measured at 0.57 relapse episodes per year, among the 18 patients with depressed ADAMTS13 activity who did not receive Rituximab therapy while in clinical remission. In this study of “pre-emptive” Rituximab therapy for remission TTP patients found to have depressed ADAMTS13 levels, 5 patients that were treated in this manner failed to maintain a durable rise in the ADAMTS13 level. Of these, one patient remained in clinical remission with administration of Rituximab every six months, and one achieved a durable rise in ADAMTS13 level after treatment using Alemtuzumab. The other three patients continued to have depressed ADAMTS13 activity despite multiple lines of additional therapy, which included cyclophosphamide, cyclosporin, mycophenolate, Bortezomib, and splenectomy, in addition to Alemtuzumab (Table 2).<sup>17</sup>

Table 2. Major Case Series of Rituximab as therapy or prophylaxis for refractory or relapsing TTP

Author	Number of patients	Rituximab with initial therapy	Rituximab as prophylaxis	Response Rate	Comments	Reference
Elliot et al, Mayo*	73	Yes (refractory cases)	No	95%	4 Mayo patients, 69 patients from literature	10
Westwood, London	86	Yes (“early” and “late”)	Yes	95%	Rituximab in 17 patients with low ADAMTS13	15
Hie, M	30	Not studied in this cohort	Yes	100%	Retrospective analysis of clinical remission patients	16

\*4 cases from Mayo Clinic, and 69 cases culled from a systematic review of the literature

A superb recent review by Joly and associates from France, the authors opine that the level of evidence for the use of corticosteroids in the initial therapy of acquired TTP is low, despite a biological rationale for immunosuppressive therapy [op. cit.]. These authors review the clinical literature regarding use of Rituximab together with PLEX for management of the first presentation of TTP, summarizing 152 patients from seven publications. Each of these publications included at least ten patients in each report. However, the role of Rituximab in prevention of relapse was reviewed only briefly by Joly and colleagues. They note that, in the context of patients with TTP in clinical remission whose ADAMTS13 level falls to below 10%, “rituximab remarkably reduces the incidence of TTP relapse by diminishing the production of anti-ADAMTS13 antibodies and restoring ADAMTS13 activity, which parallels peripheral B-cell depletion”, citing the paper by Hie and colleagues.<sup>17</sup> Tun and Villani performed a systematic review of 100-pooled cases of TTP treated using Rituximab as a component of therapy, and this report nicely characterizes the consistently favorable impact of Rituximab as a part of the treatment of inhibitor-mediated TTP.<sup>18</sup>

## Conclusion

Although Rituximab remains “off-label” as a component of therapy for patients with TTP, there is now a mature body of peer-reviewed medical literature that documents that Rituximab can be of substantial benefit in the appropriate setting. The precise indications for use of Rituximab in TTP remain to be fully defined. Rituximab appears to be of significant benefit to TTP patients at initial presentation, as an immunosuppressive agent in the initial therapy of patients with poor-risk TTP - including those with significant end-organ damage and those not responding promptly to apheresis therapy. Beyond the initial presentation, however, the literature reviewed herein provides a strong argument for the routine monitoring of the ADAMTS13 activity level in TTP patients while in hematologic remission. Further, this literature strongly suggests that profound depression of the ADAMTS13 activity in clinical remission is actionable, as such, patients are at high risk for relapse, and the use of Rituximab to prevent hematologic relapse is a highly effective strategy. The data indicates that for such patients, the majority can probably avoid the need for plasmapheresis therapy, a therapy that is cumbersome, expensive, and which has a significant risk of morbidity. The patient in this report was able to avoid hematologic relapse with use of Rituximab alone, without the need for corticosteroids. This suggests that corticosteroids and their attendant toxicities may be safely avoided in this setting. There are certainly other medical treatment options for patients with relapsed TTP that have been reported to be effective, but none as consistently as Rituximab to date. These include vinca alkaloids, proteasome inhibitors, and immunophilin inhibitors. Splenectomy is also very effective as prophylaxis in relapsing TTP. However, Rituximab has an excellent overall safety record in a wide variety of settings to date. The landscape for the management of TTP will continue to change, and the impact of Caplacizumab, is likely to be significant. Caplacizumab is an anti-von Willebrand factor humanized single-variable-domain immunoglobulin nanobody, which inhibits the interaction between ultra-large von Willebrand factor multimers and platelets. If approved, this agent will likely alter significantly the initial management of TTP, and long-term treatment as well. However, at present, for TTP patients in remission who are found to have profoundly depressed ADAMTS13 activity during surveillance, Rituximab appears to be a very useful management tool, with or without use of corticosteroids.

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## Conflict of Interest Statement

The authors report no financial or ethical conflicts of interest.



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