

# Efficacy and Safety of Rituximab for Refractory and Relapsing Thrombotic Thrombocytopenic Purpura: A Cohort of 10 Cases

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## ABSTRACT

**OBJECTIVE:** Idiopathic thrombotic thrombocytopenic purpura (TTP) is a life-threatening disorder mediated by autoantibodies directed against ADAMTS13. This provides a rationale for the use of rituximab in this disorder. We report our experience and the outcome of 10 cases of TTP (9 refractory and 1 relapsing) successfully treated with rituximab in combination with plasma exchange (PE) and other immunosuppressive treatments.

**METHODS:** The diagnosis of TTP was based on clinical criteria and supported by severe deficiency of ADAMTS13 activity and presence of inhibitors in seven cases. Rituximab was started after a median of 18.6 sessions of PE (range: 5–35) at the dose of 375 mg/m<sup>2</sup>/week for 4–8 weeks.

**RESULTS:** Complete remission was achieved in all patients after a median time of 14.4 days of the first dose (range: 6–30). After a median follow-up of 30 months (range: 8–78), eight patients were still in remission and two developed multiple relapses, treated again with the same therapy, and achieved complete responses; they are alive, and in complete remission after a follow-up of 12 and 16 months.

**CONCLUSION:** Rituximab appears to be a safe and effective therapy for refractory and relapsing TTP. However, longer follow-up is recommended to assess relapse and detect possible long-term side effects of this therapy.

**KEYWORDS:** TTP, plasma exchange, refractory, relapse, rituximab

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## Introduction

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening disorder characterized by microangiopathic hemolytic anemia, thrombocytopenia, fever, neurologic disturbances, and renal impairment.<sup>1</sup> These symptoms are related to the presence of platelet thrombi rich in von Willebrand factor (VWF) in the arterioles and capillaries. VWF is a multimeric plasma glycoprotein crucial for both platelet adhesion and aggregation, especially at the high shear rates in the microvasculature. The size of the VWF multimer is physiologically regulated in vivo by a specific metalloprotease ADAMTS13 (a disintegrin-like metalloprotease with thrombospondin type 1 motif 13) that cleaves the longest multimers to prevent the spontaneous formation of platelet thrombi in the microcirculation.<sup>2</sup> A severe deficiency in ADAMTS13 (<5% of normal activity) may be specific for TTP, and it has been proposed that severe ADAMTS13 deficiency in the presence of inhibitors now defines acquired TTP.<sup>3,4</sup> However, a severe deficiency of ADAMTS13 activity in acute idiopathic TTP was reported only in about two-thirds (33%–100%) of the cases.

ADAMTS13 deficiency may either be due to mutations in the ADAMTS13 gene in the very rare inherited forms of TTP (Upshaw–Schulman syndrome) or to circulating autoantibodies against ADAMTS13 in the more frequently acquired forms of TTP.<sup>5</sup> Idiopathic acquired TTP is a rare disease with a reported annual incidence of 4.5 per million.<sup>6</sup> Daily plasma exchange (PE) is the mainstay of treatment and has reduced mortality rates from over 90% to 10%–20%. The effectiveness of PE is generally attributed to the removal of circulating anti-ADAMTS13 autoantibodies and the concomitant supplementation of ADAMTS13 activity.<sup>7,8</sup> However, 10%–20% of TTP patients show partial or complete absence of response to daily PE or are refractory, and 20%–50% relapse after achievement of complete remission.<sup>9,10</sup> Several therapies have been used to limit the production of these autoantibodies including immunosuppressive agents (corticosteroids, vincristine, cyclophosphamide, azathioprine, cyclosporine A) or immunomodulating agents (high-dose IV immunoglobulin, staphylococcal protein A immunoadsorption). However, the lack of robust data does not allow proper suggestion of such agents in the setting of acute refractory or chronic relapsing TTP.<sup>1</sup>



Splenectomy has been proposed for patients with refractory or relapsing TTP, with reported remission rates of 50%–100%.<sup>11</sup>

Rituximab, a chimeric monoclonal antibody directed against the CD20 antigen present on B lymphocytes, has proved its efficacy in the treatment of CD20+ lymphoproliferative disorder and some autoimmune diseases. It is a promising first-line immunosuppressive treatment in patients with acute refractory and chronic relapsing TTP related to anti-ADAMTS13 antibodies.<sup>12</sup> The rationale for using rituximab in TTP lies its ability to deplete anti-ADAMTS13 producing B cells. However, several reports have shown that TTP patients without ADAMTS13 inhibitory antibodies have also responded to rituximab. Hence, it has been proposed that in TTP patients without ADAMTS13 inhibitory antibodies, B-cell depletion by rituximab may reduce excessive cytokine production, thus lowering the level of VWF multimers to the normal range.

We report here our experience with the addition of rituximab to the treatment regimen of 10 patients with refractory or relapsing TTP.

## Patients and Methods

After obtaining approval from our Institutional Review Board, we retrospectively reviewed all files of patients with TTP treated at the National Center for Cancer Care and Research between January 2007 and December 2013. The research was conducted in accordance with the Declaration of Helsinki. Twenty-three patients were treated in our center, 10 of whom were treated with rituximab.

The diagnostic criteria for TTP were negative direct antiglobulin test, microangiopathic hemolytic anemia, thrombocytopenia  $<150 \times 10^9/L$ , and the absence of an identifiable cause for thrombocytopenia and microangiopathic hemolytic anemia.<sup>13</sup>

Patients included in this study were adults aged 18 years or older diagnosed with idiopathic TTP and who fulfilled one the following criteria: TTP in a first or subsequent relapse and TTP refractory to PE. We excluded cases with secondary causes of TTP (drugs, viral or bacterial infections, transplants, autoimmune disorders, metastatic malignancy, pregnancy in the second and third trimester, and breast feeding). The investigations that were performed included the following: blood film, lactate dehydrogenase, haptoglobin, reticulocyte count, bilirubin, prothrombin time, activated partial thromboplastin time, fibrinogen, liver function test, urea and electrolytes, serum creatinine, serum troponin, calcium, thyroid function tests, HIV serology, hepatitis B and C serology, pregnancy test, blood group and antibody screen, direct antiglobulin test, cytomegalovirus serology, antinuclear antibodies, rheumatoid factor, lupus anticoagulant test, CT/MRI brain if showing neurologic symptoms, echocardiogram, and electrocardiogram. All patients underwent a total body CT scan to exclude occult malignancy.

The measurement of ADAMTS13 activity and its inhibitors was done for seven patients and samples were sent to the Blood Center of Wisconsin, USA.

We collected data on the demographics of patients (age, gender, past history, clinical presentation), laboratory results (complete blood count, creatinine, lactate dehydrogenase (LDH), ADAMTS13 activity, and inhibitors), treatment data (number of PEs, dose of rituximab and concomitant corticosteroids and cytotoxic therapy, response to treatment and complication), and outcome.

**Medical management of TTP.** All patients received daily therapeutic plasma exchange (TPE) using a COBE Spectra instrument exchanging 1–1.5 times their estimated plasma volume with donor plasma (fresh frozen plasma (FFP) and/or cryosupernatant (CSP) as replacement fluid until their platelet count reached  $150 \times 10^9/L$  and normalization of the LDH level.

PE was initiated within 8–12 hours of presentation through central line along with i.v. corticosteroids 1–2 mg/kg daily for 3–5 days, then shifted to oral prednisolone 1 mg/kg/day for 3 weeks, and followed by slow tapering schedule by 10 mg every week till discontinuation.

Patients with no or incomplete response or refractory to standard therapy as well as patients in relapse were treated with rituximab  $375 \text{ mg}/\text{m}^2/\text{week}$  for 4–8 weeks with concurrent PE and steroids after completing a consent form. PE was interrupted for 24–48 hours following each dose of rituximab. Toxicity and side effects of rituximab were recorded as per our hospital guidelines. B-cell lymphocyte count was not assessed by flow cytometer in the described cohort.

### Definition of clinical response.<sup>9,14</sup>

1. Complete remission: Complete response was defined as complete resolution of clinical symptoms and normalization of platelet count and LDH levels for three consecutive days. A response lasting more than 30 days after PE cessation was considered as remission.
2. Refractoriness: It was defined by absence or incomplete response to daily TPE after at least 1 week of adequate treatment or clinical deterioration during treatment.
3. Relapse: It was defined as a new episode of TTP occurring more than 30 days after achieving remission.

## Results

We identified 10 patients through our retrospective review of all cases of presumed TTP referred for PE (Table 1). At that time of initial TTP diagnosis, the median age of the 10 patients was 39.4 years (18–53), with 60% ( $n = 6$ ) of these patients being women.

TTP was acquired in all patients and was idiopathic in nine patients, and was associated with newly diagnosed and nontreated chronic myelogenous leukemia (CML) in chronic phase in patient 8.

The main clinical manifestation during acute TTP episode consisted of anemia symptoms ( $n = 6$ ), neurologic symptoms ( $n = 7$ ), abdominal pain and vomiting ( $n = 6$ ), bleeding ( $n = 5$ ), fever ( $n = 3$ ), and renal impairment ( $n = 0$ ).

At presentation, the mean hemoglobin level was 7.6 g/dL (range: 5–11), the mean platelet level was  $10 \times 10^9/L$  (range:



Table 1. Patients' characteristics at presentation.

PATIENT	AGE/ GENDER	PAST HISTORY	CLINICAL PRESENTATION	LABORATORY INVESTIGATION AT PRESENTATION							ADAMTS13 ACTIVITY	INHIBITORS BETHESDA REFERENCE	BETHESDA REFERENCE <0.4
				Hb g/dL	PLATELETS 10 <sup>9</sup> /L	SCHIZOCYTES	LDH (IU/L)	CREATININE ( $\mu$ mol/L)	ADAMTS13 ACTIVITY	INHIBITORS BETHESDA REFERENCE			
1	53/F	None	Anemia symptoms, Jaundice	9	10	+	2035	67	NA	NA	NA	NA	
2	28/F	None	Miscarriage at 10 weeks of pregnancy, Vaginal bleeding, Convulsions	6	19	+	1900	70	NA	NA	NA	NA	
3	52/M	None	Anemia symptoms, Abdominal pain, Headache	5.7	11	+	1700	85	<5%	<5%	Positive 1.9	Positive 1.9	
4	24/M	None	Fever, Convulsions, Anemia symptoms, Abdominal pain	6	4	+	2000	134	<5%	<5%	Positive 4.5	Positive 4.5	
5	35/F	Treated for TTP 18 months ago with PE and steroids	Abdominal pain, Vomiting, Fatigue, Petechiae, Jaundice, Headache	9.8	11	+	1500	59	<5%	<5%	Positive 2.4	Positive 2.4	
6	47/F	None	Headache, Confusion, Anemia symptoms, Jaundice	8	10	+	1753	75	NA	NA	NA	NA	
7	46/M	None	Anemia symptoms, Fever, Jaundice, Abdominal pain	5	8	+	1580	87	<5%	<5%	Positive 3.6	Positive 3.6	
8	48/F	CML	Ecchymosis, Petechiae, Headache	8.8	14	+	1600	90	<5%	<5%	Positive 5.3	Positive 5.3	
9	43/F	None	Menorrhagia, Abdominal pain, Diarrhea, Confusion Seizure, Anemia symptoms	7	9	+	1255	95	<5%	<5%	Positive 4.6	Positive 4.6	
10	18/M	None	Fever, Abdominal pain, Hematuria	11	10	+	1400	65	<5%	<5%	Positive 2	Positive 2	



$4\text{--}19 \times 10^9$ ), and LDH was more than 1000 IU/L (ref  $<250$  IU/L) in all cases.

The ADAMTS13 activity was less than 5%, with presence of autoantibodies for seven patients. All patients had TPE with a median of 18.6 sessions (range: 5–35) and steroids prior to rituximab. Two patients were additionally treated with vincristine 2 mg i.v. weekly for 4 weeks.

Rituximab was indicated for nine refractory TTP and for one relapsing TTP (Table 2). Among the nine refractory TTP, four patients did not respond to the standard therapy, and for the others, the disease recurred when we started to taper PE.

Complete remission was achieved in 100% patients after a median of 14.4 days of the first rituximab treatment (range: 6–30 days). The median complete remission duration was 30 months (range: 8–78 months). Eight patients remained in complete remission and two patients (4 and 5) developed two to three episodes of relapses. Each relapse was treated again with PE, steroids, and rituximab.

Patient 4 developed three episodes of relapse. The first episode of relapse occurred 27 months after the first episode of TTP. Complete remission duration after the first relapse sustained 21 months, the second 11 months, and the third 12 months. He had persistence of detectable anti-ADAMTS13 autoantibodies while he was in complete remission since the first episode. At each episode of relapse, the work-up for viral infection, connective tissue disease, and malignancy was negative.

Adding another immunosuppressive treatment such as cyclophosphamide, cyclosporine, or rituximab as maintenance or splenectomy was suggested, but the patient refused this regimen of treatment.

Patient 5 was treated for an initial episode of TTP with PE and steroids, and she was in complete remission for 18 months. The first relapse was treated with PE, steroids, and six doses of rituximab. The complete remission duration sustained 18 months. The second episode was treated with the same treatment (PE, steroids, and eight doses of rituximab) with additional four doses of vincristine, and she was also started on rituximab maintenance, one injection every 3 months for 2 years. After 16 months of follow-up, she is alive and in complete remission, and ADAMTS13 activity is normal and devoid of inhibitors.

Patients 2 had a miscarriage during the first trimester of pregnancy (at 10 weeks' gestation). She had no recurrence of TTP during the subsequent pregnancy.

Patient 8 was referred to the hematology clinic 3 weeks prior to the diagnosis of TTP for suspected CML, as a complete blood count showed a white blood cell count  $29.3 \times 10^9/L$ , neutrophils 50%, lymphocytes 20%, eosinophils 8%, bands 17%, myelocytes 2%, metamyelocytes 2%, basophils 1%, hemoglobin 14.2 g/dL, and platelet count  $442 \times 10^9/L$ . Peripheral smear suggested CML. Bone marrow aspirate, biopsy, and cytogenetic samples were sent to the laboratory, and the patient was

given appointment to check results and start tyrosine kinase inhibitors; however, she presented 2 days before appointment to the emergency room with a transient episode of dysarthria, confusion, and dizziness. Her laboratory results confirmed features of TTP, and pending cytogenetic tests confirmed the presence of a Philadelphia chromosome. She was initially treated for TTP, and after achieving cure, nilotinib 300 mg bid was initiated orally as upfront treatment for CML. She is currently alive and in complete remission from both disorders.

Rituximab was well tolerated in all cases, and no major side effects were seen except for mild allergic reaction (such as fever, rigor, itching) mainly after the first dose.

## Discussion

Despite the considerable improvement in survival associated with prompt initiation of daily PE in patients with idiopathic TTP, some patients have incomplete or delayed response or do not respond at all to this standard treatment, and the relapse rate after PE alone is very high at 40%.<sup>15</sup>

Although there is no generally accepted definition of refractory disease, continuation of therapy should be considered after 7–14 days of treatment with daily PE and steroids when the clinical picture deteriorates or laboratory findings do not improve.<sup>9</sup> In this case, additional therapy with immunosuppressive treatment such as steroids, vincristine, cyclophosphamide, or cyclosporine has not been proven beneficial in all investigations.<sup>9,12,15,16</sup>

Rituximab has a role to play in the treatment of acute refractory/relapsing idiopathic TTP.<sup>12,15,16</sup> Prospective studies have shown that rituximab was effective and safe in immune TTP when the patient failed to respond to daily PE and steroids and in relapsed acute TTP.<sup>4,13,17</sup>

Patients receiving rituximab showed reduction in anti-ADAMTS13 IgG antibody levels and increased ADAMTS13 activity.<sup>17</sup> The risk of relapse appears to be reduced with rituximab's use.<sup>18</sup>

Our review of 10 patients treated with rituximab for refractory TTP in 9 patients and relapsing TTP in 1 patient confirmed the efficacy of rituximab as previously reported. Our response rate was 100%, which is comparable to other series.<sup>4,5,17</sup>

The median platelet recovery period from the first dose of rituximab was 14.4 days (range: 6–30 days), which is comparable with the results of other studies.<sup>12</sup> However, caution must be maintained in the attribution of benefit solely to rituximab, as in the majority of case reports and case series concurrent therapy with PE and corticosteroids was going on at the time of rituximab administration.

After a median follow-up of 30 months (range: 8–78 months), 2 (4 and 5) of 10 patients (20%) had relapsed, especially in the group of TTP immune-mediated ADAMTS13 deficiency. The relapse rate in our patients was almost near that reported in the German<sup>5</sup> and Spanish studies,<sup>14</sup> which were 25% and 17%, respectively, after a median follow-up of 49.6 and


**Table 2.** Treatment and outcome.

PATIENTS	NUMBER OF PE SESSIONS BEFORE RITUXIMAB	INDICATION FOR RITUXIMAB <sup>1</sup>	NUMBER OF RITUXIMAB DOSES	CONCURRENT TREATMENT	RESPONSE TO RITUXIMAB	DAYS TO CR FROM FIRST INFUSION (DAYS)	TOXICITY	DURATION OF CR (MONTHS)	RELAPSE	STATUS AT LAST FOLLOW-UP	ADAMTS <sup>13</sup> ACTIVITY	INHIBITORS BETHESDA REFERENCE
1	20	Refractory	4	PE, Steroids	CR <sup>7</sup>	7	Allergic reaction	78	None	CR	NA <sup>6</sup>	NA
2	35	Refractory	8	PE, Steroids	CR	24	None	67	None	CR	NA	NA
3	10	Refractory	4	PE, Steroids	CR	12	Mild allergic reaction <sup>3</sup>	11	None	CR	90%	Negative
4	30	Refractory	6	PE, Steroids Vincristine <sup>2</sup>	CR	26	Mild allergic reaction	27	Yes (x3) <sup>4</sup>	CR	<50%	Positive
5	14	Relapse	6	PE, Steroids	CR	8	None	18	Yes (x2) <sup>5</sup>	CR	>70%	Negative
6	23	Refractory	4	PE, Steroids	CR	7	Mild allergic reaction	27	None	CR	NA	NA
7	14	Refractory	4	PE, Steroids	CR	6	None	25	None	CR	>70%	Negative
8	23	Refractory	6	PE, Steroids	CR	10	Mild allergic reaction	21	None	CR	100%	Negative
9	5	Refractory	8	PE, Steroids Vincristine <sup>2</sup>	CR	30	None	18	None	CR	100%	Negative
10	12	Refractory	4	PE, Steroids	CR	14	None	8	None	CR	70%	Negative

**Notes:** <sup>1</sup>Rituximab Dose: IV 375 mg/m<sup>2</sup>/week. <sup>2</sup>Vincristine Dose: IV 2 mg/week. <sup>3</sup>Mild allergic reaction: fever, rigor, itching. <sup>4</sup>1st Relapse (27 months). <sup>5</sup>2nd Relapse (21 months). <sup>6</sup>3rd Relapse (11 months). All relapses treated with (PE + steroids + 4 Rituximab). <sup>7</sup>Relapse (18 months) treated with (PE + steroids + 6 Rituximab). Relapse (18 months) treated with (PE + steroids + 4 Vincristine + 8 Rituximab + Maintenance). <sup>8</sup>NA: Not Available. <sup>9</sup>CR: complete Remission.



30 months, while it was lower than that reported in the study of Goyal et al,<sup>19</sup> which was around 33% after a long follow-up of 73 months. Our study probably reflects the follow-up period exceeding 2 years with transient B-cell depletion and may be due to the survival of an autoreactive B-cell clone or the proliferation of a new autoreactive B-cell clone. Our follow-up period corresponds to the usual period of relapse, which was estimated at 50% at 2 years in highly risky patients with severe deficiency of ADAMTS13 activity.<sup>20</sup> A long-term follow-up is therefore highly recommended to assess relapse and to detect possible long-term side effects of rituximab.

Patient 4 had three episodes of relapse after 27, 21, and 11 months of complete remission, and he is still alive and in complete remission after the third relapse with a follow-up of 12 months. Patient 5 also had two episodes of relapse, one after the standard therapy and the second after 18 months of complete remission after rituximab, TPE, and steroids. She is alive and in complete remission, on maintenance therapy with rituximab with a follow-up of 16 months. Both of them had severe deficiency of ADAMTS13 activity (<5%) with detectable inhibitors, which has been reported to be associated with a more complicated clinical course and increased risk of relapse. A recent collaborative review<sup>21</sup> by seven independent groups of clinical, laboratory, and outcome data of 467 TTP cases with severe versus non-severely deficient ADAMTS13 activity levels reported dramatic deficiency in rates of relapse compared to TTP with near-normal ADAMTS13 activity ( $n = 282$ ), in whom relapse rate was (0%–9%). TTP cases with severe ADAMTS13 deficiency ( $n = 185$ ) had a spontaneous relapse rate of 35%–41%.

Patient 4 had persistence of detectable inhibitors, despite which he was in complete remission, which is highly predictive of relapse. The persistence of anti-ADAMTS13 autoantibodies during remission have been reported in 30%–40% of patients with recurrent TTP.<sup>22,23</sup>

In our study, rituximab was started after 2 weeks or more of PE for nine patients and earlier at day 5 for one patient (N 9) because she had neurologic deterioration and no improvement of MAHA (microangiopathic hemolytic anemia).

Patient 8 was diagnosed to have concurrent CML in chronic phase and autoimmune TTP. There is no prior evidence reported in the literature that CML induces TTP. Only four cases were found<sup>24,25</sup>: one case with TMA in CML on hydroxyurea, and three cases with CML on interferon. ADAMTS13 studies were not carried out on them. The TMA might have been drug-induced. It has been also reported that severe immune-mediated deficiency of ADAMTS13 is very rare in patients with systemic malignancies except for lymphoproliferative disorders.<sup>26</sup> This is highly suggestive of a near coincidence rather than an actual cause–effect relationship between CML and TTP in our case.

Rituximab has a role in the treatment of refractory and relapsing autoimmune TTP due to its ADAMTS13 inhibitory antibodies. However, many important questions remain

unanswered. They include the lack of data on the optimal time schedule and the dose and duration of therapy, as well as the long-term maintenance of remission and possible risk of stratification according to the level of ADAMTS13's activity and inhibitory antibody titer. Another common question is whether ongoing plasmapheresis removes rituximab from the blood safely and about the immediate and long-term side effects of rituximab.

The optimal dose of rituximab in acute refractory and relapsing TTP has not been defined. The standard dose of 375 mg/m<sup>2</sup> administered weekly for 4 weeks seems adequate.<sup>15</sup> However, rituximab treatment may be extended to eight doses in total in those who are slow to respond, such as those with persistent low ADAMTS13 activity or detectable anti-ADAMTS13 antibodies.<sup>18</sup> There are some data to suggest that a lower dose of 100 mg may be as effective because the CD20+ B-cell burden is much lower in TTP than in lymphoma.<sup>27,28</sup>

With regard to timing, currently it is primarily used as a salvage therapy for refractory and relapsing TTP. Recent studies<sup>13,18,29</sup> demonstrate a beneficial role in the use of rituximab as first-line therapy. It was associated with faster achievement of remission, decrease in the need of PE, and reduction and delay in the incidence of relapse.

Another common concern is whether ongoing plasmapheresis removes rituximab from the blood. A pharmacokinetic study of TTP patients receiving weekly rituximab concomitantly with PE demonstrated a 65% reduction in the drug levels.<sup>30</sup>

There is also a role of rituximab during remission as a maintenance therapy, namely to avoid life-threatening and costly relapses in patients with a previous history of autoantibody-mediated TTP. Some case reports and case series<sup>31,32</sup> have demonstrated that a long-term maintenance therapy with rituximab prevents the recurrence of TTP.

Other studies<sup>4,29,33</sup> have suggested that prophylactic treatment may be considered when ADAMTS13 levels decrease and/or ADAMTS13 inhibitors reappear in the blood. The optimal schedule for ADAMTS13 testing following an initial episode is unknown, but a frequency of every 3 months seems reasonable,<sup>29</sup> and when the level of ADAMTS13 decreases below 10%, it suggested as a cutoff for the initiation of rituximab. The persistence of detectable anti-ADAMTS13 autoantibodies constitutes also an indication for prophylactic treatment.<sup>22</sup>

From our study and literature review, rituximab appears to be safe, effective, and generally well tolerated with rare serious adverse events including two deaths after the first dose of rituximab infusion<sup>13,34</sup> as well as rare viral complications such as herpes zoster transverse myelitis,<sup>16,33</sup> cytomegalovirus (CMV) reactivation, and fatal pneumonia.<sup>16</sup>

Despite our promising results, our study has some limitations. These include our study's retrospective character, which might have led to incomplete reporting of clinical data, adverse events during the follow-up period, the small sample size, as

well as the lack of ADAMTS13 levels and inhibitors for all the patients, making it difficult to establish a clear relationship between the response and ADAMTS13 levels.

In conclusion, rituximab has made a significant advance in TTP therapy as front-line and salvage therapy for refractory and relapsing TTP and also as prophylactic treatment. It, however, remains unlicensed for this life-threatening disorder. Long-term prospective and multicentric studies are recommended to determine the true efficacy and safety of rituximab with or without PE in comparison to PE alone.

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### Author Contribution

Principal investigator and primarily responsible for the paper: HEO. Participated in data collection, writing, and revising the manuscript: RYT, AG, MAY, IAH; Participated in diagnosis and care of patients: FI, MAY, HAS, ZM, GP. All authors have read the manuscript and approved the same.

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