THE ROLE OF RITUXIMAB IN THE MANAGEMENT OF PATIENTS WITH ACQUIRED THROMBOTIC THROMBOCYTOPENIC PURPURA: EVIDENCE-BASED FOCUSED REVIEW

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Short title: Rituximab for TTP

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**Case presentation**

A 40 year-old obese black woman developed abdominal pain with progressive generalized weakness over several days. Physical examination was normal except for several small bruises on her extremities. Laboratory data revealed hemoglobin, 5.0 gm/dL; platelet count, 4000/µL; creatinine, 0.8 mg/dL; LDH, 1364 U/L. Peripheral blood smear revealed many schistocytes. Acquired thrombotic thrombocytopenic purpura (TTP) was diagnosed and treatment was initiated with daily plasma exchange (PEX) and prednisone, 1 mg/kg/day. The subsequent report of ADAMTS13 activity <5% with an inhibitor titer of 3 Bethesda Units (BU) supported the diagnosis of TTP. After 6 days of PEX she was asymptomatic, her platelet count had been normal for 2 days, reaching 178,000/µL; PEX was stopped.

- Should rituximab have been given as initial treatment of TTP, in addition to PEX and corticosteroids?
- If her platelet count had decreased to 13,000/µL 3 days after PEX was stopped (an exacerbation, indicating refractory TTP), should rituximab be used in addition to resuming daily PEX?

The patient remained well following discontinuation of PEX and corticosteroids. Three years after her first episode, routine measurement of ADAMTS13 activity while she was asymptomatic documented activity of 57%. One year later, while still asymptomatic with normal laboratory evaluation, her ADAMTS13 activity was 4% with an inhibitor titer of 1 BU.

- Should rituximab be given to prevent a relapse of TTP?
Introduction

In 1991, a new era of effective treatment for acquired TTP began with documentation of the efficacy of plasma exchange (PEX), reducing mortality of acute episodes from 90% to 28%.1 In 1998, acquired TTP was found to be associated with a deficiency of ADAMTS13 caused by an inhibitor,2,3 suggesting an autoimmune etiology and providing the basis for corticosteroids as conventional initial treatment in addition to PEX.4 In 1997, rituximab (Rituxan, MabThera, Zytux) was approved by the US Food and Drug Administration for the treatment of non-Hodgkin lymphomas. Although rituximab is not approved for treatment of TTP, it has been used off-label with increasing frequency since 2002.5,6 The appropriate role of rituximab in the management of patients with TTP remains uncertain.

This review focuses on three periods during the course of TTP for which rituximab has been advocated: [1] for initial treatment of an acute episode, together with PEX and corticosteroids, [2] for treatment of a refractory episode (unsatisfactory response to initial treatment with PEX and corticosteroids), and [3] for prophylaxis in asymptomatic patients with severe ADAMTS13 deficiency following recovery but no clinical evidence of TTP to prevent relapse.
Methods

Clinical definitions
Response, exacerbation, remission, and relapse of TTP have been previously defined. Refractory TTP may be defined as failure to achieve a satisfactory response with PEX and corticosteroids, a decreased platelet count after an initial increase, the occurrence of new neurologic abnormalities while continuing treatment with PEX and corticosteroids, or an exacerbation after stopping PEX. We defined initial treatment of TTP with rituximab (together with PEX and corticosteroids) as beginning rituximab within the first three days of admission and diagnosis. We used these definitions to classify the studies included in this review into the three periods described above, although the individual studies may have used slightly different definitions.

Literature search
We searched seven databases on October 1, 2014 to identify articles describing treatment of TTP with rituximab. We used the Ovid interface to search (1) MEDLINE, (2) EMBASE, and (3) Cochrane Database of Systematic Reviews. We used the Web of Knowledge interface to search (4) Current Contents and (5) Web of Science. The EBSCO interface was used to search the (6) Cumulative Index to Nursing and Allied Health Literature (CINAHL) database. We searched the (7) PubMed interface which includes MEDLINE and additional databases. Articles were identified by using the MeSH terms or keywords thrombotic thrombocytopenic purpura and rituximab (or its trade names, Rituxan,
MabThera, Zytux). The references of reviewed articles and the authors’ files were also reviewed.

**Article selection**

English-language articles which administered one or more doses of rituximab for patients with TTP in the setting of initial TTP treatment, treatment of a refractory TTP episode, or in asymptomatic patients with prior TTP and decreased ADAMTS13 activity, and which measured one or more clinical outcomes were included. Although documentation of severe ADAMTS13 deficiency (activity <10%) with an ADAMTS13 inhibitor is the defining feature of acquired TTP, we did not exclude articles in which ADAMTS13 was not measured, since initial reports of rituximab treatment were published when ADAMTS13 measurements were not always available. We were aware of numerous case reports using rituximab for refractory TTP and decided *a priori* to exclude articles reporting less than 10 patients with rituximab used in this setting. For the other two indications (initial treatment, prophylaxis) we included all articles, including single patient case reports. We excluded single patient case reports when the patients had an additional diagnosis (e.g., systemic lupus erythematosus, HIV infection, post-transplantation). However, if such patients were included in selected case series, in which the majority of the patients did not have additional diagnoses, we did not exclude these individual patients but noted this in our Supplement Evidence Tables. We excluded articles that did not present patient data for any of the three
indications that were the focus of this review. Article selection and data extraction were performed independently by each author.

**Grading the evidence**

The GRADE (Grading of Recommendations Assessment, Development and Evaluation) system was used to classify recommendations as strong (grade 1) or weak (grade 2) based on the balance of benefits and risks and the confidence in these estimates.\(^9\) We recognize that patient values and preferences may influence the interpretation of our management recommendations. The quality of evidence was classified as high (grade A), moderate (grade B) or low (grade C) based on the study design, consistency of results and directness of the evidence.

**Results**

The literature search identified 258 citations and one additional article was identified through personal files; titles and abstracts were screened for eligibility. Of these, 238 were excluded and 21 underwent full text review. A total of 17 articles were included in our analysis (Figure 1): 3 articles (66 patients) evaluated rituximab for initial treatment together with PEX and corticosteroids;\(^8,10,11\) 7 articles (119 patients) evaluated rituximab for refractory TTP;\(^12-17,18\) 8 articles (57 patients) evaluated rituximab for prophylaxis in asymptomatic patients with decreased ADAMTS13 activity following recovery from an acute episode but no clinical evidence for TTP.\(^10,19-25\) One article
included 2 case series: patients receiving initial treatment with rituximab and asymptomatic patients receiving rituximab prophylaxis.\textsuperscript{10} One patient was reported in three articles;\textsuperscript{19,22,26} for this review we cite the most recent report.\textsuperscript{22} Patients from two cohorts appeared to be reported in multiple publications.\textsuperscript{8,10,12,17,19,25} Among the 17 included articles, three were observational studies which included a comparison group without rituximab treatment. These three articles provide the highest quality data available to assess the effect of rituximab for each of the three indications (Table 1).\textsuperscript{8,17,25} In two of these three articles,\textsuperscript{17,25} all patients in the rituximab-treated group and the historical controls had documented severe, acquired ADAMTS13 deficiency. In the third article all patients had ADAMTS13 measurements; median ADAMTS13 activity was <5\% for both groups, but values ranged up to 40\%.\textsuperscript{8} All 17 included articles are described in greater detail in the Supplement Evidence Tables.

**Rituximab for initial treatment of TTP**

Three articles\textsuperscript{8,10,11} administered rituximab as initial treatment in addition to PEX and corticosteroids for patients with a first or relapsed episode of TTP. One observational study compared 40 rituximab-treated patients with 40 historical controls who did not receive rituximab (Table 1).\textsuperscript{8} The controls in this study were matched as far as possible for 3 variables: sex, ethnicity, and number of relapses; selection was based on the completeness of data. Six of the rituximab-treated patients and nine of the control patients had one or more
previous episodes of TTP; these patients were not reported separately. This study reported that rituximab decreased the duration of hospitalization by 7 days when the 15 patients admitted to an intensive care unit (ICU) were excluded from the rituximab group. The number of patients in the control group that required ICU admission was not described. Ninety-five percent (38/40) of patients in the rituximab group received corticosteroids (typically methylprednisolone, 1000 mg/day for 3 days) in addition to PEX; 88% (35/40) of historical controls received corticosteroids (regimen not described). Fifteen control patients received treatments in addition to PEX and corticosteroids. The remission rate was 93% (37 of 40) among the patients treated with initial rituximab and was 95% (38 of 40) among the historical control patients. The frequency of relapse was 55% in the historical control patients and 11% in the rituximab-treated patients. Patients in the rituximab group were followed for at least 12 months post-admission, but the actual duration of follow-up in both rituximab and control patients was not reported. The survival curve presented in the manuscript suggests that the control patients were followed longer. In a second retrospective cohort where there was no non-rituximab comparison group, the outcomes of 54 patients treated with rituximab administered three days or less from admission, which included 31 patients from the previous study,8 were compared to 32 patients treated with rituximab administered more than three days from admission.10 However, because patient selection for earlier or later rituximab administration was not described and 31 patients
from the early rituximab group were enrolled in the previous trial, these comparisons are uninterpretable due to numerous potential confounders.

Summary. In patients with an acute episode of TTP, initial treatment with rituximab, PEX and corticosteroids appeared to result in a remission in over 90% of patients within 14-21 days. Rituximab may decrease the frequency of subsequent relapses.

Rituximab treatment for refractory episodes of TTP

Seven articles reported 119 patients treated with rituximab for a refractory first or relapsed episode of TTP. One observational study compared the outcome of 21 rituximab-treated patients with refractory TTP (defined as a platelet count increase less than two-fold after four days of PEX) with 53 historical control patients not treated with rituximab, from the years prior to common rituximab use (Table 1). Three of the 21 rituximab-treated patients had a previous history of TTP but had not received rituximab. Previous episodes of TTP were not described for the control patients. Patients treated with rituximab all had platelet count recovery within 35 days in contrast to 78% of control patients (p<0.02), and the time to achieve a normal platelet count was decreased compared to control patients (p=0.03). Although there was a non-significant decrease in relapse at 1 year in the rituximab-treated patients and no difference in long-term (>1 year) relapse between groups, the occurrence of relapse may have been delayed by rituximab treatment. Data
from five other articles similarly demonstrated that following administration of rituximab, complete responses were achieved in 83-100% of patients with refractory TTP.\textsuperscript{12-16} One article only reported patients who achieved remission.\textsuperscript{18} Relapse rates post-rituximab treatment ranged from 0% with a median follow-up of 10 months\textsuperscript{12} to 33% with a median follow-up of 73 months.\textsuperscript{18}

\textit{Summary.} In patients with an episode of refractory TTP, addition of rituximab to PEX and corticosteroids increases platelet counts in over 80\% of patients and may decrease the time required to achieve a platelet count response. The frequency of relapse in rituximab-treated patients may be decreased compared to control patients in the short-term, but may also represent a delay in relapse and not differ from control patients in long-term follow-up.

\textbf{Rituximab treatment for asymptomatic patients in remission who have ADAMTS13 deficiency}

Eight articles\textsuperscript{10,19-25} reported 57 asymptomatic patients following recovery from an acute episode with no clinical evidence of TTP who were treated with rituximab for the observation of severely decreased ADAMTS13 activity (typically <10\%). One observational cross-sectional study compared outcomes in 30 patients treated with rituximab (and other treatments) to 18 patients who were managed prior to the era of rituximab treatment or in centers where
treatment of patients who were in remission with rituximab and other treatments was not the standard of care (Table 1). This study reported that rituximab and other treatments in this setting resulted in longer relapse-free survival compared to patients who did not receive rituximab (p=0.049). The length of follow-up was longer in the control patients (median, 60 months) than in the treated patients (median, 36 months after the first prophylactic infusion of rituximab). Thirty percent (9/30) of the rituximab-treated patients received additional courses of rituximab; some patients were treated additional immunosuppressive agents and/or splenectomy; one patient received continuous rituximab infusions every 6 months and 4 patients did not have a durable increase of ADAMTS13 activity with multiple treatments.

In the two largest studies, median ADAMTS13 activity was 35% at 1 month and 46% at 3 months and in 16 of 17 episodes where ADAMTS13 was 6% or less prior to the first dose, activity increased to greater than 21% by 3 months. In other case reports and series, increases in ADAMTS13 ranged from 20 – 100% measured from 4 weeks to 9 months post-rituximab. However, approximately one-third of patients in the two largest studies did not achieve durable ADAMTS13 recovery with one course of rituximab.

**Summary.** Prophylactic treatment with rituximab may result in fewer TTP relapses, although follow-up was longer in control patients, favoring detection of relapse. In the largest study, 30% of patients had asymptomatic decreased
ADAMTS13 activity during follow-up after initial prophylactic rituximab and received additional rituximab or other treatments, some of which have greater risks than rituximab. In some asymptomatic patients sustained ADAMTS13 activity recovery does not occur even with multiple rituximab treatments. The effect of a single course of rituximab cannot be assessed.

**Discussion**

There are few publications addressing the three indications for rituximab treatment of TTP that were the focus of this review. There were no publications with high quality evidence; there were no randomized controlled trials and no observational studies with a well-matched, concurrent control group. Cohort studies can provide useful information when randomized trial data are not available. However, cohort studies are subject to selection bias and confounding due to differences in the baseline characteristics between the groups. For each of the three indications, there was one observational study with a comparison group, but the comparison groups in these studies had important limitations. First, the patients were retrospectively selected from a time period preceding the patient group receiving rituximab, introducing the potential for selection bias. Second, the frequency of corticosteroid use and other treatments for TTP were not controlled in these studies, which can confound the reported response rates. Third, shorter duration of follow-up in the treatment groups as compared to the control groups potentially biased the results to observe fewer relapses in the treatment group. B-cell depletion post-
Rituximab treatment is apparent for 9-18 months\textsuperscript{12} and patient follow-up in studies documenting relapse rates needs to be sufficiently long to observe relapses following B-cell recovery. Rituximab may only delay, not prevent, relapse.

The limitations of the control group are of lesser importance when evaluating rituximab for refractory TTP, since additional treatment is required for patients unresponsive to standard initial treatments. The available studies suggest that over 80\% of refractory patients receiving rituximab have a satisfactory platelet count response with few serious side effects but these studies observe no difference in long-term relapse rates. While a comparison group would control for the possibility that these refractory patients may have responded without rituximab, these patients are often critically ill with limited additional treatment options. The balance of risks and benefits in this setting supports rituximab use, since it appears to be effective in achieving a remission within a shorter time (Table 2).

The presence of a well-matched control group is of moderate importance in studies evaluating rituximab as initial treatment of TTP together with PEX and corticosteroids, since additional treatment for an acutely ill patient may provide additional benefit. Multiple observations document that some patients recover promptly from their acute episode of TTP with only PEX and corticosteroids and do not relapse with long-term follow-up. Therefore the
routine initial use of rituximab may not benefit all patients. When rituximab is used as initial treatment, patients who are destined to become refractory may receive earlier adjunctive treatment and may benefit. However, for patients who would have responded promptly to PEX and corticosteroids alone, a benefit is less certain, particularly regarding subsequent relapse. Because of the limitations of the comparison group in the principal study, the value of routine use of rituximab in the initial treatment of patients with an acute episode of TTP is uncertain (Table 2).

A well-matched control group, preferably in a randomized study, is critically important to evaluate rituximab for prophylaxis in asymptomatic patients with low ADAMTS13 activity following recovery from an acute episode but no clinical evidence of TTP. It remains uncertain if decreased ADAMTS13 activity in asymptomatic patients following recovery from TTP is a reliable predictor of future relapse. One case series of consecutive patients reported that relapse was more frequent among patients who have lower ADAMTS13 activity during remission but the probability of future relapses and their time of occurrence remain uncertain. Furthermore ADAMTS13 activity measurements performed with different techniques may not be equivalent. For example, ADAMTS13 activity measured in the same sample in the same laboratory by different assay techniques may report ADAMTS13 activity <10% in one assay and 30% in another. Therefore, even if severe ADAMTS13 activity was a reliable predictor of future relapse, one measurement using one
We believe that ADAMTS13 activity <10% may not be a reliable predictor of relapse. Unpublished data from the Oklahoma Registry document that among 52 asymptomatic patients who have had three or more annual measurements of ADAMTS13 activity during remission, 20 (38%) have had 1-8 annual measurements with ADAMTS13 activity <10%; none were treated. Fourteen (70%) of these 20 patients have not relapsed during 1-10 (median, 4) years of follow-up. Finally, the natural history of ADAMTS13 activity in patients following recovery from acquired TTP is not known. Among the 20 patients who have had ADAMTS13 activity <10% during remission, ADAMTS13 activity spontaneously increased to >10% in 15 patients and returned to >50% in 9 patients.

Important concerns remain regarding the use of prophylactic rituximab: [1] Duration of follow-up was likely insufficient to observe relapses in some studies. [2] Higher relapse rates were observed in the control patients in the cohort study with a comparison group, but control patients had longer follow-up than rituximab-treated patients. [3] Thirty percent of the rituximab-treated patients in this cohort study received additional treatments, including prolonged rituximab treatment, which were likely to influence the observed relapse rates. [4] In this cohort study, 13% of patients never achieved durable
ADAMTS13 responses.\textsuperscript{25} In contrast to the refractory setting, these patients are clinically well and may need no treatment. Therefore evidence that the benefits of rituximab exceed the risks must be much stronger. Given these limitations, rituximab in this setting is not recommended (Table 2).

**Recommendations**

1. We suggest rituximab be considered for initial treatment with PEX and corticosteroids in patients who present with an acute episode of TTP (Grade 2C).
2. We recommend rituximab for patients who have a refractory episode of TTP despite PEX and corticosteroids (Grade 1C).
3. We recommend against the use of rituximab in asymptomatic patients who have a severe deficiency of ADAMTS13 activity but no clinical evidence of TTP (Grade 1C).

**Patients’ values and preferences**

Patients who have experienced multiple severe episodes of TTP may place a higher value on rituximab treatment that may decrease the duration of acute episodes or decrease the risk of recurrent episodes. These patients may also place a lower value on the inconvenience and potential risks of rituximab treatment. These values and preferences should be taken into account when assessing the role of rituximab.
Acknowledgments

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Authorship

Author Contributions: WL, SKV, and JNG designed the study, performed the article selection, data abstraction and analysis and prepared the manuscript.

Conflicts of Interest Disclosure

The authors have no conflicts to declare related to this publication.


### Table 1. Rituximab for the treatment of patients with thrombotic thrombocytopenic purpura and for treatment of ADAMTS13 deficiency during remission: Studies with a comparison group

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study design</th>
<th>Patients</th>
<th>Rituximab dose &amp; treatment(s)</th>
<th>Follow-up, months</th>
<th>Outcomes</th>
<th>Rituximab</th>
<th>Control</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scully, 2011</td>
<td>Open label, prospective, multicenter study between 2006-09, compared to historical controls who did not receive rituximab (years of treatment NR)</td>
<td>Rituximab: N=40, started ≤3 d from diagnosis -34 first episode TTP, 6 relapsed</td>
<td>Rituximab 375 mg/m²/week x 4 + PEX 1-2x/d + methylprednisolone 1 g/d x 3 days</td>
<td>≥12 months post-admission, actual duration NR</td>
<td>Median no of PEX to achieve remission</td>
<td>16.5 (4-34)</td>
<td>18 (6-92)</td>
<td>P=0.5</td>
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<tr>
<td></td>
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<td></td>
<td>Median no of days admitted</td>
<td>16.5 (5-49)</td>
<td>20 (5-62)</td>
<td>P=NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean no. of days admitted</td>
<td>Decreased by 7 days in rituximab-treated patients when 15 rituximab-treated patients requiring ICU care were excluded</td>
<td>P=0.04</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Relapse</td>
<td>-Median time to relapse</td>
<td>4/37 (11%)</td>
<td>21/38 (55%)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>27 months (range 17-31)</td>
<td>18 months (range 3-60)</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>Death during admission</td>
<td>3/40 (7.5%)</td>
<td>2/40 (5.0%), 1 death in relapse</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Steroid use</td>
<td>38/40 (95%)</td>
<td>15/40 (38%) had CSA, CPM, defibrotide, VCR or splenectomy</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Additional treatment</td>
<td>6/40 (15%)</td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Response to rituximab</td>
<td>66% had platelets &gt;50 before 2nd infusion</td>
<td>2/40 (5.0%), 1 death in relapse</td>
<td>35/40 (88%)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>15/40 (38%) had CSA, CPM, defibrotide, VCR or splenectomy</td>
<td>6/40 (15%) bid PEX</td>
<td></td>
</tr>
</tbody>
</table>

**controls:**
- Matched as far as possible for sex, ethnicity, number of relapses, 31 first episode TTP, 9 relapsed
- PEX + methylprednisolone 1 g/d x 3 days then prednisone 1 mg/kg/d or prednisolone alone
- NR; longer follow-up compared to rituximab-treated patients suggested in Fig. 4
- Possible selection bias in control group, confounding of results
- Longer follow-up of control patients
- ADAMTS13 levels not used for diagnosis; median levels at presentation <5% but ranged up to 40%
**Table 1 Continued**

<table>
<thead>
<tr>
<th>Treatment for refractory episodes of TTP</th>
<th>Rituximab</th>
<th>Control</th>
<th>Possible selection bias in control group, confounding of results - Treatment of early controls may have been less intensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Froissart, 2012[1]</td>
<td>Open label, prospective, multicenter study between 2005-08, compared to historical controls from 2000-05</td>
<td>Rituximab: N=21 survivors, started median 8.4 ± 3.3 d post PEX + corticosteroids - 18 first episode TTP, 3 relapsed - 1 death</td>
<td>Controls: N=53 survivors - number of first/relapse NR: 4 deaths</td>
</tr>
<tr>
<td>Rituximab 375 mg/m² day 1 of refractory diagnosis and days 3,7,14 + PEX + corticosteroids</td>
<td>Mean 33±17.4 months - 2 patients lost to follow-up in 1st year</td>
<td>Platelet count recovery</td>
<td>21/21 (100%), within 35 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Time to durable remission</td>
<td>12±6.7 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Required plasma volume to achieve remission</td>
<td>891±402 ml/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Relapse</td>
<td>- At 1 year: 0/21 (0%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- &gt;1 year: 3/19 (15.8%)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Time to relapse</td>
<td>20 months, 2 years, 3 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ADAMTS13 activity</td>
<td>Higher at 1, 3, 6, 9 months compared to controls; no difference at 12 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Steroid use</td>
<td>15/21 (71%)</td>
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<tr>
<td></td>
<td></td>
<td>Additional treatment</td>
<td>None</td>
</tr>
</tbody>
</table>

**Mean 33±17.4 months**

21/21 (100%), within 35 days

41/53 (78%), within 35 days

12±6.7 days

NR

891±402 ml/kg

999±583 ml/kg

0/21 (0%)

3/19 (15.8%)

5/53 (9.4%)

NR

>1 year

20 months, 2 years, 3 years

Higher at 1, 3, 6, 9 months compared to controls; no difference at 12 months

15/21 (71%)

42/53 (79%)

None

3 VCR & CPM, 17 VCR only
<table>
<thead>
<tr>
<th>Table 1 Continued</th>
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</thead>
<tbody>
<tr>
<td><strong>Treatment for severe ADAMTS13 deficiency during clinical remission</strong></td>
</tr>
</tbody>
</table>

| Hie, 2014²⁵ | Cross-sectional comparison of data from multiple centers that did or did not treat patients in remission. -Included only survivors with >1 year follow-up & ADAMTS13 activity <10% during clinical remission. -ADAMTS13 activity drawn at TTP presentation, remission and every 3 months |

**Rituximab:** N=30 patients with ADAMTS13 <10% during remission. -Relapse before and after initial rituximab and between treated and control patients

**Rituximab 375 mg/m²/week x 4:** started at median 14.5 mo after last TTP episode
-10/30 (30%) had rituximab during first TTP episode
-9/30 (30%) had repeated rituximab; 1 received rituximab every 6 months

**Median 36 months post-initial rituximab infusion.** (IQR 24-65 months)

<table>
<thead>
<tr>
<th><strong>Rituximab</strong></th>
<th><strong>Control</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Calculated baseline relapse rate</strong></td>
<td>16/30 (53%) patients with previous TTP relapse; median 2 episodes within 54 months (IQR 33-63) = 0.57 relapses/year prior to rituximab</td>
</tr>
<tr>
<td><strong>Rituximab</strong></td>
<td>14/18 (78%) patients with previous TTP relapse; median 1 episode within 60 months (IQR 30-72) = 0.5 relapses/year</td>
</tr>
</tbody>
</table>

**Relapse (IQR), time to relapse**
-3/30 (10%) occurring at 14,18,43 months
-Calculating relapse rate decreased from 0.57 relapses/year (0.46-0.7) to 0 relapses/year (0-0.81) post rituximab; p<0.01

**Calculated relapse rate**
-14/18 (39%), 3 patients relapsed at 6 months; 4 patients>12 months
-Calculated relapse rate 0.5 relapses/year in controls vs. 0 relapses/year in post-rituximab group; p<0.01

| **ADAMTS13 activity (median) post 1st rituximab infusion** | 35% at 1 month, 46% (IQR 30-68%) at 3 months, increased until 12 months; not sustained in 5 patients |
| **Control** | NA |

| **Median relapse free survival** | P=0.049; 9.3 years in controls, not reached in rituximab-treated |

| **Additional treatment** | In rituximab group:
-9/30 (30%) received additional rituximab during follow-up; 1 received continuous rituximab every 6 months
-5/30 had other treatments (additional rituximab, alemtuzumab, CSA, CPM, MMF, bortezomib, splenectomy) |

**Legend:** bid, twice daily; CPM, cyclophosphamide; CSA, cyclosporine A; ICU, intensive care unit; IQR, interquartile range; MMF, mycophenolate mofetil; NA, not applicable; NR, not reported; NS, not significant; PEX, plasma exchange; TTP, thrombotic thrombocytopenic purpura; VCR, vincristine

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Table 2. Rituximab for the treatment of patients with thrombotic thrombocytopenic purpura and for treatment of ADAMTS13 deficiency during remission: Levels of evidence and interpretation

<table>
<thead>
<tr>
<th>Indication</th>
<th>Key citation</th>
<th>Grade of recommendation and evidence*</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial treatment of TTP</td>
<td>Scully, 2011(^8)</td>
<td>2C</td>
<td><em>We suggest rituximab be considered for this indication.</em> Rituximab may decrease the time to achieve remission and may delay subsequent relapse.</td>
</tr>
<tr>
<td>Treatment for refractory episodes of TTP</td>
<td>Froissart, 2012(^17)</td>
<td>1C</td>
<td><em>We recommend rituximab be considered for this indication.</em> Patients with refractory TTP require treatment in addition to PEX and conventional corticosteroid regimens, and rituximab appears to be effective.</td>
</tr>
<tr>
<td>Treatment for severe ADAMTS13 deficiency during clinical remission</td>
<td>Hie, 2014(^25)</td>
<td>1C</td>
<td><em>We recommend against the use of rituximab for this indication.</em> The benefit for relapse-free survival is marginal (P = 0.049). Patients in the rituximab group received multiple different treatments. The benefit of a single course of rituximab is not known. The natural history of ADAMTS13 activity following recovery from acquired TTP is not known. High quality evidence is required before treatment of patients with no clinical evidence of TTP can be recommended.</td>
</tr>
</tbody>
</table>

*Grade 1 represents a strong recommendation; grade 2 represents a weak recommendation; grade C represents the lowest quality of evidence
FIGURE LEGEND

Literature Search Data

* One article included two case series: one case series of patients receiving initial treatment with rituximab and another case series of asymptomatic patients receiving rituximab prophylaxis.
258 citations identified through database search (duplicates removed)

1 article identified through review of authors’ personal files

259 citations identified; title and abstract screened for eligibility

238 citations excluded
- Abstracts (46)
- Reviews, including case series, <10 patients with literature review (6)
- Additional diagnosis (17)
- No rituximab-related patient data or rituximab used for different indication (169)

4 articles excluded
- No patient data; trial design only
- Additional diagnosis
- Rituximab use for different indication
- Case report of patient reported in a subsequent article

21 full text articles reviewed for eligibility

17 articles included
- Initial treatment (3 articles)
  - 1 cohort with comparison group
  - 2 case series (3, 23 patients)*
- Refractory treatment (7 articles)
  - 1 cohort with comparison group
  - 6 case series (12-25 patients)
- Prophylactic treatment (8 articles)
  - 1 cohort with comparison group
  - 3 case series (4-14 patients)*
  - 4 case reports (1 patient)
The role of rituximab in the management of patients with acquired thrombotic thrombocytopenic purpura: evidence-based focused review

Wendy Lim, Sara K. Vesely and James N. George