Comparison of the Long-Term Remission of Rituximab and Conventional Treatment for Acquired Thrombotic Thrombocytopenic Purpura: A Systematic Review and Meta-Analysis

Weerapat Owattanapanich, MD¹, Chompunut Wongprasert, MD², Wannaphorn Rotchanananya, MD³, Natthida Owattanapanich, MD⁴, and Theera Ruchutrakool, MD¹

Abstract
The current systematic review and meta-analysis aimed to summarize the results of all available studies to compare the efficacies of rituximab and conventional treatment for acquired thrombotic thrombocytopenic purpura (TTP). Three investigators independently searched studies in the MEDLINE and EMBASE databases published before December 11, 2018. To be included in the meta-analysis, studies needed to be randomized-controlled or cohort studies comparing the efficacies of rituximab and conventional therapy for TTP treatment. The effect estimates and 95% confidence intervals (CIs) from each study were collected, and Mantel-Haenszel methods were used to pool the data. A total of 570 patients from 9 eligible studies were included in the meta-analysis (280 patients in the rituximab arm and 290 in the conventional treatment arm). Patients receiving rituximab in an acute phase to induce disease remission had a significantly lower relapse rate than those given conventional treatment (odds ratio [OR]: 0.40, 95% CI: 0.19-0.85, P = .02, I² = 43%). Similarly, the relapse rate in the rituximab group for preemptive therapy to prevent clinical relapse was also significantly lower than in the control group (OR: 0.09, 95% CI: 0.04-0.24, P < .00001, I² = 11%). Furthermore, the conventional treatment group had a significantly higher mortality rate than the rituximab group during the follow-up (OR: 0.41, 95% CI: 0.18-0.91, P = .03, I² = 0%). Rituximab offered high efficacy for the prevention of relapses and lower mortality rate in cases of acquired TTP.

Keywords
rituximab, thrombotic thrombocytopenic purpura, thrombocytopenia, relapse

Date received: 19 November 2018; revised: 17 December 2018; accepted: 20 December 2018.

Introduction
Thrombotic thrombocytopenic purpura (TTP) is a serious condition that results in classic presentations, including thrombocytopenia, microangiopathic hemolytic anemia, fever, renal insufficiency, and neurological deficits.¹ The pathogenesis is caused by a decrease in the level of a metalloprotease named ADAMTS13 (a disintegrin-like and metalloproteinase with thrombospondin type 1 motif, member 13).² ADAMTS13 normally cleaves ultralarge von Willebrand factor (VWF) multimers into small sizes. When ADAMTS13 is lacking, a number of ultralarge VWF multimers may attach to subendothelial cells and subsequently stimulate platelet adhesion, leading to
disseminated thrombosis. There are 2 main causes of TTP: inherited and acquired. Inherited TTP is caused by congenital ADAMTS13 deficiency (Upshaw-Schulman syndrome). A significant decrease in ADAMTS13 activity in congenital TTP arises from known mutations and polymorphisms in the ADAMTS13 gene. On the other hand, acquired TTP is caused by autoantibodies targeting ADAMTS13, resulting in a lowered ADAMTS13 function or an increase in the metalloprotease’s clearance. Some factors are recognized as stimulants of the autoimmune function, for example, some viral infections (Epstein-Barr virus, cytomegalovirus, and HIV), malignancy, drugs, pregnancy, and other autoimmune diseases.

In the case of acquired TTP, the treatments available comprise total plasma exchange with plasma infusion, steroids, immunomodulator agents (vincristine and cyclosporin), and rituximab; these drugs are given due to the autoimmune nature of acquired TTP. Rituximab, the humanized anti-CD20 monoclonal antibody, is introduced to reduce the incidence of relapsed TTP. Its actions are a decrease in the production of antibodies against ADAMTS13 and a resumption of ADAMTS13 activity. However, whether rituximab should be a frontline treatment or only reserved for patients with a suboptimal response to initial treatments for autoimmune TTP is controversial. The current systematic review and meta-analysis were performed with the aim of including all available studies and summarizing their results to compare the efficacies of rituximab and conventional treatment for acquired TTP.

**Methods**

**Data Sources and Searches**

Three investigators (C.W., W.O., and N.O.) independently searched studies published in the MEDLINE and EMBASE databases before December 11, 2018 using a search strategy that included the terms for TTP and rituximab. Supplementary Data 1 displays the search strategy for our meta-analysis. We further examined the references of the eligible publications to identify additional articles for inclusion. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement was used as a guideline for performing the current study; it is provided as Supplementary Data 2.

**Selection Criteria and Data Extraction**

The studies included in this meta-analysis needed to be randomized-controlled studies or cohort studies (either prospective or retrospective) that compared the efficacies of rituximab and conventional therapy for TTP treatment. Furthermore, they had to report at least one of our primary outcomes of interest, which was either the relapse rate after remission of each treatment or the mortality rate. All 3 investigators independently assessed the eligible articles. In the case of disagreements on whether a particular publication should be included, all investigators jointly reviewed it before making the final decision.

**Outcome Definitions**

Complete remission was defined as the achievement of a platelet count of $\geq 150 \times 10^9/L$ and a sustained response for $\geq 30$ days after plasma exchange was stopped. Relapse was defined as the recurrence of an acute episode of TTP after remission.

**Quality Assessment**

The quality of each included randomized-controlled study was evaluated by using the Jadad quality assessment scale. The quality of the included nonrandomized studies was evaluated with the Newcastle-Ottawa Scale. This 3-item scoring system assesses the selection of the participants, the comparability between the groups, and the ascertainment of exposure (for case-control studies) and the outcome of interest (for cohort studies).

**Statistical Analysis**

All statistical data were analyzed using Review Manager 5.3 software from the Cochrane Collaboration (London, United Kingdom). The effect estimates and 95% confidence intervals (CIs) from the individual articles were collected, and Mantel-Haenszel methods were used to pool the data. Cochran Q test was then calculated and quantified using the I$^2$ statistic to assess the statistical heterogeneity of the publications. They were classified as follows: 0% to 25% represented an insignificant heterogeneity; 26% to 50% low heterogeneity; 51% to 75% moderate heterogeneity; and >75% high heterogeneity. Due to the high likelihood of between-study heterogeneity, we preferred the random-effects to the fixed-effects model. Publication bias was not evaluated because of the small number of included studies (less than 10). Values of $P$ less than .05 were considered statistically significant.

**Results**

A total of 1877 potentially relevant articles were found in the 2 databases (348 from MEDLINE and 1529 from EMBASE). We excluded 336 duplicated reports, and the remaining 1541 were evaluated for relevance via a review of their titles and abstracts. Of those, 1513 were excluded according to the exclusion criteria, which were: (1) reviews, or meta-analyses, or commentaries; (2) reports irrelevant to TTP; (3) articles irrelevant to a comparison between rituximab and conventional treatments; and/or (4) publications with no primary end points. The full-lengths of the remaining 28 articles were manually reviewed, resulting in a further 19 being excluded because they met the exclusion criteria. Nine publications finally fulfilled the inclusion criteria for the meta-analysis; they comprised 5 prospective cohort studies and 4 retrospective cohort studies. The literature review process is summarized in Figure 1.
Baseline Patient Characteristics

A total of 570 patients were included in this meta-analysis (280 in the rituximab arm and 290 in the conventional treatment arm). The age range for the rituximab arm was 18 to 79 years, whereas it was 16 to 88 years for the conventional treatment arm. Approximately 3-quarters of the patients in each group were female. More than 30% of the rituximab group participants were either relapsed or refractory patients with TTP, whereas the corresponding figure for the conventional treatment group was noticeably lower at 22.8%. In most of the studies, the proportion of enrolled patients with TTP who had ADAMTS13 activity represented less than 10% of the participants in each group. Almost all cases in both groups received plasma exchange and corticosteroids as their TTP treatment. The rituximab protocols were divided into 2 purposes for TTP treatment in the included studies. Most included studies used rituximab in acute phase to induce disease remission, whereas other 2 studies used preemptive rituximab treatment during remission (in case of persistently low ADAMTS13 levels) to prevent clinical relapse. The baseline patient features, treatments, median follow-up periods, study types, and quality assessment scores for the 9 included studies are detailed in Table 1.

Long-Term Remission and Mortality Outcomes

The relapse rate was reported in 8 studies (a 1-year follow-up relapse rate in 1 study,18 a 2-year rate in 3 studies,19,23,24 a 3-year rate in 3 studies,20,22,26 and a 4-year rate in 1 study25). Six out of 8 studies demonstrated rituximab role in an acute phase to induce disease remission. The pooled relapse rate found that patients who received rituximab had a significantly lower relapse rate than those given conventional treatment (odds ratio [OR]: 0.40, 95% CI: 0.19-0.85, P = .02, I² = 43%; Figure 2A).18-20,23-25 Likewise, the relapse rate in the rituximab group was also significantly lower than the control group by pooling the data of other 2 studies using rituximab for preemptive therapy to prevent clinical relapse (OR: 0.09, 95% CI: 0.04-0.24, P < .00001, I² = 11%; Figure 2B).22,26 Furthermore, the conventional treatment group had a significantly higher mortality rate than the rituximab group during the follow-up (OR: 0.41, 95% CI: 0.18-0.91, P = .03, I² = 0%; Figure 3).18-24,26

Discussion

This is the first meta-analysis to compare the efficacies of rituximab and conventional treatment for patients with TTP. There were no significant differences in the baseline patient characteristics of the 2 groups (including age, gender, and the proportion of patients who had ADAMTS13 activity). However, the proportion of relapsed/refractory TTP cases in the rituximab group was higher than that in the conventional treatment group.

Although plasma exchange, significantly reducing the early mortality rate, yielded an advantage in emergency management for acquired TTP, long-term relapse rate was quite high if novel medications or immunosuppressive drugs were not integrated
Table 1. Baseline Patient Characteristics of Each Included Article.

| Reference            | Group | No. Sex (M/F) | Median Age (years, range) | Disease Status | Role of Rituximab Therapy/Rituximab Dose | ADAMTS13 Activity (%) Range | Median No. of PEX to Achieve Remission (range) | Steroid Use (%) | Additional Treatment | Median Follow-Up | Study Period | Type | Selection | comparability | outcome |
|----------------------|-------|---------------|---------------------------|----------------|-----------------------------------------|-----------------------------|-----------------------------------------------|----------------|---------------------|-----------------|-------------|------|-----------|---------------|---------|
| Scully et al, 2011   | RTX   | 40 14/26      | 42 (21-76)                | 34 de novo, 6 relapsed | Acute/weekly iv of 375 mg/m² within the first 3 days. 2: 2 doses. 3: 3 doses. 4: 4 doses. 8 doses. 32: at least 4 infusions | 32% of patients: <5% | 16.5 (4-34) | 95% | 4 Vincristine | NR | 2006-2009 | P, cohort | Selection: 4 | comparability: 2 | outcome: 2 |
| No RTX              | 40    | 7/33          | 42 (18-78)                | 31 de novo, 9 relapsed | – | 40% of patients: <5% | 18 (6-92) | 35% | 7 CSA, 5 defibrotide, 3 Cyclo, 9 Vincristine, 1 splenectomy | NR |                       |                   |            |      |           |               |         |
| Froissart et al, 2012 | RTX  | 22 8/14       | 36.8                      | 6 refractory, 16 relapsed | Acute/375 mg/m² iv on days X, X+3, X+7, and X+14 (total 4 doses) | <10% | NR | 71% | 1 Vincristine | 33 months | 2005-2008 | P, cohort | Selection: 4 | comparability: 2 | outcome: 3 |
| No RTX              | 57    | 20/37         | 41.7                      | NR | – | <10% | NR | 79% | 3 Cyclo + Vincristine, 17 Vincristine | 35 months |                       |                   |            |      |           |               |         |
| Abdel Karim et al, 2013 | RTX  | 9 0/9         | 38                        | 5 de novo, 4 relapsed | Acute/weekly iv of 375 mg/m² (total 4 doses) | NR | NR | NR | NR | 41 (7-88) | 1997-2009 | R, cohort | Selection: 3 | comparability: 2 | outcome: 2 |
| No RTX              | 13    | 3/10          | 46                        | 12 de novo, 1 relapsed | – | NR | NR | NR | NR | 20 (8-77) |                       |                   |            |      |           |               |         |
| Hie et al, 2014     | RTX   | 30 11/19      | 38 (30-44)                | 25 de novo, 5 relapsed | Preemptive/weekly iv of 375 mg/m² (1-4 doses/course) | <10% | NR | NR | 1 Alemtuzumab + Cyclo + CSA + MMF + Bortezomib | 36 months (24-65) | 2000-2012 | P, cohort | Selection: 4 | comparability: 2 | outcome: 3 |
| No RTX              | 18    | NR NR         | 4 de novo, 14 relapsed    | – | <10% | NR | NR | NR | NR | 60 months (30-72) |                       |                   |            |      |           |               |         |
| Rinott et al, 2015  | RTX   | 14 5/9        | 37 (18-77)                | 5 refractory, 9 relapsed | Acute/weekly iv of 375 mg/m² (12-4 doses. 1: 6 doses. 1: 1 dose) | <1% | 13 (12-14) | 100% | NR | Réfractory: 27 months, relapsed: 57 months | 2000-2013 | R, cohort | Selection: 2 | comparability: 2 | outcome: 2 |
| No RTX              | 31    | 10/21         | 39 (16-88)                | 31 de novo | – | <1% | 16 (5-46) | 100% | NR | 117 months |                       |                   |            |      |           |               |         |
| Page et al, 2016    | RTX   | 16 4/12       | 41 (20-79)                | 10 de novo, 6 relapsed | Acute/weekly iv of 375 mg/m² (1-4 doses) | <10% | 16 (5-79) | 100% | 2 Cyclo, 1 Vincristine | 5.7 years (2.5-92) | 2003-2014 | P, cohort | Selection: 3 | comparability: 2 | outcome: 2 |
| No RTX              | 21    | 6/15          | 38 (18-69)                | 11 de novo, 10 relapsed | – | <10% | 8 (5-24) | 100% | – | 5.7 years (2.5-92) |                       |                   |            |      |           |               |         |
| Uhl et al, 2017     | RTX   | 40 NR NR      | 25 de novo, 15 relapsed   | Acute/weekly iv of 375 mg/m² (1-4 doses) | 30 <10%, 8: >10%, 2: unknown | NR | NR | NR | NR | 1.45 years (34 days-34 years) | 2009-2012 | R, cohort | Selection: 3 | comparability: 2 | outcome: 2 |
| No RTX              | 59    | NR NR         | 45 de novo, 14 relapsed   | – | NR | NR | NR | NR | NR | 1.45 years (34 days-34 years) |                       |                   |            |      |           |               |         |
| Falter et al, 2018  | RTX   | 17 NR NR      | 17 de novo               | Acute/weekly infusions of 375 mg/m² (1-4 doses) | <10% | NR | NR | NR | NR | 2003-2014 | R, cohort | Selection: 4 | comparability: 2 | outcome: 2 |
| No RTX              | 28    | NR NR         | 28 de novo               | – | <10% | NR | NR | NR | NR | (continued) |                       |                   |            |      |           |               |         |
| Reference          | Group | No. | Sex (M/F) | Median Age (years, range) | Disease Status | Role of Rituximab Therapy/Rituximab Dose | ADAMTS13 Activity (% Range) | Median No. of PEX to Achieve Remission (range) | Steroid Use (%) | Additional Treatment | Median Follow-Up | Study Period | Type | Quality Assessment |
|-------------------|-------|-----|-----------|--------------------------|----------------|----------------------------------------|----------------------------|-----------------------------------------------|-----------------|-------------------|-----------------|--------------|------|-------------------|
| Jestin et al, 2018<sup>26</sup> | RTX   | 92  | 25/67     | 42 (33.3-51)             | >1 TTP episode | Preemptive/weekly iv of 375 or 500 mg/m² being on the days following the identification of a severe ADAMTS13 deficiency | <10% NR                  | 84% 5: CSA, 1: bortezomib               | 35.8 months     | 2012-2017    | P, cohort | Selection: 3, comparability: 1, outcome: 2 |
| No RTX            | 23    | 4/19| 38 (31-51)| NR                       |                |                                        | <10% NR                  | 85% NR                         | 7 years         |                   |                  |              |      |                   |

Abbreviations: ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif; member 13; CSA, cyclosporin A; Cyclo, cyclophosphamide; F, Female; iv, intravenously; M, male; MMF, mycophenolate mofetil; NR, not reported; P, prospectively; PEX, plasma exchange; R, retrospectively; RTX, rituximab.
Corticosteroid is commonly an adjuvant therapy combined with plasma exchange, which could decrease ADAMTS13 autoantibodies and improve ADAMTS13 activity. Nevertheless, the exacerbate rate remained not low from a recent study, with the figure nearly of 10% at the first month follow-up. Rituximab affects to reduce B-cell lymphocytes, and subsequently decrease the production of ADAMTS13 autoantibodies. It was also approved to render high sustained response in immune thrombocytopenia patients from a previous meta-analysis. The pooled forest plot of the relapse rate in TTP from this meta-analysis showed a significantly lower rate for the rituximab group in both acute and preemptive treatment purposes than the conventional treatment group during the 1- to 4-year follow-up period. The patient who received rituximab also had lower mortality rate when compared to conventional treatment. Our results indicated that rituximab combined with corticosteroid showed higher efficacy to prevent relapse rate and lower mortality rate in newly diagnosed acquired patients with TTP. Furthermore, we noticed that the proportion of relapsed/refractory patients with TTP in the rituximab group represented nearly one-third of the total cases. We therefore support the use of rituximab as an adjuvant treatment in combination with plasma exchange in newly-diagnosed TTP and as a second-line treatment for patients with acquired TTP.

There are some limitations to this study. Firstly, none of the included studies is randomized trial; therefore, these studies are subjected to have selection biases especially the differences in baseline characteristics between 2 groups such as a proportion of age-group, a proportion of refractory disease patients, and other additional immunosuppressive therapies. There may be more immunosuppressive therapies in rituximab group because the disease is generally more resistant. For instance, more

### Figure 2
Forest plots of the odds ratio of the relapse rates after complete remission of the rituximab and conservative treatment arms dividing on roles of rituximab therapy: (A) acute treatment; (B) preemptive treatment.

| Study or Subgroup | Rituximab | Control | Odds Ratio | Heterogeneity | Test for overall effect |
|-------------------|-----------|---------|------------|---------------|------------------------|
| M-H | Random | 95% CI | M-H | Random | 95% CI |
| Scully 2011 | 3 | 41 | 38 | 19.3% | 0.10 | [0.03, 0.33] | 2011 |
| Freissart 2012 | 3 | 19 | 16 | 53 | 17.1% | 0.43 | [0.11, 1.70] | 2012 |
| Rinott 2015 | 4 | 14 | 9 | 40 | 16.9% | 1.38 | [0.35, 5.48] | 2016 |
| Page 2016 | 1 | 6 | 4 | 21 | 8.3% | 0.28 | [0.03, 2.82] | 2016 |
| Uhl 2017 | 5 | 36 | 10 | 48 | 20.0% | 0.58 | [0.18, 1.87] | 2018 |
| Falet 2018 | 5 | 17 | 14 | 28 | 18.3% | 0.42 | [0.12, 1.50] | 2018 |
| Total | 139 | 226 | 100.0% | 0.40 | [0.19, 0.85] |
| Total events | 22 | 74 | 100.0% | 2.39 | (0.02) |

### Figure 3
Forest plots of the odds ratios of the mortality rates of the rituximab and conservative treatment arms.

| Study or Subgroup | Rituximab | Control | Odds Ratio | Heterogeneity | Test for overall effect |
|-------------------|-----------|---------|------------|---------------|------------------------|
| M-H | Random | 95% CI | M-H | Random | 95% CI |
| Hie 2014 | 3 | 30 | 7 | 18 | 35.7% | 0.17 | [0.04, 0.60] | 2014 |
| Jestin 2016 | 14 | 92 | 17 | 23 | 64.3% | 0.06 | [0.02, 0.19] | 2016 |
| Total | 122 | 41 | 100.0% | 0.09 | [0.04, 0.24] |
| Total events | 17 | 24 | 100.0% | 4.93 | (0.00001) |

Figure 2. Forest plots of the odds ratio of the relapse rates after complete remission of the rituximab and conservative treatment arms dividing on roles of rituximab therapy: (A) acute treatment; (B) preemptive treatment.

Figure 3. Forest plots of the odds ratios of the mortality rates of the rituximab and conservative treatment arms.
steroid uses in Scully et al study and some of more other additional immunosuppressive therapies use in Page et al and Jestin et al studies. Immunosuppression may suppress ADAMTS13 antibody, resulting in lower relapse rate. Moreover, the studies that used historical controls have longer follow-up time in the control groups, and leads to falsely high relapse rate and mortality rate in Hie et al, Rinott et al, and Jestin et al studies. In addition, due to limited number of studies included in the meta-analysis, a publication bias assessment could not be performed.

Conclusions
Rituximab provided a high efficacy to prevent relapses in cases of newly diagnosed acquired TTP. Additionally, its effectiveness with the subgroup of patients with relapsed/refractory TTP was demonstrated through the provision of good outcomes.

Author’s Note
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. Our institution does not require ethical approval for performing a meta-analysis as this study did not directly involve human subjects. Informed consent for patient information to be published in this article was not obtained because this study did not directly involve human subjects.

Author’s Contributions
All authors designed the study. WO, CW, and NO collected the data. WO performed the statistical analyses. WO, CW, and WR drafted the manuscript and revised the final manuscript. TR made critical revisions to the manuscript. All authors read and approved the final manuscript.

Declaration of Conflicting Interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD
Weerapat Owattanapanich https://orcid.org/0000-0002-1262-2005

Supplemental Material
Supplemental material for this article is available online.

References
1. Amorosi EL, Ultmann JE. Thrombotic thrombocytopenic purpura: report of 16 cases and review of the literature. Medicine. 1966;45(2):139-159.
2. Moake JL, Rudy CK, Troll JH, et al. Unusually large plasma factor VIII: von Willebrand factor multimers in chronic relapsing thrombotic thrombocytopenic purpura. N Engl J Med. 1982; 307(23):1432-1435.
3. Dong JF, Moake JL, Nolasco L, et al. ADAMTS-13 rapidly cleaves newly secreted ultralarge von Willebrand factor multimers on the endothelial surface under flowing conditions. Blood. 2002;100(12):4033-4039.
4. Kokame K, Kokubo Y, Miyata T. Polymorphisms and mutations of ADAMTS13 in the Japanese population and estimation of the number of patients with Upshaw-Schulman syndrome. J Thromb Haemost. 2011;9(8):1654-1656.
5. Miyata T, Kokame K, Matsumoto M, et al. ADAMTS13 activity and genetic mutations in Japan. Haemostaseologie. 2013;33(2):131-137.
6. Scheiflinger F, Knöbl P, Trattner B, et al. Nonneutralizing IgM and IgG antibodies to von Willebrand factor-cleaving protease (ADAMTS-13) in a patient with thrombotic thrombocytopenic purpura. Blood. 2003;102(9):3241-3243.
7. Coppo P, Froissart A. Treatment of thrombotic thrombocytopenic purpura beyond therapeutic plasma exchange. Hematology Am Soc Hematol Educ Program. 2015;2015:637-643.
8. de la Rubia J, Moscardo F, Gómez MJ, et al. Efficacy and safety of rituximab in adult patients with idiopathic relapsing or refractory thrombotic thrombocytopenic purpura: results of a Spanish multicenter study. Transfus Apher Sci. 2010;43(3):299-303.
9. Coppo P, Veyradier A. Current management and therapeutical perspectives in thrombotic thrombocytopenic purpura. Presse Med. 2012;41(3 pt 2):e163-e176.
10. Scully M, Cohen H, Cavenagh J, et al. Remission in acute refractory and relapsing thrombotic thrombocytopenic purpura following rituximab is associated with a reduction in IgG antibodies to ADAMTS-13. Br J Haematol. 2007;136(3):451-461.
11. Benhamou Y, Paintaud G, Azoulay E, et al. Efficacy of a rituximab regimen based on B cell depletion in thrombotic thrombocytopenic purpura with suboptimal response to standard treatment: results of a phase II, multicenter noncomparative study. Am J Hematol. 2016;91(12):1246-1251.
12. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535.
13. Vesely SK, George JN, Lammle B, et al. ADAMTS13 activity in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: relation to presenting features and clinical outcomes in a prospective cohort of 142 patients. Blood. 2003; 102(1):60-68.
14. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17(1):1-12.
15. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25(9):603-605.
16. Borenstein M, Hedges LV, Higgins JPT, et al. Introduction to Meta-Analysis. Hoboken, NJ: John Wiley & Sons, West Sussex; 2009.
17. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-560.
18. Scully M, McDonald V, Cavenagh J, et al. A phase 2 study of the safety and efficacy of rituximab with plasma exchange in acute acquired thrombotic thrombocytopenic purpura. Blood. 2011; 118(7):1746-1753.
19. Page EE, Kremer Hovinga JA, Terrell DR, Vesely SK, George JN. Rituximab reduces risk for relapse in patients with thrombotic thrombocytopenic purpura. *Blood*. 2016;127(24):3092-3094.

20. Froissart A, Buffet M, Veyradier A, et al. Efficacy and safety of first-line rituximab in severe, acquired thrombotic thrombocytopenic purpura with a suboptimal response to plasma exchange. Experience of the French Thrombotic Microangiopathies Reference Center. *Crit Care Med*. 2012;40(1):104-111.

21. Abdel Karim N, Haider S, Siegrist C, et al. Approach to management of thrombotic thrombocytopenic purpura at University of Cincinnati. *Adv Hematol*. 2013;2013:195746.

22. Hie M, Gay J, Galicier L, et al. Preemptive rituximab infusions after remission efficiently prevent relapses in acquired thrombotic thrombocytopenic purpura. *Blood*. 2014;124(2):204-210.

23. Rinott N, Mashiach T, Horowitz NA, et al. A 14-year experience in the management of patients with acquired immune thrombotic thrombocytopenic purpura in Northern Israel. *Acta Haematol*. 2015;134(3):170-176.

24. Uhl L, Kiss JE, Malynn E, Terrell DR, Vesely SK, George JN. Rituximab for thrombotic thrombocytopenic purpura: lessons from the STAR trial. *Transfusion*. 2017;57(10):2532-2538.

25. Falter T, Herold S, Weyer-Ellerich V, et al. Relapse rate in survivors of acute autoimmune thrombotic thrombocytopenic purpura treated with or without rituximab. *Thromb Haemost*. 2018;118(10):1743-1751.

26. Jestin M, Benhamou Y, Schelpe AS, et al. Preemptive rituximab prevents long-term relapses in immune-mediated thrombotic thrombocytopenic purpura. *Blood*. 2018;132(20):2143-2153.

27. Bandarenko N, Brecher ME. United States Thrombotic Thrombocytopenic Purpura Apheresis Study Group (US TTP ASG): multicenter survey and retrospective analysis of current efficacy of therapeutic plasma exchange. *J Clin Apher*. 1998;13(3):133-141.

28. Cataland SR, Kourlas PJ, Yang S, et al. Cyclosporine or steroids as an adjunct to plasma exchange in the treatment of immune-mediated thrombotic thrombocytopenic purpura. *Blood Adv*. 2017;1(23):2075-2082.

29. Masias C, Cataland SR. Novel therapies in thrombotic thrombocytopenic purpura. *Res Pract Thromb Haemost*. 2017;2(1):19-26.

30. Arai Y, Jo T, Matsui H, et al. Comparison of up-front treatments for newly diagnosed immune thrombocytopenia—a systematic review and network meta-analysis. *Haematologica*. 2018;103(1):163-171.