ADAMTS13 Autoantibodies and Burden of Care in Immune Thrombotic Thrombocytopenic purpura: New Evidence and Future Implications

Cristina Dainese, MD1, Federica Valeri, PhD, MD1, Eleonora Pizzo, MD2, Alessandra Valpreda, BS2, Piera Sivera, MD4, Barbara Montaruli, PhD5, Annamaria Porreca, PhD6, Massimo Massaia, PhD7, Benedetto Bruno, PhD, MD8, and Alessandra Borchiellini, MD1

Abstract
The introduction Caplacizumab in the management of Immune thrombotic thrombocytopenic purpura (iTTP) has raised different questions, considering its cost-efficacy and the optimal immunosuppressive treatment (IST) to associate. A retrospective multicenter collection of 42 first iTTP cases was conducted to identify variables associated with a higher burden of care and necessity of an implemented IST with early Rituximab (RTX) rescue. A significant correlation resulted between ADAMTS13 inhibitors (ADAMTS13inh) at diagnosis with total plasma exchange (PEXtot) and PEX needed to achieve clinical response (PEXtoCR, \( r = 0.46 \); \( r = 0.48 \)), along with age (\( r = -0.31 \); \( r = -0.35 \)), platelet count (\( r = -0.30 \); \( r = -0.30 \)), LDH (\( r = 0.44 \); \( r = 0.41 \)) and total bilirubin (\( r = 0.54 \); \( r = 0.35 \)). ADAMTS13inh also correlated with number of days of hospitalization (DoH, \( r = 0.44 \)). A significant difference was observed in terms of median ADAMTS13inh titer at diagnosis in patient treated with RTX rescue and those responding to only steroid treatment. Thus, ADAMTS13inh titer resulted a marker of iTTP burden of care, associated with higher number of PEXtot, PEXtoCR, DoH and higher probability of needing RTX rescue to achieve clinical response and could be a useful tool for management of new iTTP cases and an interesting variable to optimize iTTP cases stratification in future Caplacizumab cost-efficacy analysis.

Keywords
thrombotic microangiopathies, thrombotic thrombocytopenic purpura, caplacizumab, ADAMTS13 inhibitors, moskowitz syndrome

Date received: 7 July 2022; accepted: 26 August 2022.
### Introduction

Immune Thrombotic thrombocytopenic purpura (iTTP) is a rare and life-threatening thrombotic microangiopathy characterized by microangiopathic hemolytic anemia, severe thrombocytopenia, and organ ischemia linked to disseminated microvascular platelet-rich thrombi. From the clinicians’ point of view, the introduction of Caplacizumab has drastically changed the management of acute iTTP episodes, but also raised several questions, including cost-effectiveness, and integration with immunosuppressive treatment (IST), especially in the initial treatment of iTTP which remains a matter of debate in terms of Rituximab (RTX) intensification. With regards to prognostic scores currently available, the PLASMIC and the French scores have a diagnostic purpose; the modified Rose, the Benhamou and colleagues\(^6\) the Wyllie and colleagues\(^7\) and the Goel and colleagues\(^8\) scores consider as endpoint iTTP mortality and survival rate. However, none of the available scores has been developed to predict treatment intensity and burden of care needed to manage an initial acute iTTP episode. We report the results of a multicenter, retrospective study in which we have analyzed the management of 42 first iTTP episodes with the aim to identify clinical and/or laboratory variables associated with a greater burden of care.

### Methods

A retrospective analysis of all first iTTP episodes diagnosed and treated in three distinct hematology units in Piedmont (City of Health and Science University Hospital of Turin, Ordine Mauriziano Hospital of Turin and Santa Croce e Carle Hospital of Cuneo) from 2007 and 2020, before Caplacizumab introduction was conducted. All patients included have previously signed informed consent to be addressed in the regional registry of rare disease (MARARE). iTTP cases were defined as a severe ADAMTS13 activity (ADAMTS13act) deficiency (<10%) associated with detectable ADAMTS13 inhibitors (ADAMTS13inh). Congenital TTP (cTTP) cases (reduction in ADAMTS13 activity <10% with no measurable antiADAMTS13inh), relapsed iTTP cases and recent iTTP cases treated with Caplacizumab were excluded from the analysis. Demographic, clinical and laboratory data were collected in the first 24 h after presentation, including age, sex, comorbidities (Charlson comorbidity index\(^9\) for each patient), possible triggers, symptoms at hospital arrival, hemoglobin level (Hb), Platelet count (Plts), White blood cell (Wbc), Reticulocyte (Ret), Creatinine (Creat), Hepatic enzymes, Lactic dehydrogenase (LDH), Total Bilirubin (Bil tot) and Indirect fraction (Bil Ind), Haptoglobin (Hapt) was collected. For each patient PLASMIC score was also calculated. ADAMTS13act assays were performed with chromogenic ELISA kit (Technozym ADAMTS13 Activity, Technoclone Gmbh, Wien, Austria). ADAMTS13inh were detected and measured with ELISA methodology (Technozym ADAMTS13 Inh, Technoclone, Gmbh, Wien, Austria). Together with ADAMTS13act and ADAMTS13inh, number of total Plasma Exchange (PEX, PEXtot) sessions, number of PEX needed to achieve clinical response (PExtoCR) and days of hospitalization (DoH) were also included. Data regarding immunosuppressive treatment (IST) used and their duration were collected when available. Clinical response (CR) exacerbation and relapse were defined in current guidelines\(^{10-12}\):

- Clinical response (CR): sustained normalization of Plts counts above the lower limit of the established reference range (> 150 × 10^9/L) and of LDH (< 1.5 upper limit of normal [ULN]) after cessation of PEX.
- Refractory iTTP: persistent thrombocytopenia, lack of a sustained Plts count increment or Plts counts of < 50 × 10^9/L and a persistently raised LDH level (> 1.5 ULN) despite five PEX and steroid treatment.
- Exacerbation: reduction in plts count to below the lower limit of the established reference range (<150 × 10^9/L), an increased LDH level, and the need to restart PEX within 30 days of the last PEX after a clinical response to PEX.
- Relapse: fall in platelet count to below the lower limit of the established reference range (<150 × 10^9/L), with or without clinical symptoms > 30 days after stopping of PEX for an acute TTP episode, requiring reinitiating of therapy. This is usually associated with a new increase in the LDH level.

Shapiro Wilks test was performed to evaluate the normal distribution of the data. Continuous normally distributed variables were reported as the mean value ± standard deviation (SD). Continuous non-normally distributed variables were presented as the median, IQR (q1 = first quartile and q3 = third quartile). Absolute frequency (column percentage) was used to summarize categorical variables. The unpaired t-test and Mann U Whitney test were used to compare continuous variables, as appropriate. Correlation network analysis (CAN) was applied using Pearson correlation coefficient (r) as the measurement of the strength of the relationship between PExtot, PExtoCR and DoH to laboratoristic and demographic continuous variables. All statistical tests were 2-sided, with a significance level set at p < 0.05. Statistical analysis was performed using R software environment for statistical computing and graphics version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/).

### Results

A total of 42 patients with a first iTTP episode were identified and retrospectively analyzed. Demographic and laboratory characteristics of the cohort are resumed in Table 1. Patient’s characteristics after hospital admission are shown in Table 2. The median value of ADAMTS13 Activity Percentage was 0.02 IU (0.01, 0.02) IU, while the mean value of ADAMTS13inh (BU/ml) titer was 66.37 (34.59). The PEX sessions were started soon after hospital admission: median days from hospital admission and PEX start were 0.04 days (0.02,
For 8 patients (19.00%) CS were associated with ticsosteroids (CS) at standard dose (methylprednisolone 1 mg/kg or equivalent). For 38 patients (90.50%) and 41 (97.60%), respectively. The median time from CS start to RTX start was 10 days (range 2-30 days). Finally, 3 patients (7.10%) received adjunctive treatments: 2 patients were treated after CS and RTX also with Vincristine, another one also received Cyclophosphamide. The last patient was treated with Cyclophosphamide after being treated with CS. Pearson correlation coefficient (r) was used to assess the association between the number of PEXtot, PEXtoCR, DoH and demographic and laboratory variables collected in the first 24 h after hospital admission (Table 3). PEXtot was significantly positively correlated with age (r = -0.31, p = 0.040), LDH (r = 0.44, p = 0.006), Total Bilirubin (r = 0.54, p = 0.001) and ADAMTS13inh (r = 0.46, p = 0.002). PEXtoCR were significantly associated with Age (r = -0.35, p = 0.030), Platelets (r = -0.30, p = 0.048), Lactic Dehydrogenase (r = 0.41, p = 0.012), Total Bilirubin (r = 0.35, p = 0.04), ADAMTS13inh (r = 0.48, p = 0.025). Indeed, ADAMTS13inh resulted significantly positively correlated with DoH (r = 0.44, p = 0.005). ADAMTS13act did not correlate neither with the total number of PEX, the PEXtoCR and DoH. Finally, the Mann U Whitney test confirms no difference in the median number of Total PEX Session, PEX to achieve CR and DoH between males and females, Charlson Comorbidity Index score (≤2 or >2), and for presence or absence of neurological, hemorrhagic, or systemic symptoms at hospital admission (Table 3). Considering variables statistically significantly associated with the total PEX Session and PEX to achieve CR (Table 3), the Mann U Whitney test was also performed to evaluate differences for RTX rescue necessity to achieve CR (Table 4). No significant differences were found for Age, Plts and, LDH level at hospital admission in patients receiving RTX rescue and those not necessitating such treatment. In contrast, a statistically significant mean value difference was observed for ADAMTS13inh titer at diagnosis (88.80 ± 29.38 vs 52.20 ±

| Table 1. Patients’ Characteristics at Hospital Admission 1: Neurological Symptoms Included Stupor, Coma, Dizziness, Headache, Migraine, TIA, or Stroke Symptoms with Sensorial or Motor Deficiency. § Systemic Symptoms Included Generalized Malaise, Asthenia, Fever, Abdominal Pain, Nausea. |
| --- |
| **Patients’ characteristics at hospital admission** |
| **Age (years), mean (SD)** | 49.40 (13.74) |
| **Gender, n (%)** |  |
| Male | 19 (45.20) |
| Female | 23 (54.80) |
| **Charlson Comorbidity Index (CCI), n (%)** |  |
| 0 | 17 (40.50) |
| 1 - 2 | 17 (40.50) |
| > 2 | 8 (19.00) |
| **Symptoms, n (%)** |  |
| Neurological§ | 24 (57.00) |
| Hemorrhagic | 20 (54.70) |
| Systemic§ | 16 (38.10) |
| **Laboratory Features, median (IQR)** |  |
| Hemoglobin (g/dl) | 8.60 (7.20, 10.10) |
| Median Cell Volume (fl) | 87.50 (85.90, 90.00) |
| White Blood Cell (/mmc) | 9415.00 (6642.00,12485.00) |
| Platelets (/mmc) | 13000.00 (11250.00,19000.00) |
| Lactic Dehydrogenase (U/l) | 1806.00 (1332.00, 2485.00) |
| INR | 1.10 (1.06,1.15) |
| Fibrinogen (mg/dl) | 365.00 (291.00, 406.00) |
| Creatinine (mg/dl) | 0.99 (0.76,1.22) |
| Alanine Transferrase (U/l) | 29.00 (21.00, 43.00) |
| Aspartate Transferrase (U/l) | 48.00 (34.00, 60.00) |
| Total Bilirubin (mg/dl) | 2.50 (1.52,2.67) |
| Indirect Bilirubin (mg/dl) | 2.20 (1.30,3.10) |
| Haptoglobin (mg/dl) | 0.21 (0.06, 10.00) |
| **PLASMIC Score, n (%)** |  |
| ≤ 6 | 9 (21.40) |
| 6 - 7 | 18 (42.80) |
| **Etiology, n (%)** |  |
| Idiopathic | 36 (85.70) |
| Sepsis induced | 2 (4.70) |
| Drugs | 3 (7.10) |
| Surgery | 1 (2.40) |

0.06). Number of PEXtoCR and PEXtot sessions were available for 38 patients (90.50%) and 41 (97.60%), respectively. The median number of PEX sessions to achieve CR was 7.00 (4.00, 14.75), median number of total PEX was 14.00 (8.00, 19.00). Data on DoH and admission in the intensive care unit (ICU) were available for 41 patients (97.60%); median DoH were 20.00 (12.00, 27.00), median days in ICU were 1.00 (0.00, 11.00). Based on available data, 6 patients (14.90%) experienced an exacerbation during the first 30 days of treatment. These patients presented with a median ADAMTS13 activity of 0.02 UI, median ADAMTS13inh of 49.95 BU, median number of PEXtot of 18 sessions and 13 median sessions of PEXtoCR. For exacerbated cases median DoH was 21 days. After a median follow-up of 26 months, nine patients (21.40%) experienced at least one relapse.

Considering IST strategy, 100% of the patients received corticosteroids (CS) at standard dose (methylprednisolone 1 mg/kg or equivalent). For 8 patients (19.00%) CS were associated with intravenous immunoglobulins, in 17 patients (40.50%) with Rituximab (RTX), 375 mg/sqm, single weekly infusion for four consecutive weeks. Median time from CS start to RTX start was 10 days (range 2-30 days). Finally, 3 patients (7.10%) received adjunctive treatments: 2 patients were treated after CS and RTX also with Vincristine, another one also received Cyclophosphamide. The last patient was treated with Cyclophosphamide after being treated with CS. Pearson correlation coefficient (r) was used to assess the association between the number of PEXtot, PEXtoCR, DoH and demographic and laboratory variables collected in the first 24 h after hospital admission (Table 3). PEXtot was significantly positively correlated with age (r = -0.31, p = 0.040), LDH (r = 0.44, p = 0.006), Total Bilirubin (r = 0.54, p = 0.001) and ADAMTS13inh (r = 0.46, p = 0.002). PEXtoCR were significantly associated with Age (r = -0.35, p = 0.030), Platelets (r = -0.30, p = 0.048), Lactic Dehydrogenase (r = 0.41, p = 0.012), Total Bilirubin (r = 0.35, p = 0.04), ADAMTS13inh (r = 0.48, p = 0.025). Indeed, ADAMTS13inh resulted significantly positively correlated with DoH (r = 0.44, p = 0.005). ADAMTS13act did not correlate neither with the total number of PEX, the PEXtoCR and DoH. Finally, the Mann U Whitney test confirms no difference in the median number of Total PEX Session, PEX to achieve CR and DoH between males and females, Charlson Comorbidity Index score (≤2 or >2), and for presence or absence of neurological, hemorrhagic, or systemic symptoms at hospital admission (Table 3). Considering variables statistically significantly associated with the total PEX Session and PEX to achieve CR (Table 3), the Mann U Whitney test was also performed to evaluate differences for RTX rescue necessity to achieve CR (Table 4). No significant differences were found for Age, Plts and, LDH level at hospital admission in patients receiving RTX rescue and those not necessitating such treatment. In contrast, a statistically significant mean value difference was observed for ADAMTS13inh titer at diagnosis (88.80 ± 29.38 vs 52.20 ±
30.81 BU/ml, p = 0.001) in patients requiring RTX rescue and those who responded to IST without the monoclonal antibody (Figure 1). Moving away from the aim of the current study, we found no differences for ADAMTS13act at diagnosis. Finally, the median value of ADAMTS13inh titer did not differ between patients experiencing an exacerbation in the first 30 days or a relapse (Table 4).

Discussion

The aim of this work was to identify predictive markers of burden of care in first acute iTTP episode. Epidemiology and demographics of our patient series were very similar to the Milan registry,13 the Regional UK TTP14 Korean TTP,15 Australian TTP/TMA16 and the Oklahoma registries,17 the placebo arms of the TITAN18 and HERCULES19 trial. Zheng20 and colleagues study suggested that high-titer ADAMTS13inh was associated with delayed response to PEX or refractory disease. Also Alwan and colleagues prospectively analyzed ADAMTS13inh21: in 292 patients identified from the UK registry, ADAMTS13 IgG levels were found to be significantly associated with increased mortality rate and higher troponin levels. In the same work, ADAMTS13inh already resulted related with a longer period of PEX to achieve normal platelet count. Coppo et. al22 also analyzed the prognostic role of detectable ADAMTS13inh, associated with a delayed platelet count recovery, a higher plasma volume requirement to achieve CR, and a trend for more frequent episodes exacerbation.

Our data partially confirm these observations but in a new perspective, considering as outcomes of interest not severity nor mortality but iTTP related burden of care markers (PEXtot, PEXtoCR, DoH). For example, high-titer ADAMTS13inh was associated with delayed response to PEX or refractory disease. Also Alwan and colleagues...
with CS plus RTX to achieve CR. Other clinical variable possibly related to a higher burden of care could be young age, lower platelet count, elevated LDH and total bilirubin, but the same ones seem not to predict a longer hospitalization or the need to implement IST with RTX (Figure 1 and 2).

Although needing further validation, if confirmed these data could lead to important clinical implications. iTTP cases are not all the same and as such should not be considered in cost-effectiveness studies. The possibility of optimizing iTTP cases stratification could modify results of such analyzes with important repercussions especially in limited resource Centers. For example, in such settings, Caplacizumab could be reserved for those iTTP cases with higher inhibitors titer, with higher expected burden of care, while in those cases with lower titer, especially if middle-advanced age also presenting with a higher platelet count and lower LDH level and total bilirubin, standard treatment could be considered. Also, for peripheral Center, the possibility of differentiating milder cases from those requiring transfer to expert units for an expected major burden of care could also be useful in the management of patients at the local level. Furthermore, as Caplacizumab leading to a faster platelet count normalization, it does not allow to have a direct picture of iTTP response to IST, making it more difficult for clinicians to decide when to implement it or not. ADAMTS13inh could again be a useful marker to evaluate the early use of RTX and avoid overtreatment.

Our analysis carries different limits: despite concerning a rare disease, data emerging from our limited cohort require a
larger validation. The multicentricity of the registry partly determines differences in clinical management (i.e., PEX cessation criteria, CS tapering scheme, etc), especially before univocal guidelines were available. The retrospective nature of the study does not allow to collect all possible variables of interest: for example, organ damage markers (NTproBNP, Troponin I, Creatinine, etc) were available only for a minority of cases and for this reason it was not possible to incorporate them in the statistical analysis. Lastly, ADAMTS13 may not be rapidly available in some Centers, making the results of our study difficult to apply. However, it should be noted that ISTH guidelines do not recommend the initiation of Caplacizumab prior to laboratory diagnostic confirmation, and consequently the use of RTX should be deferred until the outcome of these tests.

On the other hand, our study has possible interesting future developments: the confirmation of our results on larger registries and on TITAN and HERCULES trial population and in prospective studies could for example implement the beneficial effect of Caplacizumab in those cases in which a higher burden of care is awaited. Furthermore, the same extensions could lead to the confirmation of the role of ADAMTS13inh as a potential guide to early RTX use in iTTP, the identification of different variables relating with iTTP burden of care. Another interesting development could be the incorporation of ADAMTS13inh or further associated variables in future Caplacizumab cost-effectiveness analyses, for a better stratification of iTTP cases. Unfortunately, sample size did not allow any statistical analyzes aimed to identifying a threshold to differentiate a high or low inhibitor titer based on the possibility of response to corticosteroid treatment alone, but this constitutes another interesting starting point for future studies.

Conclusions

From our analysis, ADAMTS13 inhibitor titer at diagnosis emerges as marker of iTTP burden of care, associated with higher total number of PEX sessions, PEX needed to achieve clinical response, days of hospitalization, and a higher probability of needing RTX rescue to achieve clinical response. In other words, ADAMTS13inh titre identifies those iTTP cases in which Caplacizumab can bring the greatest benefits compared with standard of care, and the cases in which early intensification of immunosuppressive treatment is indicated. Thus, despite the need for further validation, ADAMTS13 inhibitors titer could be a useful tool for guiding clinician defining optimal first line immunosuppressive treatment of new iTTP cases and could be included in future Caplacizumab cost-efficacy analysis to better optimize iTTP cases stratification.

Declaration of Conflicting Interests

Dainese C. invited speaker for Novartis. Valeri F. invited speaker and accommodation consultant bureau for Roche, Bayer. Borchelli A. received fees as a consultant or invited speaker by Bayer, Novo Nordisk, Roche, Sobi and Takeda. Pizzo E., Valpreda A., Montaruli B., Sivera P., Porreca A., Massaia M, Bruno B. declare no conflict of interest.

Funding

The statistical analysis was supported by Healthcare Network Partner (HNP). Data collection and interpretation and preparation of this manuscript were performed by the authors. All authors reviewed the manuscript and approved its submission for publication.

Author Contributions

CD drafted the manuscript and partly calculated statistics. AP calculated statistics and prepared the figures. All authors were involved in patients’ management, data collection and proofreading. The manuscript has been read and approved for submission by all authors.

Ethics and Patients Consent

Informed consent for patient information to be published in this article was not obtained because all patients included have previously signed informed consent to be addressed in the regional registry of rare disease (MARARE) which provides for the use of data in anonymous form for scientific research purposes.

ORCID iD

Cristina Dainese https://orcid.org/0000-0002-8672-1372

References

1. Goshua G, Sinha P, Hendrickson JE, Torney CA, Bendapudi P, Lee AI. Cost effectiveness of caplacizumab in acquired thrombotic thrombocytopenic purpura. Blood. 2020;137(7):969-976. doi:10.1182/blood.2020006052
2. Picod A, Veyradier A, Coppo P. Should all patients with immune-mediated thrombotic thrombocytopenic purpura receive caplacizumab? J Thromb Haemostasis. 2021;19(1):58-67. doi:10.1111/jth.15194
3. Bendapudi PK, Hurwitz S, Fry A, et al. Derivation and external validation of the PLASMIC score for rapid assessment of adults with thrombotic microangiopathies: a cohort study. The Lancet Haematology. 2017;4(4):e157-e164. doi:10.1016/S2352-3026(17)30026-1
4. Coppo P, Schwarzinger M, Buffet M, et al. Predictive features of severe acquired ADAMTS13 deficiency in idiopathic thrombotic microangiopathies: the French TMA reference center experience. PLoS ONE. 2010;5(4):e10208. doi: 10.1371/journal.pone.0010208
5. Rose M, Rowe JM, Eldor A. The changing course of thrombotic thrombocytopenic purpura and modern therapy. Blood Rev. 1993;7(2):94-103. doi:10.1016/SD268-960X(05)80019-0
6. Benhamou Y, Assié C, Boelle PY, et al. Development and validation of a predictive model for death in acquired severe ADAMTS13 deficiency-associated idiopathic thrombotic thrombocytopenic purpura: the French TMA reference center experience. Haematologica. 2012;97(8):1181-1186. doi:10.3324/haematol.2011.049676
7. Wylie BF, Garg AX, Macnab J, Rock GA, Clark WF. Thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome: a new index predicting response to plasma exchange. Br J Haematol. 2006;132(2):204-209. doi:10.1111/j.1365-2141.2005.05857.x
8. Goel R, King KE, Takemoto CM, Ness PM, Tobian AAR. Prognostic risk-stratified score for predicting mortality in hospitalized patients with thrombotic thrombocytopenic purpura: nationally representative data from 2007 to 2012. *Transfusion (Paris)*. 2016;56(6):1451-1458. doi:10.1111/trf.13586

9. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383. doi:10.1016/0021-9681(87)90171-8

10. Scully M, Cataland S, Coppo P, et al. Consensus on the standardization of terminology in thrombotic thrombocytopenic purpura and related thrombotic microangiopathies. *J Thromb Haemostasis*. 2017;15(2):312-322. doi:10.1111/jth.13571

11. Zheng XL, Vesely SK, Cataland SR, et al. ISTH Guidelines for treatment of thrombotic thrombocytopenic purpura. *J Thromb Haemostasis*. 2020;18(10):2496-2502. doi:10.1111/jth.15010

12. Zheng XL, Vesely SK, Cataland SR, et al. ISTH Guidelines for the diagnosis of thrombotic thrombocytopenic purpura. *J Thromb Haemostasis*. 2020;18(10):2486-2495. doi:10.1111/jth.15006

13. Mancini I, Pontiggia S, Palla R, et al. Clinical and laboratory features of patients with acquired thrombotic thrombocytopenic purpura: fourteen years of the milan TTP registry. *Thromb Haemostasis*. 2019;119(05):695-704. doi:10.1055/S-0039-1679907

14. Scully M, Yarranton H, Liesner R, et al. Regional UK TTP registry: correlation with laboratory ADAMTS 13 analysis and clinical features. *Br J Haematol*. 2008;142(5):819-826. doi:10.1111/j.1365-2141.2008.07276.x

15. Jang MJ, Chong SY, Kim IH, et al. Clinical features of severe acquired ADAMTS13 deficiency in thrombotic thrombocytopenic purpura: the Korean TTP registry experience. *Int J Hematol*. 2011;93(2):163-169. doi:10.1007/S12185-011-0771-5

16. Blombery P, Kiivitali L, Pepperell D, et al. Diagnosis and management of thrombotic thrombocytopenic purpura (TTP) in Australia: findings from the first 5 years of the Australian TTP/thrombotic microangiopathy registry. *Intern Med J*. 2016;46(1):71-79. doi:10.1111/IMJ.12935

17. Page EE, Kremer Hovinga JA, Terrell DR, Vesely SK, George IN. Thrombotic thrombocytopenic purpura: diagnostic criteria, clinical features, and long-term outcomes from 1995 through 2015. *Blood Advances*. 2017;1(10):590-600. doi:10.1182/BLOODADVANCES.2017005124

18. Peyvandi F, Scully M, Kremer Hovinga JA, et al. Caplacizumab for acquired thrombotic thrombocytopenic Purpura. *N Engl J Med*. 2016;374(6):511-522. doi:10.1056/NEJMoa1505533

19. Scully M, Cataland SR, Peyvandi F, et al. Caplacizumab treatment for acquired thrombotic thrombocytopenic Purpura. *N Engl J Med*. 2019;380(4):335-346. doi:10.1056/NEJMoa1806311

20. Zheng XL, Kaufman RM, Goodnough LT, Sadler JE. Effect of plasma exchange on plasma ADAMTS13 metalloprotease activity, inhibitor level, and clinical outcome in patients with idiopathic and nonidiopathic thrombotic thrombocytopenic purpura. *Blood*. 2004;103(11):4043-4049. doi:10.1182/BLOOD-2003-11-4035

21. Alwan F, Vondravin C, Vanhoorelbeke K, et al. Presenting ADAMTS13 antibody and antigen levels predict prognosis in immune-mediated thrombotic thrombocytopenic purpura. *Blood*. 2017;130(4):466-471. doi:10.1182/BLOOD-2016-12-758656

22. Coppo P, Wolf M, Veyradier A, et al. Prognostic value of inhibitory anti-ADAMTS13 antibodies in adult-acquired thrombotic thrombocytopenic purpura. *Br J Haematol*. 2006;132(1):66-74. doi:10.1111/j.1365-2141.2005.05837.x