Received: 18 June 2021 | Revised: 10 September 2021 | Accepted: 15 September 2021

DOI: 10.1002/rth2.12606

rpth research & practice in thrombosis & haemostasis

CASE REPORT

Immune thrombotic thrombocytopenic purpura: Personalized therapy using ADAMTS-13 activity and autoantibodies

Francesca Palandri MD[1] | Christian Di Pietro MD[1,2] | Francesca Ricci PhD[3] | Pier Luigi Tazzari MD[3] | Vanda Randi MD[3] | Daniela Bartoletti MSc[1,2] | Michele Cavo MD[1,2] | Nicola Vianelli MD[1] | Giuseppe Auteri MD[1,2]

[1]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Bologna, Italy

[2]Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna, Bologna, Italy

[3]IRCCS Azienda Ospedaliero-Universitaria di Bologna, U.O. Immunoematologia e Medicina Trasfusionale, Bologna, Italy

Correspondence
Francesca Palandri, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Bologna, Italy.
Email: francesca.palandri@unibo.it

Handling Editor: Pantep Angchaisuksiri.

Abstract

Recently, treatment of immune-mediated thrombotic thrombocytopenic purpura (ITTP) has changed with the advent of caplacizumab in clinical practice. The International Working Group (IWG) has recently integrated the ADAMTS-13 activity/autoantibody monitoring in consensus outcome definitions. We report three ITTP cases during the coronavirus disease 2019 pandemic, that received a systematic evaluation of ADAMTS-13 activity and autoantibodies. We describe how the introduction of caplacizumab and ADAMTS-13 monitoring could change the management of ITTP patients and discuss whether therapeutic choices should be based on the clinical response alone. ADAMTS-13 activity/antibodies were assessed every 5 days. Responses were evaluated according to updated IWG outcome definitions. These kinetics, rather than clinical remission, guided the therapy, allowing early and safe caplacizumab discontinuation and sensible administration of rituximab. Caplacizumab was cautiously discontinued after achieving ADAMTS-13 complete remission. These cases illustrate that prospective ADAMTS-13 evaluation and use of updated IWG definitions may improve real-life patients' management in the caplacizumab era.

KEYWORDS
ADAMTS-13, caplacizumab, COVID-19, rituximab, thrombotic thrombocytopenic purpura, TTP

Essentials

- An expert group has advised ADAMTS-13 blood tests in immune-mediated thrombotic thrombocytopenic purpura (ITTP).
- We used ADAMTS-13 monitoring to guide treatment in three patients with ITTP.
- This approach allowed cautious stopping of caplacizumab and less rituximab use.
- This new treatment approach may be helpful to others.

1 | INTRODUCTION

Immune-mediated thrombotic thrombocytopenic purpura (ITTP) is a life-threatening thrombotic microangiopathy caused by severe deficiency of ADAMTS-13 mediated by autoantibodies.[1] Diagnosis is based on reduced (<10%) ADAMTS-13 activity. Since this test is frequently unavailable, clinical prediction tools are generally used to estimate the likelihood of severe ADAMTS-13 deficiency in a suspected TTP. Among them, the PLASMIC score (composed of: **PL**atelet count, **A**bsence of active neoplasia/of an organ or stem-cell transplant, **S**erum creatinine, **M**ean corpuscular value; **I**nternational normalized ratio and **C**ombined hemolysis variable) is the most validated.[2]

The cornerstones of treatment are therapeutic plasma exchange (TPE), corticosteroids and caplacizumab.[3] Caplacizumab is a nanobody that targets the A1 domain of the von Willebrand factor (VWF) and inhibits the interaction with platelets, thus preventing thromboses.[4] In the HERCULES phase 3 randomized trial, caplacizumab proved its superiority over placebo in reducing time to platelet normalization and TTP-related events including TTP exacerbations/resistance and death.[5] These results were recently confirmed in real-life cohorts.[6,7]

So far, definitions of response, exacerbation, remission, and relapse have been based on platelet count and benchmarked against the timing of discontinuation of daily TPE.[8] The advent of anti-VWF therapy and the increased ability to test ADAMTS-13 in many centers have recently prompted a revision of response criteria with incorporation of ADAMTS-13 activity.[9]

We hereby report three cases of ITTP followed at our hematology center, in which the updated response criteria were used to personalize the therapeutic approach and optimize the use of rituximab and caplacizumab. This was of importance also in light of the current coronavirus disease 2019 (COVID-19) pandemic. To this end, ADAMTS-13 activity and autoantibodies were performed systematically every 5 days.

2 | CASE DESCRIPTIONS

2.1 | Case report 1

In December 2020, a 73-year-old woman was admitted to the emergency room (ER) with paresthesia of the left upper extremity, dysarthria, and headache (Figure 1A). A brain computed tomography (CT) scan showed an acute ischemic lesion in the left frontal area. Medical history included type 2 diabetes, hypertension, dyslipidemia, and acute myocardial infarction (2015).

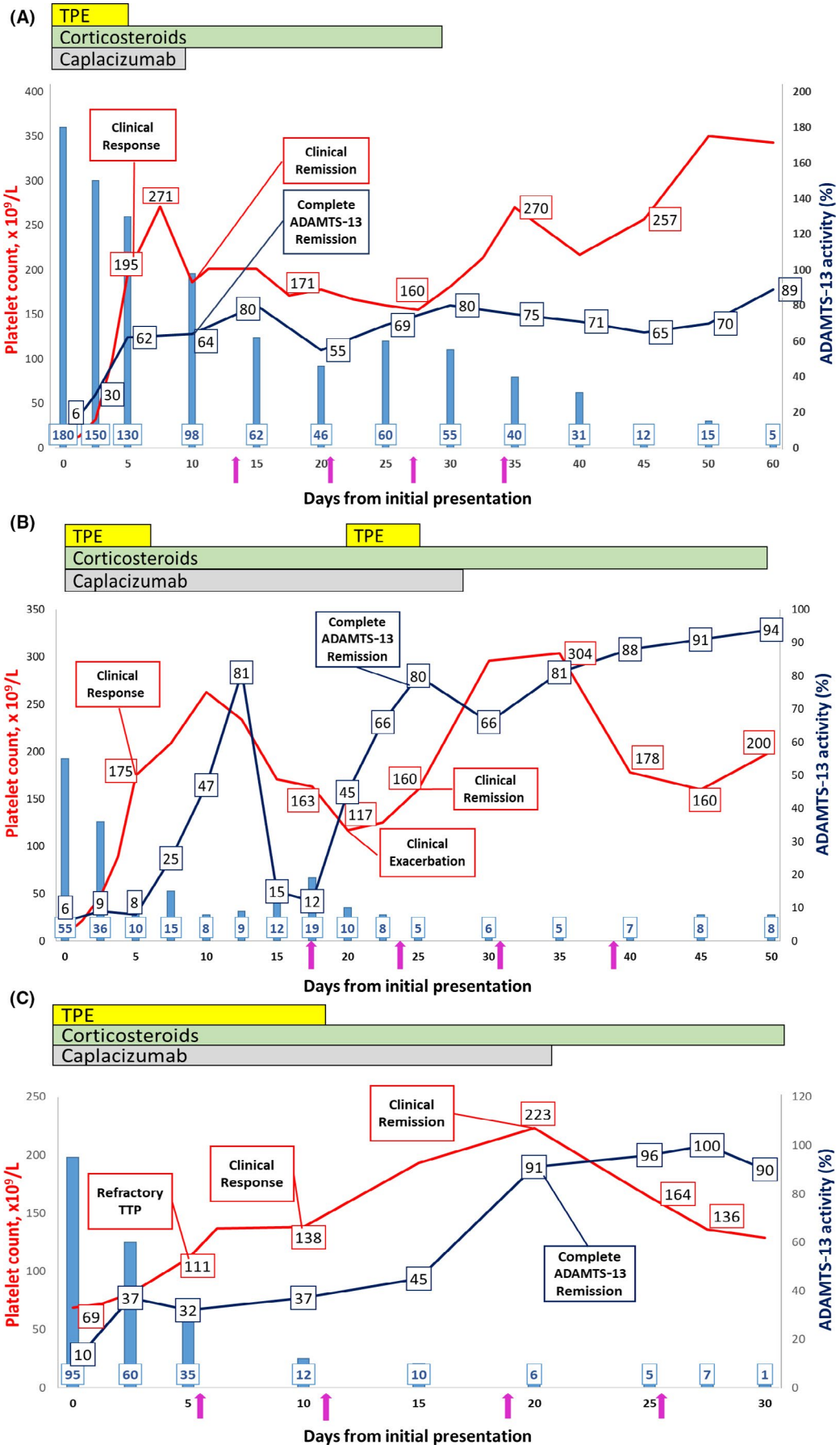
Laboratory tests showed mild hemolytic Coombs-negative anemia (hemoglobin [Hb], 9.5 g/dL) and severe thrombocytopenia (platelet count, 13×10^9/L), 3% schistocytes on peripheral blood smear, increased lactate dehydrogenase (LDH; 1190 U/L), increased indirect bilirubin (total bilirubin, 2.5 mg/dL, indirect bilirubin, 2.2 mg/dL), haptoglobin <30 mg/dL with normal renal function (creatinine 1.24 mg/dL), and coagulative parameters (PLASMIC score, 7). Based on the features, we assumed a diagnosis of ITTP, and we started treatment with TPE, caplacizumab, and prednisone. Twenty-four hours later, baseline ADAMTS-13 activity was 6%, with elevated antibodies titer (180 U/mL). Clinical response was achieved on day 5 from TPE start; accordingly, daily TPE was stopped. On day 10, the patient was in complete ADAMTS-13 remission, and caplacizumab was discontinued. Despite a stable ADAMTS-13 remission, anti–ADAMTS-13 antibody titer was persistently high (98 U/mL). Based on this laboratory pattern, rituximab was started on day 13, with progressive decrease of antibody titer and no TTP exacerbations. On day 60, the patient was in stable ADAMTS-13 remission.

2.2 | Case report 2

In January 2021, a 49-year-old man was admitted to the ER due to fever, macrohematuria, and skin petechiae over the previous week (Figure 1B). Soon after admission, he suffered a transient ischemic attack (transient aphasia with negative brain CT scan). Nasal swab was negative for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Medical history included obesity and presence of lupus anticoagulant and antiphospholipid antibodies and deficiency of factor XII.

Laboratory tests showed Coombs-negative hemolysis (Hb. 10.3 g/dL) and severe thrombocytopenia (platelet count, 22×10^9/L), 4% schistocytes on peripheral blood smear, increased LDH (1034 U/L), increased indirect bilirubin (total bilirubin, 2.2 mg/dL; indirect bilirubin, 1.8 mg/dL), haptoglobin <30 mg/d with normal renal function (creatinine, 1.07 mg/dL) and coagulative tests (PLASMIC score, 7). Based on the features, we assumed a diagnosis of ITTP, and we started treatment with TPE, caplacizumab and prednisone. Notably, a secondary ITTP could be suspected because of

FIGURE 1 Clinical course of the three patients (1A, 1B, and 1C) with ITTP followed at our hematology center. No bleeding or thrombotic episodes were reported during caplacizumab therapy. Corticosteroids consisted in prednisone, starting dose 1 mg/kg/d. Purple arrows indicate rituximab 375 mg/m^2. The anti–ADAMTS-13 autoantibody titers are shown as light blue columns. ADAMTS-13 activity and platelet count are represented by dark blue and red lines, respectively. Clinical response was assessed using revised response criteria and included resolution of neurological signs in patient 1. A clinical remission is defined as sustained clinical response with either (i) no TPE and no anti-VWF therapy for ≥30 days or (ii) with attainment of ADAMTS-13 remission (partial or complete), whichever occurs first. Our patients were defined in clinical remission because they met this second definition (ie, they had achieved an ADAMTS-13 remission). According to update response criteria, partial ADAMTS-13 remission is defined as ADAMTS-13 activity ≥20%, while complete ADAMTS13 remission requires an activity to be the lower limit of normalor greater. Notably, an ADAMTS-13 relapse may occur in patients with clinical response.[9] ADAMTS-13 activity and anti–ADAMTS-13 autoantibodies of IgG class were assessed by a commercially available ELISA (TECHNOZYM ADAMTS-13 INH; Technoclone, Vienna, Austria).[21] According to the manufacturer's specifications, a titer of >15 U/mL represents a positive anti–ADAMTS-13 autoantibody result (negative, <12 U/mL; and undetermined, 12-15 U/mL). ADAMTS-13 activity >50% corresponded to the lower limit of normal in our laboratory. Von Willebrand factor activity (eg, VWF:GPIbR or VWF:GPIbM) was not used to monitor caplacizumab. TPE, therapeutic plasma exchange; TTP, thrombotic thrombocytopenic purpura


(A)
TPE
Corticosteroids
Caplacizumab
Clinical Response
Clinical Remission
Complete ADAMTS-13 Remission
Platelet count, x 10⁹/L
ADAMTS-13 activity (%)
Days from initial presentation
(B)
TPE
TPE
Corticosteroids
Caplacizumab
Complete ADAMTS-13 Remission
Clinical Response
Clinical Remission
Clinical Exacerbation
Platelet count, x 10⁹/L
ADAMTS-13 activity (%)
Days from initial presentation
(C)
TPE
Corticosteroids
Caplacizumab
Clinical Remission
Clinical Response
Refractory TTP
Complete ADAMTS-13 Remission
Platelet count, x10⁹/L
ADAMTS-13 activity (%)
Days from initial presentation

the presence of antiphospholipid antibodies. However, the patient never met the clinical criterium for antiphospholipid antibody syndrome diagnosis (vascular thrombosis).

Twenty-four hours later, baseline ADAMTS-13 activity was 6%, with anti–ADAMTS-13 antibodies 55 U/mL. On day 5, a clinical response was achieved, but ADAMTS-13 activity was <20%. Accordingly, daily TPE was stopped and caplacizumab was continued. After a single peak at 81% on day 12 (negative anti–ADAMTS-13 antibodies), ADAMTS-13 activity suddenly decreased to 15% on day 15 (anti–ADAMTS-13–positive antibodies, 12 U/mL). Based on this ADAMTS-13 pattern, rituximab was introduced on day 17 and caplacizumab was continued.

On day 20, a clinical exacerbation was observed (platelet count, 117×10^9/L, increased LDH [540 U/L], no signs of other causes of thrombocytopenia including infections, anti–platelet factor 4 antibodies, concomitant medications that may decrease platelet count). ADAMTS-13 activity was 45%. Daily TPEs were performed until the second clinical response (day 25). On day 27, the patient achieved a confirmed ADAMTS-13 remission, discontinuing caplacizumab. On day 50, the patient remained in ADAMTS-13 remission.

2.3 | Case report 3

In February 2021, a 58-year-old woman was admitted to the cardiology unit of our hospital because of infection of the pouch of her defibrillator, implanted in 2017 due to atrioventricular block. Medical history included Sjogren syndrome, celiac disease, osteoporosis, and deep vein thrombosis requiring anticoagulant therapy since 2017. In 2017, she had also been diagnosed with ITTP and treated with TPE and corticosteroids.

During the hospital stay, a sudden fall in platelet count (69×10^9/L) and Coombs-negative hemolytic anemia (Hb, 9.5 g/dL; LDH, 500 U/L; total bilirubin 1.6 mg/dL; indirect bilirubin, 1 mg/dL) were observed with normal renal function (creatinine, 0.8 mg/dL) (PLASMIC score, 4) (Figure 1C). Since her pathological history, ADAMTS-13 activity was immediately tested and confirmed the relapse of ITTP. Daily TPE, caplacizumab, and corticosteroids were started. On day 5, platelet count remained low, with increased LDH (524 U/L). Due to refractory disease, standard-dose weekly rituximab was introduced. On day 10, a clinical response was achieved and daily TPE was discontinued. Complete ADAMTS-13 remission was achieved on day 15 and confirmed on day 20. Consequently, caplacizumab was discontinued on day 21. On day 30, the patient remained in ADAMTS-13 remission.

3 | DISCUSSION

A weekly evaluation of ADAMTS-13 levels has been recently recommended as standard of care in patients with active ITTP, with the suggestion that caplacizumab be discontinued once ADAMTS-13 remission is achieved, rather than 30 days after the end of daily TPE.[9] Based on postmarketing experience with caplacizumab that observed no TTP recurrences when the drug was stopped in patients with ADAMTS-13 activity >10% regardless of the timing of interruption of daily TPE, the achievement of a stable partial remission (ADAMTS-13 activity >20%) was suggested as the threshold for safe anti-VWF therapy discontinuation.[6-10]

At our institution, ADAMTS-13 was performed every 5 days to ensure a very close monitoring of the disease. This schedule could be escalated as needed (ie, in case of drop of platelet count). Also, caplacizumab was cautiously discontinued only once a complete ADAMTS-13 remission was confirmed in at least two subsequent evaluations. This allowed an early discontinuation of caplacizumab (5, 7, and 10 days after cessation of daily TPE), with no disease exacerbations. In patient 2, a single ADAMTS-13 activity >50% (corresponding to the lower limit of normal) was followed by acute ADAMTS-13 relapse. Whether this fluctuation was real or was caused by laboratory variability is uncertain. Also, the minimum ADAMTS-13 level and duration above which patients are protected from relapse is unclear. Regardless, this observation may support the importance to validate twice ADAMTS-13 remission before making therapeutic decisions in real life. Also, we observed that the drop in ADAMTS-13 activity was followed by clinical exacerbation, confirming ADAMTS-13 as an early biomarker of disease relapse.[11-13]

Early rituximab administration, along with TPE, corticosteroids, and caplacizumab, has been shown to improve prognosis in ITTP.[14,15] The front-line use of rituximab was consequently recommended (with a very low certainty of evidence) by the ISTH guidelines.[3] However, the SARS-CoV-2 pandemic represented a relative contraindication to escalated immunosuppression with rituximab that could cause a more severe COVID-19 syndrome in case of infection. To avoid unnecessary treatment, at our institution rituximab use was guided by the kinetics of ADAMTS-13 activity/antibodies rather than by platelet count (persistently high antibody titer in patient 1; sudden and severe decline in ADAMTS-13 activity in patient 2; low ADAMTS-13 activity with refractory ITTP in patient 3).[3] Notably, the administration of rituximab in patient 1, while ADAMTS-13 activity was normal is not part of the standard of care.[3] However, anti–ADAMTS-13 antibodies were persistently high and they may play a pathogenic role, increasing the likelihood of recurrences in presence of normal ADAMTS-13 activity.[11,16]

Also, according to current guidelines, rituximab front-line should have been considered in patient 3 who presented a relapse of ITTP with possible additional pathogenetic factors contributing to thrombocytopenia, as suggested by a refractory ITTP with 32% ADAMTS-13 activity on day 5 and by the drop in platelet count on day 27. However, the patient had an active infection and was hospitalized during the COVID-19 worldwide pandemic. In this case, availability of caplacizumab with timely and prospective monitoring of ADAMTS-13 activity allowed judicious use of rituximab, that may increase the risk of infections including COVID-19–related death and complications.[17-20]

Finally, a drop in platelet count was observed in all patients soon after caplacizumab discontinuation, in absence of disease exacerbation/relapse. Whether this phenomenon was related to early caplacizumab discontinuation, with persistence of circulating VWF multimers, or to other variables, remains to be clarified. Nonetheless, no severe cases of thrombocytopenia or major bleedings were observed.

Overall, a center treating ITTP patients needs the laboratory facilities to have an ADAMTS-13 activity assay (and optimally also an

ADAMTS-13 inhibitor assay, and possibly an anti–ADAMTS-13 autoantibody assay by ELISA) within a short time frame, optimally within 24 hours but at least within 3 days.[3,13] This will also be needed for optimally guiding the anti-VWF therapy, currently caplacizumab.

Prospective studies are needed to define the threshold of ADAMTS-13 activity required for safe discontinuation of caplacizumab. Despite growing evidence that ADAMTS-13 tailored treatment duration is safe and effective, this approach still cannot be recommended in routine practice and standard duration of caplacizumab therapy, according to marketing authorization, is still 30 days after the end of TPE.

Overall, these ITTP cases illustrate the value of updated definitions and systematic follow-up of ADAMTS-13 activity/antibodies to personalize treatment strategy in real-life practice.

ACKNOWLEDGMENTS

We thank Prof. Flora Peyvandi for her valuable advice in the preparation of the manuscript.

RELATIONSHIP DISCLOSURE

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

FP, CDP, GA, and NV designed and coordinated the study. FP, CDP, and GA wrote the paper. All authors revised and gave final approval, and DB prepared and submitted the final manuscript.

ORCID

Francesca Palandri https://orcid.org/0000-0001-8367-5668
Christian Di Pietro https://orcid.org/0000-0002-9970-5021
Daniela Bartoletti https://orcid.org/0000-0003-2036-2896
Giuseppe Auteri https://orcid.org/0000-0001-5769-6772

REFERENCES

1. Kremer Hovinga JA, Coppo P, Lämmle B, Moake JL, Miyata T, Vanhoorelbeke K. Thrombotic thrombocytopenic purpura. *Nat Rev Dis Prim*. 2017;3:17020. https://doi.org/10.1038/nrdp.2017.20
2. 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. *Lancet Haematol*. 2017;4:e157-e164. https://doi.org/10.1016/s2352-3026(17)30026-1
3. Zheng XL, Vesely SK, Cataland SR, et al. ISTH guidelines for treatment of thrombotic thrombocytopenic purpura. *J Thromb Haemost*. 2020;18:2496-2502. https://doi.org/10.1111/jth.15010
4. Hanlon A, Metjian A. Caplacizumab in adult patients with acquired thrombotic thrombocytopenic purpura. *Ther Adv Hematol*. 2020;11:2040620720902904. https://doi.org/10.1177/2040620720902904
5. Scully M, Cataland SR, Peyvandi F, et al. Caplacizumab treatment for acquired thrombotic thrombocytopenic purpura. *N Engl J Med*. 2019;380:335-346. https://doi.org/10.1056/NEJMoa1806311
6. Völker LA, Kaufeld J, Miesbach W, et al. Real-world data confirm the effectiveness of caplacizumab in acquired thrombotic thrombocytopenic purpura. *Blood Adv*. 2020;4:3085-3092. https://doi.org/10.1182/bloodadvances.2020001973
7. Dutt T, Shaw RJ, Stubbs M, et al. Real-world experience with caplacizumab in the management of acute TTP. *Blood*. 2021;137:1731-1740. https://doi.org/10.1182/blood.2020007599
8. Scully M, Cataland S, Coppo P, et al. Consensus on the standardization of terminology in thrombotic thrombocytopenic purpura and related thrombotic microangiopathies. *J Thromb Haemost*. 2017;15:312-322. https://doi.org/10.1111/jth.13571
9. Cuker A, Cataland SR, Coppo P, et al. Redefining outcomes in immune TTP: an international working group consensus report. *Blood*. 2021;137:1855-1861. https://doi.org/10.1182/blood.2020009150
10. Völker LA, Kaufeld J, Miesbach W, et al. ADAMTS13 and VWF activities guide individualized caplacizumab treatment in patients with aTTP. *Blood Adv*. 2020;4:3093-3101. https://doi.org/10.1182/bloodadvances.2020001987
11. Peyvandi F, Lavoretano S, Palla R, et al. ADAMTS13 and anti-ADAMTS13 antibodies as markers for recurrence of acquired thrombotic thrombocytopenic purpura during remission. *Haematologica*. 2008;93:232-239. https://doi.org/10.3324/haematol.11739
12. Sui J, Cao W, Halkidis K, et al. Longitudinal assessments of plasma ADAMTS13 biomarkers predict recurrence of immune thrombotic thrombocytopenic purpura. *Blood Adv*. 2019;3:4177-4186. https://doi.org/10.1182/bloodadvances.2019000939
13. Roose E, Schelpe AS, Tellier E, et al. Open ADAMTS13, induced by antibodies, is a biomarker for subclinical immune-mediated thrombotic thrombocytopenic purpura. *Blood*. 2020;136:353-361. https://doi.org/10.1182/blood.2019004221
14. Westwood JP, Webster H, McGuckin S, McDonald V, Machin SJ, Scully M. Rituximab for thrombotic thrombocytopenic purpura: benefit of early administration during acute episodes and use of prophylaxis to prevent relapse. *J Thromb Haemost*. 2013;11:481-490. https://doi.org/10.1111/jth.12114
15. Owattanapanich W, Wongprasert C, Rotchanapanya W, Owattanapanich N, Ruchutrakool T. Comparison of the long-term remission of rituximab and conventional treatment for acquired thrombotic thrombocytopenic purpura: a systematic review and meta-analysis. *Clin Appl Thromb Hemost*. 2019;25:1076029618825309. https://doi.org/10.1177/1076029618825309
16. Froehlich-Zahnd R, George JN, Vesely SK, et al. Evidence for a role of anti-ADAMTS13 autoantibodies despite normal ADAMTS13 activity in recurrent thrombotic thrombocytopenic purpura. *Haematologica*. 2012;97:297-303. https://doi.org/10.3324/haematol.2011.051433
17. Tepasse PR, Hafezi W, Lutz M, et al. Persisting SARS-CoV-2 viraemia after rituximab therapy: two cases with fatal outcome and a review of the literature. *Br J Haematol*. 2020;190:185-188. https://doi.org/10.1111/bjh.16896
18. Quartuccio L, Treppo E, Binutti M, Del Frate G, De Vita S. Timing of rituximab and immunoglobulin level influence the risk of death for COVID-19 in ANCA-associated vasculitis. *Rheumatology*. 2021;60(7):3476-3477. https://doi.org/10.1093/rheumatology/keab175
19. Smith JS, Said JT, Elman SA, Smith CEP, Merola JF. Seroconversion of severe acute respiratory syndrome coronavirus 2-infected patients on immunosuppression: a retrospective analysis. *J Am Acad Dermatol*. 2021;84:1409-1412. https://doi.org/10.1016/j.jaad.2021.01.100
20. Gerber V, Velay A, Boehn L, et al. Protracted SARS-CoV-2 pneumonia with rituximab treatment: about two cases. *J Med Virol*. 2021;93:4141-4144. https://doi.org/10.1002/jmv.26921
21. Tripodi A, Peyvandi F, Chantarangkul V, et al. Second international collaborative study evaluating performance characteristics of methods measuring the von Willebrand factor cleaving protease (ADAMTS-13). *J Thromb Haemost*. 2008;6:1534-1541. https://doi.org/10.1111/j.1538-7836.2008.03099.x

How to cite this article: Palandri F, Di Pietro C, Ricci F, et al. Immune thrombotic thrombocytopenic purpura: Personalized therapy using ADAMTS-13 activity and autoantibodies. *Res Pract Thromb Haemost*. 2021;5:e12606. https://doi.org/10.1002/rth2.12606