

Conflict-of-interest disclosure: W.B.-E. reported receiving grants (site PI for multicenter study) from Gilead Sciences and funds to institution and grants from VA Health Services Research and Development Service outside of the submitted work. M.B. reported receiving nonfinancial support from the VA Cooperative Studies Program during the conduct of the study. A.Y.L. reported receiving grants from the Department of Defense outside of the submitted work. N.C.M. reported receiving personal fees from Bristol Myers Squibb, Janssen, Amgen, Takeda, OncoPep, AbbVie, Karyopharm, Novartis, Legend, Raqia, Adaptive Biotechnology, and Pfizer outside the submitted work; in addition, N.C.M. had a patent for OncoPep licensed and held stocks in C4 Therapeutics. The remaining authors declare no competing financial interests.

ORCID profiles: J.T.-Y.W., 0000-0003-2388-1827; W.B.-E., 0000-0002-9658-5124; L.H., 0000-0002-2266-7610; S.S.H., 0000-0002-2013-6883; A.Y.L., 0000-0002-7150-4623; N.R.F., 0000-0002-8058-3423.

Correspondence: Nikhil C. Munshi, VA Boston Healthcare System, Dana-Farber Cancer Institute, Harvard Medical School, Jerome Lipper Multiple Myeloma Center, 450 Brookline Ave, Boston, MA 02215; e-mail: nikhil_munshi@dfci.harvard.edu.

Footnotes

Submitted 16 March 2022; accepted 30 April 2022; prepublished online on *Blood* First Edition 23 May 2022.

*J.L., J.T.-Y.W., N.R.F., and N.C.M. contributed equally to this study.

†J.L. and J.T.-Y.W. are joint first authors.

‡N.R.F., and N.C.M. are joint senior authors.

REFERENCES

- Chari A, Samur MK, Martinez-Lopez J, et al. Clinical features associated with COVID-19 outcome in multiple myeloma: first results from the International Myeloma Society data set. *Blood*. 2020;136(26):3033-3040.
- Wang L, Berger NA, Xu R. Risks of SARS-CoV-2 breakthrough infection and hospitalization in fully vaccinated patients with multiple myeloma. *JAMA Netw Open*. 2021;4(11):e21137575.
- Terpos E, Trougakos IP, Gavriatopoulou M, et al. Low neutralizing antibody responses against SARS-CoV-2 in older patients with myeloma after the first BNT162b2 vaccine dose. *Blood*. 2021;137(26):3674-3676.
- Henriquez S, Zerbit J, Bruel T, et al. Anti-CD38 therapy impairs SARS-CoV-2 vaccine response against alpha and delta variants in multiple myeloma patients. *Blood*. 2022;139(6):942-946.
- Van Oekelen O, Gleason CR, Agte S, et al; PVI/Seronet team. Highly variable SARS-CoV-2 spike antibody responses to two doses of COVID-19 RNA vaccination in patients with multiple myeloma. *Cancer Cell*. 2021;39(8):1028-1030.
- Ludwig H, Sonneveld P, Facon T, et al. COVID-19 vaccination in patients with multiple myeloma: a consensus of the European Myeloma Network. *Lancet Haematol*. 2021;8(12):e934-e946.
- Wu JT-Y, La J, Branch-Elliman W, et al. Association of COVID-19 vaccination with SARS-CoV-2 infection in patients with cancer: a US Nationwide Veterans Affairs Study. *JAMA Oncol*. 2022;8(2):281-286.
- Terpos E, Gavriatopoulou M, Ntanasis-Stathopoulos I, et al. The neutralizing antibody response post COVID-19 vaccination in patients with myeloma is highly dependent on the type of anti-myeloma treatment. *Blood Cancer J*. 2021;11(8):138.
- Rognvaldsson S, Eythorsson E, Thorsteinsdottir S, et al. Monoclonal gammopathy of undetermined significance and COVID-19: a population-based cohort study. *Blood Cancer J*. 2021;11(12):191.
- Chan WY, Howells L, Wilson W, et al. Serological response to the BNT162b2 mRNA or ChAdOx1 nCoV-19 COVID-19 vaccine after first and second doses in patients with plasma cell disorders: influence of host and disease factors. *Br J Haematol*. 2022;196(3):e21-e26.
- Fillmore NR, Yellapragada SV, Ifeorah C, et al. With equal access, African American patients have superior survival compared to white patients with multiple myeloma: a VA study. *Blood*. 2019;133(24):2615-2618.
- Fillmore NR, La J, Zheng C, et al. The COVID-19 hospitalization metric in the pre- and post-vaccination eras as a measure of pandemic severity: a retrospective, nationwide cohort study. *Infect Control Hosp Epidemiol*. 2022;1-24.
- Kompaniyets L, Pennington AF, Goodman AB, et al. Underlying medical conditions and severe illness among 540,667 adults hospitalized with COVID-19, March 2020–March 2021. *Prev Chronic Dis* 2021;18:E66. <http://dx.doi.org/10.5888/pcd18.210123external>.
- Dona' A, Viola D, Caserta E, et al. Proteasome inhibitors impair the innate antiviral immune response and potentiate pelareorep-based viral therapy in multiple myeloma [abstract]. *Blood*. 2019;134(suppl_1):Abstract 1816.

DOI 10.1182/blood.2022016317

© 2022 by The American Society of Hematology. Licensed under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0), permitting only noncommercial, nonderivative use with attribution. All other rights reserved.

TO THE EDITOR:

Prevalence of neuropsychiatric symptoms and stroke in patients with hereditary thrombotic thrombocytopenic purpura

Azra Borogovac,¹ Erika Tarasco,^{2,3} Johanna A. Kremer Hovinga,^{2,3} Kenneth D. Friedman,⁴ Adam S. Asch,¹ Sara K. Vesely,⁵ Calin I. Prodan,⁶ Deirdra R. Terrell,⁵ and James N. George^{1,5}

¹Hematology-Oncology Section, Department of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK; ²Department of Hematology and Central Hematology Laboratory, Inselspital, Bern University Hospital, and ³Department for BioMedical Research (DBMR), University of Bern, Bern, Switzerland; ⁴Hematology-Oncology Section, Department of Medicine, Medical College of Wisconsin, Milwaukee, WI; ⁵Department of Biostatistics and Epidemiology, Hudson College of Public Health, Oklahoma City, OK; and ⁶Department of Neurology, University of Oklahoma Health Sciences Center, Oklahoma City, OK

Hereditary thrombotic thrombocytopenic purpura (hTTP) is a rare (0.5-2.0 patients per 10^6 population) autosomal recessive disorder caused by a severe deficiency of ADAMTS13, a plasma metalloprotease that cleaves ultralarge von Willebrand factor (ULVWF).¹ The persisting ULVWF multimers can create von Willebrand factor-platelet microthrombi causing microvascular thrombosis and organ ischemia.¹ The clinical features of hTTP are extremely diverse. Some patients appear to have excellent health, whereas others may die soon after birth or have major morbidities.^{2,3} Patients with immune-mediated TTP (iTTP) often have disorders of cognitive function, depression,⁴⁻¹⁰ and silent cerebral infarctions during clinical remission.¹¹⁻¹⁴ Stroke is also frequent in patients who have reduced ADAMTS13 activity (median, 43%) during remission following iTTP.¹⁵ Aims of the present study were to determine the neurological long-term effects in patients with hTTP by documenting their rates of stroke, stroke-related disability, and presence of neuropsychiatric symptoms.

Patients living in the United States who had enrolled and previously consented to participate in the International hTTP Registry³ were contacted to schedule an interview. Those interested signed a new consent to participate in this study. Hereditary TTP was confirmed in all patients by identification of biallelic pathogenic ADAMTS13 mutations and ADAMTS13 activity <10%. Author A.B. interviewed the patients and/or parents of minors by telephone for 30 to 60 minutes using discussion guides specific for young children (≤ 6 years old), older children (7-17 years), or adults (≥ 18 years old). Participants were asked about neuropsychiatric symptoms (Table 1) and stroke, the age they occurred, and residual symptoms or disability. The occurrence of stroke was accepted from the patients' descriptions of symptoms, diagnostic evaluations, diagnosis conveyed to them by treating physicians, and clinical course. Participants were also asked about prophylaxis, when it began, and any adverse reactions. The interview questions regarding hospitalizations, prophylaxis, and stroke are detailed in supplemental Table 1, available on the *Blood* Web site. Neuropsychiatric symptoms were compared between patients with or without history of stroke.

As of July 2021, 45 US patients with confirmed hTTP had been enrolled into the International hTTP Registry. Twelve previously enrolled US patients had been lost to follow-up, 2 died, and 4 did not consent (supplemental Figure 1). Twenty-seven patients from 17 US states were interviewed between April 2020 and July 2021: 25 adults (ages 19-63 years, median age, 38 years) and 2 children (ages 20 months and 12 years). The participants were predominantly female (70%) and white (89%) and had a college or postgraduate education (72%) (supplemental Table 2). The patients' sex, mutations, number of strokes, age of first symptoms, diagnosis, and follow-up are presented in supplemental Table 3. Twenty-five of 26 (96%) patients (excluding the infant) reported 2 to 14 (median, 6) of the 14 neuropsychiatric symptoms (Table 1). Symptom onset occurred across all ages. Common symptoms were recurrent headaches (88%), poor concentration (65%), and depression (62%). Headache with aura (presumed migraine) was reported by 15 (58%) patients. Only dysarthria was more common in patients with a history of stroke (Table 1). The symptoms were often described as beginning during "childhood," during "high school," or after a

significant hTTP event, such as a hospitalization. These data suggest that patients of all ages are at risk for neuropsychiatric symptoms.

Strokes had occurred in 17 (63%; 95% confidence interval, 42%-81%) patients. The median age of the first stroke was 26 years (range, newborn to 58 years); the occurrence increased with age (Figure 1). All 6 patients whose age was ≥ 49 years had had a stroke. In 12 patients, stroke preceded the diagnosis of hTTP. Three of the 12 patients were diagnosed at the time of their first stroke; the other 9 patients were diagnosed with hTTP 2 months to 19 years after their first stroke. Eleven of the 17 patients had residual symptoms; 7 suffered recurrent strokes. Seven patients have received stroke-related disability benefits, beginning at a median age of 43 years (18-55 years) (supplemental Table 4).

Twenty-five (93%) patients had received plasma for treatment of symptoms or for prophylaxis; 21 patients described allergic reactions to plasma: rash/itching (14), dyspnea/chest pain (4), anaphylaxis (2), or infection (1 [hepatitis C]) (supplemental Table 5). Seventeen (63%) of the 27 patients were on prophylaxis at the time of interview: 12, plasma; 5, pdFVIII. Prophylaxis was begun at age 2 months to 63 years (median, 30 years) and continued for a duration of 1 to 53 years (median, 4.5 years). None of the 17 patients were on prophylaxis at the time of their first stroke. Of the 7 patients with recurrent strokes, none received prophylaxis at the time of their second stroke but were subsequently placed on prophylaxis. Four of those 7 had another stroke while on prophylaxis. Five patients who switched to pdFVIII from plasma reported improved convenience of self-administration.

Like patients in remission from iTTP, almost all patients with hTTP have neuropsychiatric symptoms. Our data emphasize that patients with hTTP have life-altering neuropsychiatric symptoms beginning at young ages that continue throughout their lives. The occurrence of neuropsychiatric symptoms must be confirmed in future studies using standardized assessments, such as the Repeatable Battery for the Assessment of Neuropsychological Status for cognitive decline and the Patient Health Questionnaire-9, for depression.⁴⁻⁷ The impact of the neuropsychiatric symptoms on the patients' lives must be described by qualitative evaluation.¹⁶

Fifty-eight percent of patients had headaches with aura, presumed migraine. Previous studies have demonstrated that migraine with aura is an independent risk factor for stroke, especially cryptogenic ischemic stroke,¹⁷ and is associated with silent brain infarcts.¹⁸ The high frequency of strokes among patients with hTTP suggests that the neuropsychiatric symptoms may be caused by silent cerebral infarction, similar to patients with iTTP.¹¹⁻¹⁴ The overall occurrence of stroke was 63%, more than twice the rate from prior reports, possibly because the median age of our patients is >10 years older than in prior reports,^{2,3} because patients with stroke may be more likely to be enrolled in the Registry and to participate in this study, or because of the small size of this study. Strokes often preceded the diagnosis of hTTP. Therefore, in patients with an embolic stroke of undetermined source,^{19,20} measurement of ADAMTS13 activity is important.

Table 1. Recurrent neuropsychiatric symptoms stratified by history of stroke

Neuropsychiatric symptoms* with associated questions	All 26 patients† (%)	10 patients No stroke (%)	16 patients Stroke (%)	P‡
Headaches Do you have regular headaches?	23 (88)	10 (100)	13 (81)	.26
Poor concentration Do you feel that you have poor concentration? For example, do you have difficulty focusing on a task or at work/school?	17 (65)	6 (60)	11 (69)	.70
Depression Have you ever had significant depression, now or in the past?	16 (62)	6 (60)	10 (63)	1.0
Headache with aura (presumed migraine)§ Do you have any vision changes prior to your headaches?	15 (58)	7 (70)	8 (50)	.43
Vision changes Do you ever get blurry vision or changes in your vision?	12 (46)	4 (40)	8 (50)	.70
Forgetfulness Do you feel that you often forget things, or your memory is not as good as others around you?	12 (46)	3 (30)	9 (56)	.25
Fatigue Do you often feel very tired or like your whole body is weak?	12 (46)	4 (40)	8 (50)	1.0
Neuropathy Do you ever feel numbness or tingling in your hands or feet?	11 (42)	2 (20)	9 (56)	.11
Dysarthria Do you ever have difficulty with speaking, such as slurring of your speech?	10 (38)	1 (10)	9 (56)	.04
Loss of vision Do you ever have loss of vision?	7 (27)	3 (30)	4 (25)	1.0
Seizure Have you ever had a seizure?	6 (23)	2 (20)	4 (40)	1.0
Transient weakness Do you ever have sudden weakness in 1 part of the body, such as an arm or leg?	5 (19)	1 (10)	4 (25)	.39
Falls Have you fallen frequently?	5 (19)	1 (10)	4 (25)	.62
Dysphagia Do you ever have difficulty swallowing?	3 (12)	0	3 (19)	.26
No symptoms	1 (4)	0	1 (6)	NA

NA, not applicable.

*These neuropsychiatric symptoms were chosen based on the interviews with hTTP patients. All questions were followed up with: "How often? When did it start? Please describe."

†The 20-mo-old patient is not included in the table because these symptoms did not apply to him. His parents were only asked about seizures, which he did not have. He appears to have normal development.

‡ χ^2 analysis or Fisher's exact test (if there were <5 subjects per category) was performed to assess the difference in frequency of symptoms in patients with or without stroke.

§Patients were asked about auras as a follow-up question if they answered yes to having headaches. The auras were described as "sparkly eyes," "flashes of lights," "wavy lines," or transient vision loss.

||The asymptomatic patient is a 12-y-old girl who was diagnosed at birth after having cardiac arrest and stroke as a newborn. She currently reports no symptoms since the start of the plasma-derived factor VIII concentrate (pdFVIII) for prophylaxis.

Our data emphasize the significance of beginning effective, life-time prophylaxis at a young age. Current common practice is to begin plasma prophylaxis when a major complication has occurred. We recommend a baseline cerebral magnetic resonance imaging at the first occurrence of neuropsychiatric

symptoms to identify silent strokes and to document the need for prophylactic therapy.¹¹⁻¹⁴ However, the inconvenience of plasma administration and the frequent allergic reactions to plasma may cause hesitancy to begin prophylaxis and insufficient frequency once prophylaxis has begun. A report of the

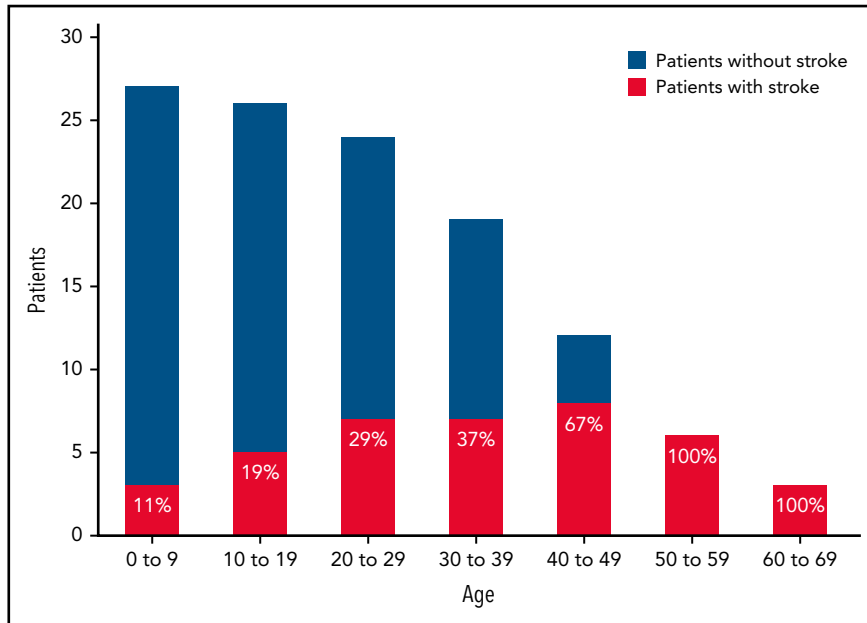


Figure 1. Frequency of the initial occurrence of stroke related to decade of life. Each bar represents the total number of patients within each age group. For example, all 27 patients are represented in the 0 to 9 age group, of which 3 (11%) had a stroke before age 10 years. All 6 patients who were 50 years or older at the time of interview had a previous stroke.

International hTTP Registry found no statistical difference in the frequency of acute episodes of hTTP in patients with or without prophylactic plasma.²¹ These observations highlight the limitations of current prophylaxis. Until recombinant ADAMTS13²² is available, an adequate amount of plasma (≥ 15 mL/kg) at frequent intervals (≤ 2 weeks) to maintain ADAMTS13 activity is appropriate.

Our data have significant limitations. The number of patients is small because hTTP is a rare disorder.¹ In addition, there is potential for selection bias, as enrollment into the International hTTP Registry requires motivation of the patient and awareness of the Registry by the patient's hematologist.

Despite these limitations, our data document that almost all patients have neuropsychiatric symptoms, suggesting the need for regular cognitive and depression screening of hTTP and effective prophylaxis when abnormalities are identified.

Acknowledgments

The authors acknowledge everyone who contributes to the International Hereditary TTP Registry, including patients, researchers, and the financial support from Takeda, Inc.

Authorship

Contribution: A.B. conducted all interviews, collected and synthesized the data, designed the tables and figures, and wrote the manuscript; E.T. and J.A.K.H. were key in the recruitment of patients and management of data through the International hTTP Registry; K.D.F. and J.A.K.H. performed the genetic testing; A.S.A., S.K.V., C.I.P., D.R.T., and J.N.G. are mentors for A.B. and provided valuable suggestions and insight throughout this study; J.N.G. created the concept for this study and helped with writing the initial versions of the manuscript; and all authors edited the manuscript and approved of the final version before submission.

Conflict-of-interest disclosure: J.A.K.H. has received a grant from Baxalta US Inc; serves as consultancy and on the speakers bureau for Shire and

Abylnx; serves as consultancy for the Federal Office of Public Health; and is currently employed by Insel Gruppe AG. K.D.F. serves as consultancy for Bayer, Siemens, Genentech, Sanofi, and Instrumentation Laboratories and serves on the speakers bureau for Alexion. C.I.P. has received a grant from US Department of Veterans Affairs Merit award CX000340 and the Oklahoma Center for the Advancement of Science and Technology grant OCAST HR 19-111. The remaining authors declare no competing financial interests.

ORCID profiles: A.B., 0000-0002-5093-1634; E.T., 0000-0002-4387-8476; J.A.K.H., 0000-0002-1300-7135; S.K.V., 0000-0003-3448-0156; D.R.T., 0000-0003-0794-5851; J.N.G., 0000-0002-4243-2691.

Correspondence: Azra Borogovac, University of Oklahoma Health Sciences Center, Stephenson Cancer Center, 800 NE 10th St, Room 5029, Oklahoma City, OK 73104; e-mail: azrab88@gmail.com.

Footnotes

Submitted 22 February 2022; accepted 3 May 2022; prepublished online on *Blood* First Edition 18 May 2022.

The online version of this article contains a data supplement.

There is a *Blood* Commentary on this article in this issue.

REFERENCES

1. Kremer Hovinga JA, George JN. Hereditary thrombotic thrombocytopenic purpura. *N Engl J Med*. 2019;381(17):1653-1662.
2. Borogovac A, Reese JA, Gupta S, George JN. Morbidities and mortality in patients with hereditary thrombotic thrombocytopenic purpura. *Blood Adv*. 2022;6(3):750-759.
3. van Dorland HA, Taleghani MM, Sakai K, et al; Hereditary TTP Registry. The International Hereditary Thrombotic Thrombocytopenic Purpura Registry: key findings at enrollment until 2017. *Haematologica*. 2019; 104(10):2107-2115.
4. Lewis QF, Lanneau MS, Mathias SD, Terrell DR, Vesely SK, George JN. Long-term deficits in health-related quality of life after recovery from

- thrombotic thrombocytopenic purpura. *Transfusion*. 2009;49(1):118-124.
5. Kennedy AS, Lewis QF, Scott JG, et al. Cognitive deficits after recovery from thrombotic thrombocytopenic purpura. *Transfusion*. 2009;49(6):1092-1101.
 6. Deford CC, Reese JA, Schwartz LH, et al. Multiple major morbidities and increased mortality during long-term follow-up after recovery from thrombotic thrombocytopenic purpura. *Blood*. 2013;122(12):2023-2029, quiz 2142.
 7. Han B, Page EE, Stewart LM, et al. Depression and cognitive impairment following recovery from thrombotic thrombocytopenic purpura. *Am J Hematol*. 2015;90(8):709-714.
 8. Chaturvedi S, Oluwole O, Cataland S, McCrae KR. Post-traumatic stress disorder and depression in survivors of thrombotic thrombocytopenic purpura. *Thromb Res*. 2017;151:51-56.
 9. Falter T, Schmitt V, Herold S, et al. Depression and cognitive deficits as long-term consequences of thrombotic thrombocytopenic purpura. *Transfusion*. 2017;57(5):1152-1162.
 10. Riva S, Mancini I, Maino A, et al. Long-term neuropsychological sequelae, emotional wellbeing and quality of life in patients with acquired thrombotic thrombocytopenic purpura. *Haematologica*. 2020;105(7):1957-1962.
 11. Cataland SR, Scully MA, Paskavitz J, et al. Evidence of persistent neurologic injury following thrombotic thrombocytopenic purpura. *Am J Hematol*. 2011;86(1):87-89.
 12. Prodan CI, Vijayvargiya P, Feisal JK, Khawandanah MO, Jiang Y, George JN. Embolic stroke of undetermined source in a young woman. *Am J Hematol*. 2019;94(9):1044-1048.
 13. Alwan F, Mahdi D, Tayabali S, et al. Cerebral MRI findings predict the risk of cognitive impairment in thrombotic thrombocytopenic purpura. *Br J Haematol*. 2020;191(5):868-874.
 14. Yu J, Wei A, Pan X-Z, et al. Silent cerebral infarction on brain MRI is associated with cognitive impairment in ITP survivors in hematological remission [abstract]. *Blood*. 2021;138(suppl 1). Abstract 774.
 15. Upreti H, Kasmani J, Dane K, et al. Reduced ADAMTS13 activity during TTP remission is associated with stroke in TTP survivors. *Blood*. 2019;134(13):1037-1045.
 16. Terrell D, Cataland S, Beebe L, et al. Impact of residual effects and complications of thrombotic thrombocytopenic purpura (TTP) on daily living: a qualitative study [abstract]. *Blood*. 2019;134(suppl_1). Abstract 931.
 17. Martinez-Majander N, Artto V, Ylikotila P, et al; SECRETO Study Group. Association between migraine and cryptogenic ischemic stroke in young adults. *Ann Neurol*. 2021;89(2):242-253.
 18. Tietjen GE, Maly EF. Migraine and ischemic stroke in women. A narrative review. *Headache*. 2020;60(5):843-863.
 19. Hart RG, Diener HC, Coutts SB, et al; Cryptogenic Stroke/ESUS International Working Group. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol*. 2014;13(4):429-438.
 20. Delmas Y, Renou P, Sibon I. Hereditary thrombotic thrombocytopenic purpura. *N Engl J Med*. 2020;382(4):393-394.
 21. Tarasco E, Büttikofer L, Friedman KD, et al. Annual incidence and severity of acute episodes in hereditary thrombotic thrombocytopenic purpura. *Blood*. 2021;137(25):3563-3575.
 22. Scully M, Knobl P, Kentouche K, et al. Recombinant ADAMTS-13: first-in-human pharmacokinetics and safety in congenital thrombotic thrombocytopenic purpura. *Blood*. 2017;130(19):2055-2063.

DOI 10.1182/blood.2022016044

© 2022 by The American Society of Hematology

TO THE EDITOR:

Thrombopoietin receptor agonists in adult Evans syndrome: an international multicenter experience

Bruno Fattizzo,^{1,2} Nicola Cecchi,^{1,2} Marta Bortolotti,^{1,2} Giulio Giordano,³ Andrea Patriarca,⁴ Andreas Glenthøj,⁵ Silvia Cantoni,⁶ Marco Capecchi,^{1,2} Frederick Chen,⁷ Maria Eva Mingot-Castellano,⁸ Mariasanta Napolitano,⁹ Henrik Frederiksen,¹⁰ Tomàs José González-Lopez,¹¹ and Wilma Barcellini¹

¹Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; ²Department of Oncology and Hemato-oncology, University of Milan, Milan, Italy; ³Unità Operativa Complessa (UOC), Medicina Servizio e Ambulatorio di Ematologia Ospedale di Riferimento Regionale "Antonio Cardarelli," Campobasso, Italy; ⁴Department of Translational Medicine, University of Eastern Piedmont, Novara, Italy; ⁵Department of Hematology, Copenhagen University Hospital-Rigshospitalet, Copenhagen, Denmark; ⁶Niguarda Cancer Center, Azienda Socio-Sanitaria Territoriale (ASST) Grande Ospedale Metropolitano Niguarda, Milano, Italy; ⁷Clinical Haematology, Barts Health National Health Service (NHS) Trust and Queen Mary University, London, United Kingdom; ⁸Servicio de Hematología, Área de Banco de Sangre y Establecimiento de Tejidos Hospital, Universitario Virgen del Rocío, Sevilla, Spain; ⁹Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties (ProMISE), University of Palermo, Palermo, Italy; ¹⁰Department of Hematology, Odense University Hospital, Odense, Denmark; and ¹¹Servicio de Hematología, Hospital Universitario de Burgos, Burgos, Spain

Evans syndrome (ES) is a rare condition, defined as the presence of 2 autoimmune cytopenias: more frequently, autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP) and, rarely, autoimmune neutropenia (AIN).¹⁻³ ES can be classified as primary or secondary to various conditions, including lymphoproliferative disease, primary immune deficiencies, or other systemic autoimmune diseases. The onset of ES may be acute and life threatening, whereas its clinical course is usually chronic and marked by several relapses of AIHA, ITP, or both. In addition, risks of thrombosis and infections were ~2 times those observed

in primary AIHA or ITP in a recent European study.³ First-line therapy is based on steroids, with or without intravenous immunoglobulins (IVIg), followed by a second-line treatment largely depending on the cytopenia, and include rituximab, splenectomy, and cytotoxic immunosuppressants. Since their arrival, thrombopoietin receptor agonists (TPO-RAs), such as romiplostim and eltrombopag, have been increasingly used in primary ITP with high efficacy, and a good safety profile.⁴ However, their use in ES has never been systematically studied, and only a few case reports are available for this challenging population.⁵⁻¹² In this