Received: 8 April 2022 | Revised: 17 June 2022 | Accepted: 25 July 2022

DOI: 10.1002/rth2.12814

rpth research & practice in thrombosis & haemostasis

ORIGINAL ARTICLE

Hereditary thrombotic thrombocytopenic purpura and COVID-19: Impacts of vaccination and infection in this rare disease

Erika Tarasco PhD[1,2] | Anne Sophie von Krogh MD[3,4] | Radomira Hrdlickova MD[5] | Thomas R. Braschler MD[6] | Teresa Iwaniec PhD[7] | Paul N. Knöbl MD[8] | Eriko Hamada MD[9] | Oleg Pikovsky MD[10] | Stefan Farese MD[11] | Odit Gutwein MD[12] | Petr Kessler MD[13] | Nina H. Schultz MD[14] | Charis von Auer MD[15] | Jerzy Windyga MD[16] | Kenneth Friedman MD[17] | Ingrid Hrachovinova PhD[18] | James N. George MD[19] | Masanori Matsumoto MD[9] | Reinhard Schneppenheim MD[20] | Bernhard Lämmle MD[1,21] | Johanna Anna Kremer Hovinga MD[1,2]

[1]Department of Hematology and Central Hematology Laboratory, Inselspital, Bern University Hospital, Bern, Switzerland

[2]Department for BioMedical Research (DBMR), University of Bern, Bern, Switzerland

[3]Department of Hematology, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway

[4]Department of Clinical and Molecular Medicine, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway

[5]Blood Center, University Hospital Ostrava, Ostrava, Czech Republic

[6]Center for Clinical Hematology, Luzerne Kantonsspital, Lucerne, Switzerland

[7]Department of Hematology, Jagiellonian University Medical College, Krakow, Poland

[8]Division of Hematology and Hemostasis, Department of Medicine I, Medical University of Vienna, Vienna, Austria

[9]Department of Blood Transfusion Medicine, Nara Medical University, Kashihara, Japan

[10]Transfusion Medicine Institute, Faculty of Health Sciences, Ben-Gurion University of the Negev, Soroka University Medical Center, Beer-Sheva, Israel

[11]Department of Nephrology, Burgerspital, Solothurn, Switzerland

[12]Department of Hematology, Shamir Medical Center, Zerifin, Israel

[13]Department of Hematology and Transfusion Medicine, Hospital Pelhrimov, Pelhrimov, Czech Republic

[14]Department of Hematology, Oslo University Hospital, Oslo, Norway

[15]Department of Hematology, Oncology, and Pneumology, Center for Thrombosis and Hemostasis, University Medical Center Mainz, Mainz, Germany

[16]Department of Haemostasis Disorders and Internal Medicine, Institute of Hematology and Transfusion Medicine, Warsaw, Poland

[17]Division of Hematology and Oncology, Versiti Blood Center of Wisconsin, Medical College of Wisconsin, Milwaukee, Wisconsin, USA

[18]Institute of Hematology and Blood Transfusion, Prague, Czech Republic

[19]Department of Biostatistics & Epidemiology, College of Public Health, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA

[20]Department of Pediatric Hematology and Oncology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

[21]Center for Thrombosis and Hemostasis, University Medical Center Mainz, Mainz, Germany

Correspondence
Erika Tarasco, Department of Hematology and Central Hematology Laboratory, Bern University Hospital, Inselspital, CH-3010 Bern, Switzerland.
Email: erika.tarasco@insel.ch

Funding information
Answering TTP Foundation, Grant/Award Number: 1009; Baxalta US Inc, Grant/Award Number: H16-36165; GTH Congress Presidential Fund; ISTH 2007 Presidential Fund; Mach-Gaensslen Foundation Switzerland; NFG Foundation; Schweizerischer Nationalfonds zur Förderung der Wissenschaftlichen Forschung, Grant/Award Number: 310030-185233

Handling Editor: Dr Neil Zakai

Abstract

Introduction: Severe COVID-19 is associated with an important increase of von Willebrand factor and mild lowering of ADAMTS13 activity that may, in the presence of a strong inflammatory reaction, increase the risk of acute thrombotic thrombocytopenic purpura (TTP). Although acute episodes of immune-mediated TTP associated with COVID-19 or SARS-CoV-2 vaccination have been reported, data about clinical evolution of hereditary TTP (hTTP) during the pandemic are scarce.

Method: We conducted a survey among adult patients of the International Hereditary TTP Registry about SARS-CoV-2 vaccination, COVID-19, and occurrence of acute hTTP episodes.

Results: Of 122 adult hTTP patients invited to participate, 86 (70.5%) responded. Sixty-five had been vaccinated (75.6%), of which 14 had received in addition a booster, resulting in 139 individual vaccine shots. Although vaccinations in patients on plasma prophylaxis were done within 1 week of the last plasma infusion, all 23 patients treated with plasma on demand were vaccinated without prior plasma infusions. One patient on uninterrupted weekly plasma infusions presented within 3 days from his second vaccination with neurological symptoms and computed tomography scan 9 days later showed subacute ischemic/hemorrhagic frontal lobe infarction. A second male patient developed acute myocarditis after his second dose of mRNA-1273 vaccine. Twelve (14%) patients had COVID-19, associated with an acute hTTP episode in three of them: one patient had a transient ischemic attack, one a stroke, and a pregnant woman was hospitalized to intensify plasma treatment.

Discussion: The risk of an acute episode triggered by COVID-19 seems higher than following vaccination in hTTP patients, who can be safely vaccinated against SARS-CoV-2.

KEYWORDS
COVID-19, congenital thrombotic thrombocytopenic purpura (cTTP), hereditary thrombotic thrombocytopenic purpura (hTTP), SARS-CoV-2, vaccines

Essentials

- Do COVID-19 or COVID-19 vaccination trigger acute episodes in hereditary thrombotic thrombocytopenic purpura (hTTP)?
- Survey of 86 adult hTTP patients from the International hTTP registry.
- One TTP event after 139 vaccinations (65 patients), 3 TTP events in 12 COVID-19-infected patients.
- hTTP patients can and should be vaccinated against SARS-CoV-2.

1 | INTRODUCTION

By the end of February 2022, the number of globally confirmed cases of COVID-19 had passed 435 million, and that of COVID-19-associated deaths 5.94 million.[1–3] Effective vaccines have been developed and authorized over the past 2 years and are applied in ever-increasing numbers to control the SARS-CoV-2 pandemic.[4]

Hereditary thrombotic thrombocytopenic purpura (hTTP) is a rare autosomal recessively inherited disease, characterized by severe congenital ADAMTS13 deficiency, and acute hTTP episodes resulting in morbidity and premature death.[5–8] Infections and to a lesser extent vaccinations have been identified or suggested as triggers of acute hTTP episodes.[6–8] Recently, Dykes and Kessler[9] described the case of a 50-year-old female hTTP patient who had suffered from a number of acute cerebrovascular accidents over a period of 20 years. She was on plasma-prophylaxis with extended intervals of 4–6 weeks or even longer. Six weeks after a plasma infusion, she received her second dose of mRNA-1273 (Moderna) SARS-CoV-2 vaccine; 1 week later she presented with a new acute cerebrovascular accident with a generalized seizure. At that time, her platelet count was 98 G/L. So far, there are no reports of COVID-19 in hTTP patients.

Immune-mediated TTP (iTTP) is more prevalent than hTTP[10,11] and a number of case reports and case series have described first acute iTTP episodes as well as relapses associated with COVID-19[12–15] and with SARS-CoV-2 vaccination.[16] Nevertheless, two comprehensive epidemiologic studies suggest that SARS-CoV-2 vaccination does not increase the risk of first episodes of iTTP, but may induce an acute iTTP bout or a relapse in asymptomatic subjects with a (severely) deficient ADAMTS13 activity.[17,18] Patients with an iTTP diagnosis are usually followed up with regular ADAMTS13 activity measurements, and preemptive immunosuppressive treatment is started when ADAMTS13 activity drops to <15%–20% to avert a clinical iTTP relapse.[10,11] At many centers, treating physicians have postponed SARS-CoV-2 vaccination in iTTP patients when ADAMTS13 activity was <20% and have tried to first correct ADAMTS13 activity levels, often with a course of steroids over 2–4 weeks. Although patients treated with anti-CD20 monoclonal antibodies (i.e., rituximab and others) can develop an immune response to SARS-CoV-2 vaccines, the risk of non-seroconversion following recent therapy and in patients with depleted B-cell pools is high.[19,20]

In hTTP patients, ADAMTS13 activity <15%–20% is often present for prolonged times, even in patients on regular plasma prophylaxis.[6–8] Whether withholding vaccination in hTTP patients, as proposed by Dykes and Kessler,[9] is warranted should be further investigated. Therefore, we decided to conduct a survey on SARS-CoV-2 vaccination, COVID-19, and of associated possibly triggered acute hTTP episodes in adult confirmed hTTP patients followed in the International Hereditary TTP Registry.

2 | METHODS

Confirmed adult hTTP patients, having signed the informed consent of the International Hereditary TTP Registry (NCT01257269) were eligible for this study (Figure 1). Pediatric patients (<18 years of age) were not considered because recommendations and regulations regarding SARS-CoV-2 vaccination in children vary greatly among countries.

The survey was sent out mid-January 2022 to treating physicians and/or directly to the patients who were asked to respond within 30 days. The survey was built on yes/no and free text answers, with a "prefer not to answer" option for all questions. We recorded the SARS-CoV-2 vaccination status, number of doses administered and the product given, any vaccination-associated side effects, including acute hTTP episodes, their temporal onset in relation to vaccination, and the last plasma infusion.

In addition, we recorded COVID-19 cases, the associated clinical course, and the need for consultation, hospitalization, and additional plasma treatment during COVID-19.

The Cantonal Ethics Committee Bern (KEK #031/06) approved the Hereditary TTP Registry in 2006.

3 | RESULTS

Of 122 adult confirmed hTTP patients eligible to participate in this survey, 86 patients responded (Figure 1). The 52 female and 34 male patients had a median age of 40.24 years (range 18.22–75.86) and

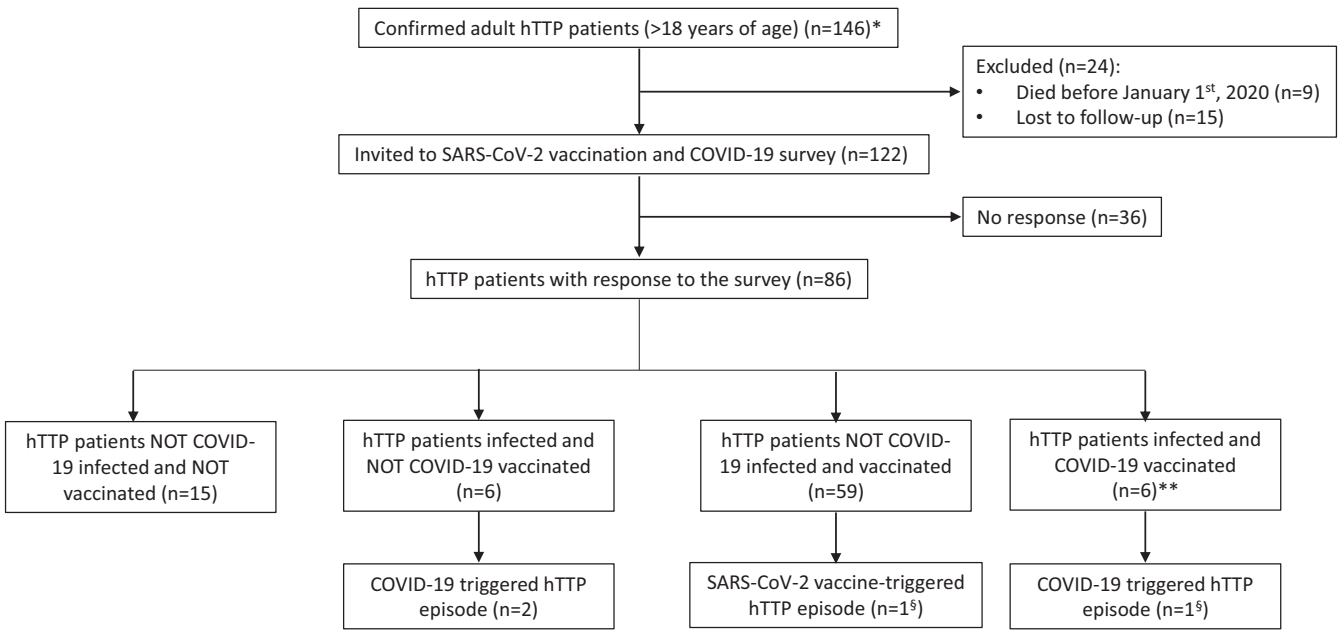

FIGURE 1 Study flowchart. Adult patients with a confirmed diagnosis of hereditary TTP in the International Hereditary TTP Registry at the end of January 2022. *Including 34 Japanese patients.[28] **Four of the six patients were vaccinated when suffering from COVID-19; two patients were vaccinated after COVID-19. §One patient had a COVID-19-triggered hTTP episode as well as a vaccination complication (myocarditis). hTTP, hereditary thrombotic thrombocytopenic purpura.

TABLE 1 Survey on SARS-CoV-2 vaccination and COVID-19 in adult patients with confirmed hereditary TTP enrolled in the International Hereditary TTP Registry

	n	*N*	%
hTTP patients invited to participate in survey	122		
hTTP patients responding to the survey	86	122	70.5
Not vaccinated	21	86	24.4
Vaccinated	65	86	75.6
Partially vaccinated[a]	2	65	3.1
Fully vaccinated[a]	63	65	96.9
Boosted[a]	14	63	22.2
Total vaccine doses administered[b]	139		
SARS-CoV-2 vaccine-triggered acute hTTP episodes (no. dose)[c]	1 (second)	139	0.7
SARS-CoV-2 vaccine-triggered other severe adverse event (myocarditis following second dose of mRNA-1273)	1[d]	139	0.7
COVID-19 in hTTP patients	12	86	14
Outpatient treatment	10	12	83.3
Hospital admission	2	12	16.7
Intensive care unit admission or death	0		
COVID-19 triggered acute hTTP episodes[c]	3[d]	12	25
COVID-19 triggered other severe adverse events	0		

Abbreviation: hTTP, hereditary thrombotic thrombocytopenic purpura.

[a]Partially vaccinated: received one dose of mRNA vaccine; fully vaccinated: received two doses of mRNA vaccine (BNT162b2, mRNA-1273) or one dose of Ad26.COV.S; boosted: received a third dose of SARS-CoV-2 vaccine (either BNT162b2, mRNA-1273 or Ad26.COV.S).

[b]For three vaccinated patients, the product used was not retrievable; we assumed that they had received the minimum possible: one dose of vaccine.

[c]The possibly SARS-CoV-2 vaccine-triggered acute hTTP episode was severe (ischemic stroke, score 3[8]). The three acute hTTP episodes triggered by COVID-19 were moderate (transient ischemic attack, score 2), severe (ischemic stroke, score 3), and moderate (necessary hospitalization during pregnancy with intensification of plasma therapy, score 2), respectively.[8]

[d]One patient is presented twice. He had a COVID-19-triggered hTTP episode and then a complication following vaccination (myocarditis).

were mainly Caucasians (46/86, 53.5%) and Asians (30/86, 34.8%). Epidemiological and clinical characteristics of responding patients did not differ from those in patients who did not respond to our survey. Although 65 (75.6%) patients were vaccinated, 21 were not (Table 1). An mRNA-based SARS-CoV-2 vaccine was used in 61/65 (93.8%) patients, of which 83% received BNT162b2 (Pfizer/BioNTEch) and 17% mRNA-1273 (Moderna). One patient was vaccinated with Ad26.COV2.S (Janssen/Johnson-Johnson). For three vaccinated patients, the product used was not retrievable. At the time of survey, 14 patients had received one SARS-CoV-2 vaccine booster shot in addition. Of the vaccinated patients, 41 were on regular prophylaxis (2–3 plasma units, every 7–21 days,[8] a plasma-derived factor VIII product, or recombinant ADAMTS13); most of them received the vaccination within 1–3 days, and all within 1 week of prophylaxis. All 23 hTTP patients treated with plasma on demand were vaccinated without prior plasma infusions. We have no recent information on the plasma treatment for one patient.

Together, the 65 hTTP patients received at least 139 doses of SARS-CoV-2 vaccine (for the three patients without indication of product, we assumed that they had received the minimum of one dose). The most common side effects reported were injection site reactions, fatigue, fever, and muscle and joint pain, and thus were similar to what had been described as side effects of BNT162b2, mRNA-1273, and Ad26.COV2.S before.[21–23] Two male patients experienced complications, which were considered possibly or probably related to or triggered by the vaccine. One of them, a 52-year-old Caucasian, known for a history of severe hTTP with two prior ischemic strokes (one while on regular plasma prophylaxis), two transient ischemic attacks, and idiopathic venous thromboembolism, is on weekly plasma prophylaxis and regularly seen by his treating physician. On uninterrupted plasma prophylaxis, he was hospitalized with a normal platelet count for altered mental status with aggressive behavior 3 days after receiving his second dose of BNT162b2. Nine days later, a computed tomography scan showed a new ischemic infarction with a component of hemorrhage in the left frontal lobe. An additional 4 weeks later, during a planned plasma infusion, he experienced loss of function of his left arm with suspected stroke and platelet count dropped to 114 G/L. A new computed tomography scan showed no new lesions nor a thrombus. The next day, neurological symptoms had resolved. Thus, this patient with several prior ischemic cerebrovascular events

suffered from a possibly vaccine-triggered stroke within 3 days from his second dose of BNT162b2 and a transient ischemic attack 6 weeks later, despite weekly plasma prophylaxis.

The other patient, a 37-year-old Caucasian male on regular plasma prophylaxis, presented 14 days after his second dose of mRNA-1273 SARS-CoV-2 vaccine in August 2021 with chest pain. His complete blood count was normal with a platelet count of 183 G/L, high-sensitivity troponin T was 75 ng/L (normal <14 ng/L) at presentation and reached a maximum of 184 ng/L during the course. He had a normal coronary angiogram and echocardiogram. The further course was uneventful, and he was discharged 4 days later with a diagnosis of myocarditis, a recognized adverse reaction to mRNA-based SARS-CoV-2 vaccines.[24]

Twelve of 86 (14%) hTTP patients participating in the survey reported to have suffered from COVID-19, of which four were vaccinated when infected and nine (75%) presented a mild course of COVID-19 infection. There were probably COVID-19-triggered acute hTTP episodes in three patients, all not vaccinated at the time, leading to hospitalization in two (Table 1). The first patient had mild thrombocytopenia when diagnosed with COVID-19 and noticed blurred vision (considered a transient ischemic attack[8]) later on without seeking medical help. The second patient, mentioned previously as having developed myocarditis following mRNA-1273 SARS-CoV-2 vaccination, had suffered from COVID-19 8 months earlier. At that time, he was admitted to the hospital with fever and an altered state of consciousness resulting from an ischemic stroke. During the hospitalization, he developed chest pain, dyspnea requiring oxygen supplementation, and hemoptysis. His high-sensitivity troponin T ranged from 3 to 32 ng/L during the stay. Besides plasma infusions, he received cephalosporin, fluconazole, and favipiravir and was discharged after 11 days without sequelae. The third patient, a 34-year-old Caucasian female, contracted COVID-19 in her 31st week of pregnancy and was hospitalized because of melalgia, mild respiratory problems, and to better monitor the course of her disease and her pregnancy. Besides regular plasma infusions and anticoagulant therapy, she received casirivimab/imdevimab. She recovered within days and delivered a healthy baby by cesarean section in gestational week 37.

4 | DISCUSSION

The COVID-19 pandemic has emerged as a major health threat with constantly increasing numbers of confirmed cases and COVID-19 associated deaths.[1–3] Over the past 2 years, effective vaccines have been developed and large SARS-CoV-2 vaccination programs have been successfully implemented. A number of autoimmune phenomena and diseases have been described in the context of COVID-19[15] and after SARS-CoV-2 vaccinations.[24] COVID-19 has been reported as a trigger for first episodes of iTTP as well as relapses[12–15] and SARS-CoV2 vaccination was suggested also as a trigger of iTTP.[16] Nevertheless, two epidemiologic studies clearly suggest that SARS-CoV-2 vaccination is unlikely to trigger new-onset iTTP.[17,18]

Hereditary TTP is an ultra-rare disease characterized by a severe congenital ADAMTS13 deficiency resulting from biallelic *ADAMTS13* mutations and recurring acute disease episodes associated with considerable morbidity and premature death.[5–8] Infections are well known and common triggers of acute hTTP episodes, whereas vaccination-triggered episodes have been reported only occasionally.[6–8] Inflammatory conditions and infections are associated with increased von Willebrand factor (VWF) levels and VWF-mediated thrombosis.[25] This mechanism is also implicated in severe COVID-19, where ADAMTS13 activity is often mildly reduced,[26,27] and in microvascular thrombosis of acute TTP episodes where, in the absence of ADAMTS13 activity, ultra-large VWF multimers remain unprocessed and aggregate spontaneously with platelets.[11]

Our survey documented 139 SARS-CoV-2 vaccination shots administered to 65 hTTP patients, of which one shot (0.7%) was possibly associated with an acute episode in a patient on regular plasma prophylaxis. This 52-year-old patient with several prior cerebrovascular infarctions suffered from a new stroke 3 days and from a transient ischemic attack 6 weeks after his second BNT162b2 vaccine shot. Because of the time window of only 3 days, the stroke may very well have been triggered by the vaccination. However, given the patient's severe and burdened medical history, the recurring stroke may also be explained by his severe congenital ADAMTS13 deficiency and his hTTP.

Most common side effects were injection site reactions, fatigue, fever, and muscle and joint pain. This is in line with findings in a smaller national cohort in Japan[28] and to what has been described globally as side effects of BNT162b2, mRNA-1273, and Ad26.COV2.S.[21–23] One grade 2 adverse event was documented in a male patient who developed myocarditis following the second dose of mRNA-1273.

As a precautionary measure, SARS-CoV-2 vaccinations were performed within 1 week of plasma infusion in all 41 patients on regular prophylaxis; of the 23 patients treated on demand, none received a plasma infusion before the SARS-CoV-2 vaccinations, and none experienced an acute hTTP episode.

On the other hand, three of 12 (25%) COVID-19 infections were associated with moderate to severe hTTP episodes,[8] including a transient ischemic attack with mild thrombocytopenia, a stroke, and a hospitalization to intensify plasma treatment in a pregnant woman.

In conclusion, hTTP patients can be safely vaccinated against SARS-CoV-2, which seems to be beneficial because 25% of COVID-19 infections triggered important hTTP episodes. A prophylactic plasma infusion 1–3 days before the scheduled vaccination is an effective and reasonable precautionary measure, although may not be necessary in all patients.

AUTHOR CONTRIBUTIONS

E.T. and J.A.K.H. designed the survey and collected and interpreted data. E.T. wrote the first manuscript, which was revised by B.L. and J.A.K.H., A.S.v.K., R.H., T.B., T.I., P.N.K., E.H., O.P., S.F., O.G., P.K., N.H.S., C.v.A., and J.W. took care of the patients. A.S.v.K., K.F., I.H., P.N.K., R.S., M.M., J.N.G., and B.L. are members of the steering

committee of the International Hereditary TTP Registry providing advice and support. All authors provided editorial comments and approved the final manuscript.

ACKNOWLEDGMENTS

We thank all the patients and physicians that participated in this survey.

FUNDING INFORMATION

The International Hereditary TTP Registry has received support through grants from the Swiss National Science Foundation (grant 310030–185233), the Mach-Gaensslen Foundation Switzerland, the Answering T.T.P. Foundation (Project ID 1009), the ISTH 2007 Presidential Fund, the GTH Congress President Fund, the NFG Foundation, as well as a research grant (H16-36165) from Baxalta US Inc., member of the Takeda group of companies, Bannockburn, IL, USA.

RELATIONSHIP DISCLOSURE

E.T. received congress travel support and/or lecture fees from Bayer, SOBI, and Takeda. All honoraria go to the employer, Insel Gruppe AG. R.H. received consultancy and advisory board fees, speaker honoraria from Takeda, Roche, Sobi, Octapharma, Novo-Nordisk, and Bayer. P.N.K. received consultancy and advisory board fees, speaker honoraria, and travel grants from Ablynx/Sanofi, Alexion, and Shire/Takeda. J.W. received grant support or lectures honoraria from Alexion, Alnylam Pharmaceuticals, Baxalta, CSL Behring, Ferring Pharmaceuticals, Novo Nordisk, Octapharma, Rigel Pharmaceuticals, Roche, Sanofi/Genzyme, Shire/Takeda, Sobi, and Werfen. K.D.F. received speaker honoraria from Siemens, has consulted for GUARDIAN Therapeutics, and has participated in an advisory board for Werfen. M.M. is a member of the advisory board of Takeda, Alexion, and Sanofi. B.L. is chairman of the data safety monitoring committees for the Baxalta 281102 and the TAK-755-3002 study (both investigating recombinant ADAMTS13 in hereditary TTP) and for the Takeda SHP655-201 study (recombinant ADAMTS13 in immune-mediated TTP), all three now run by Takeda. He is a member of the advisory board of Ablynx, now part of Sanofi, for the development of caplacizumab; and received congress travel support and/or lecture fees from Baxter, Ablynx, Alexion, Siemens, Bayer, Roche, and Sanofi. J.A.K.H. is a member of the advisory board of Shire, member of the Takeda group of companies, for the development of recombinant ADAMTS13, and of Ablynx, now part of Sanofi, for the development of caplacizumab. She received congress travel support and/or lecture fees from Ablynx/Sanofi, Bayer, Roche, SOBI, and Takeda. All honoraria go to the employer, Insel Gruppe AG. The remaining authors declare no competing financial interests.

ORCID

Erika Tarasco https://orcid.org/0000-0002-4387-8476
Paul N. Knöbl https://orcid.org/0000-0002-7909-7225
Eriko Hamada https://orcid.org/0000-0003-0913-2475
Ingrid Hrachovinova https://orcid.org/0000-0003-0300-2063
Masanori Matsumoto https://orcid.org/0000-0002-7243-3126
Bernhard Lämmle https://orcid.org/0000-0003-4538-5154
Johanna Anna Kremer Hovinga https://orcid.org/0000-0002-1300-7135

REFERENCES

1. Johns Hopkins Institute March 23, 2022. 2022. https://coronavirus.jhu.edu/map.html
2. WHO Coronavirus (COVID-19) 2022. https://covid19.who.int/
3. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis*. 2020;20(5):533-534. doi:10.1016/S1473-3099(20)30120-1
4. Mathieu E, Ritchie H, Ortiz-Ospina E, et al. A global database of COVID-19 vaccinations. *Nat Hum Behav*. 2021;5(7):947-953. doi:10.1038/s41562-021-01122-8
5. Kremer Hovinga JA, George JN. Hereditary thrombotic thrombocytopenic purpura. *N Engl J Med*. 2019;381(17):1653-1662. doi:10.1056/NEJMra1813013
6. Alwan F, Vendramin C, Liesner R, et al. Characterization and treatment of congenital thrombotic thrombocytopenic purpura. *Blood*. 2019;133(15):1644-1651. doi:10.1182/blood-2018-11-884700
7. van Dorland HA, Taleghani MM, Sakai K, et al. The International Hereditary Thrombotic Thrombocytopenic Purpura Registry: key findings at enrollment until 2017. *Haematologica*. 2019;104(10):2107-2115. doi:10.3324/haematol.2019.216796
8. Tarasco E, Butikofer L, Friedman KD, et al. Annual incidence and severity of acute episodes in hereditary thrombotic thrombocytopenic purpura. *Blood*. 2021;137(25):3563-3575. doi:10.1182/blood.2020009801
9. Dykes KC, Kessler CM. First report of COVID-19 vaccine induced flare of compensated congenital thrombotic thrombocytopenic purpura. *Blood Coagul Fibrinolysis*. 2022;33(1):71-73. doi:10.1097/MBC.0000000000001097
10. Joly BS, Coppo P, Veyradier A. Thrombotic thrombocytopenic purpura. *Blood*. 2017;129(21):2836-2846. doi:10.1182/blood-2016-10-709857
11. Sadler JE. Pathophysiology of thrombotic thrombocytopenic purpura. *Blood*. 2017;130(10):1181-1188. doi:10.1182/blood-2017-04-636431
12. Capecchi M, Mocellin C, Abbruzzese C, Mancini I, Prati D, Peyvandi F. Dramatic presentation of acquired thombotic thrombocytopenic purpura associated with COVID-19. *Haematologica*. 2020;105(10):e540. doi:10.3324/haematol.2020.262345
13. Beaulieu MC, Mettelus DS, Rioux-Masse B, Mahone M. Thrombotic thrombocytopenic purpura as the initial presentation of COVID-19. *J Thromb Haemost*. 2021;19(4):1132-1134. doi:10.1111/jth.15231
14. Schwaegermann MK, Hobohm L, Rausch J, et al. COVID-19 as a potential trigger for immune thrombotic thrombocytopenic purpura and reason for an unusual treatment: a case report. *Hamostaseologie*. 2021. doi:10.1055/a-1497-1054
15. Taherifard E, Taherifard E, Movahed H, Mousavi MR. Hematologic autoimmune disorders in the course of COVID-19: a systematic review of reported cases. *Hematology*. 2021;26(1):225-239. doi:10.1080/16078454.2021.1881225
16. Maayan H, Kirgner I, Gutwein O, et al. Acquired thrombotic thrombocytopenic purpura: a rare disease associated with BNT162b2 vaccine. *J Thromb Haemost*. 2021;19(9):2314-2317. doi:10.1111/jth.15420
17. Picod A, Rebibou JM, Dossier A, et al. Immune-mediated thrombotic thrombocytopenic purpura following COVID-19 vaccination. *Blood*. 2022;139(16):2565-2569. doi:10.1182/blood.2021015149

18. Shah H, Kim A, Sukumar S, et al. SARS-CoV-2 vaccination and immune thrombotic thrombocytopenic purpura. *Blood*. 2022;139(16):2570-2573. doi:10.1182/blood.2022015545
19. Moor MB, Suter-Riniker F, Horn MP, et al. Humoral and cellular responses to mRNA vaccines against SARS-CoV-2 in patients with a history of CD20 B-cell-depleting therapy (RituxiVac): an investigator-initiated, single-centre, open-label study. *Lancet Rheumatol*. 2021;3(11):e789-e797. doi:10.1016/s2665-9913(21)00251-4
20. Schietzel S, Anderegg M, Limacher A, et al. Humoral and cellular immune responses on SARS-CoV-2 vaccines in patients with anti-CD20 therapies: a systematic review and meta-analysis of 1342 patients. *RMD Open*. 2022;8(1):e002036. doi:10.1136/rmdopen-2021-002036
21. CDC. Johnson & Johnson's Janssen COVID-19 vaccine overview and safety. Dec 28, 2021. 2021.
22. CDC. Moderna COVID-19 vaccine overview and safety. Jan 7, 2022. 2022.
23. CDC. Pfizer-BiontECH COVID-19 vaccine (also known as COMIRNATY) overview and safety. Jan 6, 2022. 2022.
24. Oster ME, Shay DK, Su JR, et al. Myocarditis cases reported after mRNA-based COVID-19 vaccination in the US from December 2020 to August 2021. *JAMA*. 2022;327(4):331-340. doi:10.1001/jama.2021.24110
25. Chen J, Chung DW. Inflammation, von Willebrand factor, and ADAMTS13. *Blood*. 2018;132(2):141-147. doi:10.1182/blood-2018-02-769000
26. Favaloro EJ, Henry BM, Lippi G. Increased VWF and decreased ADAMTS-13 in COVID-19: creating a milieu for (micro) thrombosis. *Semin Thromb Hemost*. 2021;47(4):400-418. doi:10.1055/s-0041-1727282
27. Joly BS, Darmon M, Dekimpe C, et al. Imbalance of von Willebrand factor and ADAMTS13 axis is rather a biomarker of strong inflammation and endothelial damage than a cause of thrombotic process in critically ill COVID-19 patients. *J Thromb Haemost*. 2021;19(9):2193-2198. doi:10.1111/jth.15445
28. Hamada E, Sakai K, Yamada S, Kubo M, Hayakawa M, Matsumoto M. No aggravation of congenital thrombotic thrombocytopenic purpura by mRNA-based vaccines against COVID-19: a Japanese registry survey. *Ann Hematol*. 2022;101:1115-1117. doi:10.1007/s00277-022-04774-2

How to cite this article: Tarasco E, von Krogh AS, Hrdlickova R, et al. Hereditary thrombotic thrombocytopenic purpura and COVID-19: Impacts of vaccination and infection in this rare disease. *Res Pract Thromb Haemost*. 2022;6:e12814. doi: 10.1002/rth2.12814