Relapse of immune-mediated thrombotic thrombocytopenic purpura following mRNA COVID-19 vaccination: a prospective cohort study

Gaetano Giuffrida,[1*] Uros Markovic[1,2,3*] Annalisa Condorelli,[1,4] Marianna Calagna,[1,4] Stephanie Grasso,[1] Andrea Duminuco,[1,4] Carla Riccobene,[1] Angelo Curto Pelle,[1,4] Guido Zanghi[5] and Francesco Di Raimondo[1,4]

[1]Division of Hematology, AOU "Policlinico G. Rodolico-San Marco", Catania; [2]Unità Operativa di Oncoematologia e BMT Unit, Istituto Oncologico del Mediterraneo, Viagrande; [3]Department of Biomedical, Dental, Morphological and Functional Imaging Sciences, University of Messina, Messina; [4]Postgraduate School of Hematology, University of Catania, Catania and [5]Department of Surgery (CHIR), School of Medicine, University of Catania, Catania, Italy.

GG and UM contributed equally as co-first authors.

Correspondence: U. Markovic
urosmarkovic09041989@gmail.com

Received: February 24, 2022.
Accepted: April 22, 2022.
Prepublished: May 5, 2022.

https://doi.org/10.3324/haematol.2022.280702

Abstract

Immune-mediated thrombotic thrombocytopenic purpura (iTTP) is a rare and life-threatening disease. Vaccination has been reported to be a trigger of onset and relapse of autoimmune diseases. We evaluated after mRNA COVID-19 vaccination 32 adult patients previously diagnosed with iTTP by means of weekly monitoring of complete blood count and ADAMTS13 testing. Thirty of 32 patients received at least one dose of Pfizer-BioNTech, the remaining two received Moderna. A total of five patients, all vaccinated with Pfizer-BioNTech, had a biochemical relapse at a median post-vaccination time of 15 days following the second or third vaccine dose, presenting without measurable ADAMTS13 activity and a median anti-ADAMTS13 autoantibody value of 34 U/mL. Four of five cases had concomitant clinical relapse and were treated with corticosteroids alone or daily sessions of plasma exchange and caplacizumab, while one patient was closely monitored with ADAMTS13 with no onset of anemia and thrombocytopenia. Although the benefits of vaccination exceed its potential risks, clinicians should be aware that iTTP relapse might follow COVID-19 vaccination. Therefore, laboratory and clinical monitoring of iTTP patients should be done in the first post-vaccination month, in order to promptly diagnose and treat any relapse.

Introduction

Immune-mediated thrombotic thrombocytopenic purpura (iTTP), a rare and life-threatening disease with an annual incidence of roughly 1.5 new cases/million, is characterized by microangiopathic hemolytic anemia, thrombocytopenia and ischemic end organ injury due to microvascular platelet-rich thrombi.[1] The formation of microvascular thrombi is caused by the deficiency of the von Willebrand factor-cleaving protease ADAMTS13, due to the presence of anti-ADAMTS13 autoantibodies.[2] A major challenge in iTTP is the risk of relapse after remission.[3] Although the predictors of relapse remain unsettled, a multi-center study by Sun and colleagues showed that a history of prior relapse, age younger than 25 years and non-O blood group were associated with an increased risk.[4] ADAMTS13 activity monitoring during follow-up has shown that patients without measurable levels of ADAMTS13 and/or high levels of anti-ADAMTS13 during clinical remission have a three-fold greater likelihood of relapse.[5] A pre-emptive therapy with the anti-CD20 monoclonal antibody rituximab has been shown to prevent clinical relapses in most patients by maintaining in them measurable ADAMTS13 activity.[6,7] However, not all patients with persistently low levels of ADAMTS13 have clinical relapse, suggesting the need for such additional hits as infection and/or inflammation.[8]
Disease onset or relapse of iTPP was described following different vaccines, including pneumococcal, influenza and rabies.[9–13] Given the current massive vaccination due to the SARS-CoV-2 pandemic, new onset iTTP has been documented following a vector based Ad26.COV2-S vaccine[14] and we recently described two new onset cases following the first dose of the Pfizer-BioNTech COVID-19 vaccine.[15,16] Here we describe our real-life single center experience of iTTP

monitoring following mRNA COVID-19 vaccination in order to early detect any disease relapse.

Methods

Patients' selection

In our center 42 adult patients had a prior diagnosis of iTTP. Diagnosis had been made on the presence of Coombs-negative microangiopathic hemolytic anemia, acute thrombocytopenia in the absence of any identifiable cause accompanied by the severe acquired deficiency of ADAMTS13 activity (<10%) and the presence of anti-ADAMTS13 antibodies.

Clinical relapse of iTTP was defined as the reappearance after a clinical remission (defined as a sustained clinical response for at least 30 days after the last PEX/caplacizumab) of a platelet count <150x10^9/L with other causes of thrombocytopenia ruled out, with or without clinical evidence of new ischemic organ injury.[17] A clinical relapse must be confirmed by documentation of severe ADAMTS13 deficiency.

Biochemical relapse of iTTP was defined as ADAMTS13 plasma levels <20% after ADAMTS13 remission was achieved, i.e., at least a partial remission with ADAMTS13 level >20% but in the absence of clinical symptoms, microangiopathic hemolytic anemia and thrombocytopenia. Biochemical remission was defined as ADAMTS13 level >40%, while patients with ADAMTS13 level between 20% and 40% were defined to have partial biochemical responses.[17]

A total of 32 of 42 iTTP patients received a COVID-19 mRNA vaccination (Pfizer-BioNTech or Moderna) between February 2021 and January 2022 (Figure 1). They were characterized according to age, sex, presence of biochemical relapse prior to vaccination, type of COVID-19 vaccine, number of vaccine doses, prevaccination ADAMTS13 activity and anti-ADAMTS13 autoantibodies and development of clinical or biochemical signs of disease relapse (Table 1). The study was conducted in accordance with International Conference on Harmonization Guidelines on Good Clinical Practice and the principles of the Declaration of Helsinki. All patients provided written informed consent.

Laboratory methods

Complete blood count (CBC), ADAMTS13 activity and anti-ADAMTS13 antibodies were employed for weekly monitoring during the month following each vaccine dose. Measurement of both ADAMTS13 activity was performed in plasma, prior to incubation by using TECHNOZYM® ADAMTS13 ELISA (Alifax™ Spa), a chromogenic enzyme-linked immunosorbant assay (ELISA) for the measurement of ADAMTS13 activity in human plasma. Severe ADAMTS13 deficiency was defined as activity less than 10%, moderate ADAMTS13 deficiency between 10% and 40%, normal ADAMTS13 between 40-130%. Anti-ADAMTS13 antibodies were measured by using the same chromogenic ELISA kit (TECHNOZYM® ADAMTS13 INH-Alifax™ Spa) quantified by the spectrophotometer and the threshold for the positivity was ≥12 U/mL. ADAMTS13 measurement was done prior to vaccine administration and subsequently either as prescheduled follow-up controls or in case of suspected disease relapse.

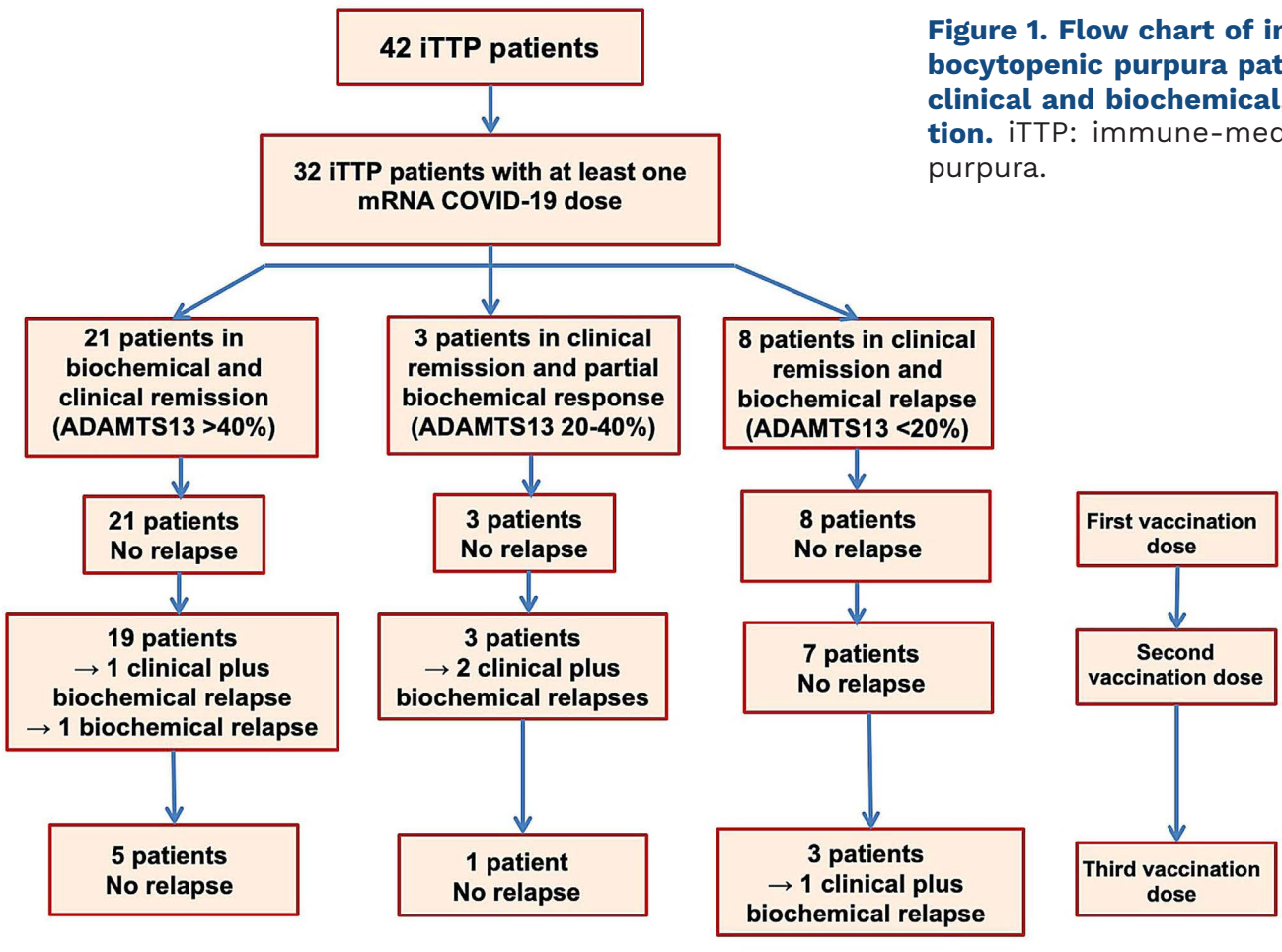

Figure 1. Flow chart of immune-mediated thrombotic thrombocytopenic purpura patients and subsequent relapses, both clinical and biochemical, following mRNA COVID-19 vaccination. iTTP: immune-mediated thrombotic thrombocytopenic purpura.

Results

Characteristics of the immune-mediated thrombotic thrombocytopenic purpura cohort following vaccination

A total of 32 iTTP cases (median age 47 years) were vaccinated with at least one dose of either Pfizer-BioNTech (30 cases) or Moderna (2 cases) COVID-19 mRNA vaccines (Figure 1). After a median follow-up of 71 months (range, 6-389 months) from the original iTTP disease diagnosis, these patients were re-evaluated prior to vaccination with CBC, that was within the normal range in all cases. Moreover, median ADAMTS13 activity was 48.5% and the titer of anti-ADAMTS13 was 5 U/mL, but seven patients were in biochemical relapse prior to COVID-19 vaccination (Table 1), while three additional patients had a partial biochemical response. Within a median follow-up period of 8 months following the first vaccine dose (range, 1-11 months), five patients (13%) had a clinical or biochemical relapse, all following the second or third Pfizer-BioNTech vaccine dose, at a median time interval of 15 days (range, 7-25 days) from vaccination, presenting without measurable ADAMTS13 activity and a median anti-ADAMTS13 value of 34 U/mL (range, 17-70 U/mL). Four of five cases concomitantly suffered from clinical relapse, while one patient had no signs of anemia and thrombocytopenia. None of the two patients with Moderna vaccination relapsed. In case of severe thrombocytopenia (less than 20.000/mmc) and the presence of hemolytic anemia patients were treated with steroids + plasma exchange (PEX) + caplacizumab, while others were started on steroids alone and in case of lack of response switched to steroids + PEX + caplacizumab.

Table 1. Clinical and laboratory characteristics of 32 immune-mediated thrombotic thrombocytopenic purpura patients who received mRNA COVID-19 vaccination.

Age prior to vaccination	
Median in years (range)	47 (19-73)
≤50 years, N (%)	18 (56)
>50 years, N (%)	14 (44)
Biochemical relapse prior to vaccination	
Yes, N (%)	7 (22)
No, N (%)	25 (78)
ADAMTS13 prior to vaccination	
ADAMTS13 activity, % (range)	48.5 (0-100)
ADAMTS13 autoantibodies, U/mL (range)	5 (1-92)
COVID-19 vaccine type	
Pfizer-BioNTech, N (%)	30 (94)
Moderna, N (%)	2 (6)
N of vaccination doses	
One, N (%)	3 (9)
Two,N (%)	20 (63)
Three, N (%)	9 (28)
iTTP relapse post-vaccination	
Clinical relapse, N (%)	4 (13)
Biochemical relapse, N (%)	1 (3)
Relapse outcome (4 patients)	
Clinical remission, N (%)	3 (75)
Early relapse, N (%)	1 (25)
Recurrent TTP Patients (at least 2 previous relapse)	
Yes, N (%)	6 (18)
No, N (%)	26 (82)

iTTP: immune-mediated thrombotic thrombocytopenic purpura.

Case description of immune-mediated thrombotic thrombocytopenic purpura relapses following vaccination

A summary description of the five iTTP cases who had a post-vaccination relapse is shown in Table 2, and more details are listed below.

A 44-year-old A-positive woman with a diagnosis of iTTP made in 2017 and in complete remission since then, received two doses of the Pfizer-BioNTech COVID-19 vaccine between May and September 2021. Before vaccination, ADAMTS13 activity was 20% and ADAMTS13 antibodies 3.2 U/mL. Three weeks after the second vaccine dose, complete blood count (CBC) showed the appearance of anemia (Hb 8.1 g/dL), thrombocytopenia (42.000/mmc) along with positive hemolysis markers. ADAMTS13 activity was not measurable (<10%), with a markedly increased anti-ADAMTS13 (34 U/mL, normal values [n.v.] 12-15 U/mL). The patient was admitted to hospital and treated with intravenous methylprednisolone at a daily dosage of 1 mg/kg, achieving clinical response after 7 days of treatment with normalization of both hemoglobin and platelet count, subsequent steroid tapering and stopping. However, there was no biochemical remission with persistently not measurable ADAMTS activity and a high titer of anti-ADAMTS13 (36 U/mL) at the last check-up 3 months following clinical relapse.

A 53-year-old O-positive woman with a iTTP diagnosis made in 2017 and a single clinical relapse in 2020, was in complete clinical and biochemical remission prior to COVID-19 vaccination, with 30% ADAMTS13 activity and antibody level of 5.5 U/mL. Two doses of the Pfizer-BioNTech vaccine were administered in the period between May and June 2021. Three weeks after the second dose she developed a clinical relapse, with the presence of a low platelet count (68.000/mmc), positive hemolysis markers and schistocytes in the blood smear. ADAMTS13 testing confirmed biochemically the clinical relapse, showing not measurable activity (<10%) and high titer anti-ADAMTS13 (44 U/mL). Treated in the outpatient setting with oral prednisone at the dosage of 1 mg/kg, clinical and biochemical responses were both obtained 8 days after treatment initiation, with 70% ADAMTS13 activity at her last check-up seven months from last disease relapse.

Table 2. Summary of the immune-mediated thrombotic thrombocytopenic purpura relapses following mRNA COVID-19 vaccination (all after the Pfizer-BioNTech vaccine).

Patient age/sex	ADAMTS13 level before vaccination	N doses before relapse	Relapse type	Time from last vaccination to relapse	ADAMTS13	Anti-ADAMTS13	Treatment
44 y/F	20%	Two	Clinical	20 days	<10%	34 U/mL	Steroids only
53 y/F	30%	Two	Clinical	25 days	<10%	44 U/mL	Steroids only
32 y/F	58%	Two	Clinical	15 days	<10%	70 U/mL	PEX+steroids+ caplacizumab
44 y/M	<10%	Three	Clinical	15 days	<10%	17 U/mL	PEX+steroids+ caplacizumab
55 y/M	42%	Two	Biochemical	7 days	<10%	16 U/mL	None

ITTP: immune-mediated thrombotic thrombocytopenic purpura; N: number; y: years; F: female; M: male; PEX: plasma exchange.

A 32-year-old O-positive woman had had a diagnosis of iTTP in 2007 and subsequently experienced two clinical relapses in 2015 and 2018, both during gestation with complete remission after parturition. Complete clinical and biochemical remission was confirmed prior to COVID-19 vaccination, with 58% ADAMTS13 activity and low antibody level (4.6 U/mL). She received a two-dose Pfizer-BioNTech vaccine between September and October 2021 within an interval of 4 weeks. Two weeks after the second dose she experienced intense headache with fatigue and was admitted to the hospital emergency room. CBC revealed anemia (Hb 9,5 gr/d) with schistocytes, severe thrombocytopenia (14.000/mmc) and positive hemolysis markers. ADAMTS13 activity was not measurable (<10%) with a high anti-ADAMTS13 (70 U/mL). She was treated with seven daily sessions of PEX, intravenous steroids (1 mg/kg) and a standard caplacizumab dosage (10 mg intravenously before the first PEX and 10 mg subcutaneously daily until day 30 from the last PEX). After an initial clinical response to the treatment with normalization of both hemoglobin and platelet count but with persistently not measurable ADAMTS13 activity, she had a clinical relapse 50 days after treatment initiation (20 days after the end of caplacizumab) at the time of steroid tapering. The platelet count was low again (46.000/mmc), with anemia (Hb 10.4 g/dL) and a high titer of anti-ADAMTS13 (93 U/mL), so she was restarted on the same initial therapy with steroids, PEX and caplacizumab, obtaining again a clinical response after 5 days. This patient completed weekly immunotherapy with rituximab at the standard dosage of 375 mg/m^2 for a total of four weekly doses, with still not measurable ADAMTS13 activity following the last rituximab dose at the end of January 2022.

A 44-year-old O-positive man had a diagnosis of iTTP in 2018 and experienced three clinical relapses since then. ADAMTS13 testing prior to vaccination revealed a biochemical relapse (activity of 10%, with 16 U/mL anti-ADAMT13) in the absence of anemia and thrombocytopenia. He received two doses of Pfizer-BioNTech in March and April 2021, with no signs of thrombocytopenia in the frame of weekly CBC controls. However, 2 weeks after the third booster dose at the end of December, a CBC control revealed severe thrombocytopenia (23.000/mmc) but no anemia (Hb 15,9 g/dL), therefore he was treated in the outpatient setting with oral prednisone at the dosage of 1 mg/kg. Two days later moderate anemia (Hb 11.1 g/dL) with the presence of schistocytes in the blood smear as well as severe thrombocytopenia (5.000/mmc) were found, along with blood chemistry markers of hemolysis. ADAMTS13 testing showed no measurable activity (<10%) and high anti-ADAMTS13 antibodies (17.3 U/mL). The patient was hospitalized and treated with daily sessions of PEX, intravenous steroids and caplacizumab (10 mg intravenously before the first PEX and 10 mg subcutaneously until 30 days from the last PEX), with an initial platelet response after 6 days of PEX and a biochemical response 14 days after treatment initiation, with 20% of ADAMTS13 and low anti-ADAMTS13 values (1.4 U/mL).

A 55-year-old B-negative man was diagnosed with iTTP in 2013 and subsequently experienced five biochemical relapses, three of them being also clinical relapses. Seven days after receiving the second Pfizer-BioNTech vaccine dose in June 2021 ADAMTS13 activity decreased from 42% to <10% with an increase in the antibody level (from 8 to 16 U/mL) but no CBC change. The patient was regularly monitored with CBC in the following few months without any treatment and in December 2021 received a third booster vaccine dose with a subsequent increase in anti-ADAMTS13 values (29 U/mL) without measurable ADAMTS13 activity and without signs of hemolytic anemia and thrombocytopenia.

Discussion

Onset of autoimmune diseases following vaccination is a known phenomenon, caused by the vaccine through molecular mimicry, epitope spreading and polyclonal activation.[18] Vaccine adjuvants are an alternative possible cause of autoimmunity, and the autoimmune/inflammatory syndrome induced by adjuvants (ASIA) has been described as a hyperactive immune response to adjuvants.[19] Given the autoimmune-origin of acquired TTP, it is not surprising that vaccination may be a trigger for disease relapse.[9–13]

Given the global COVID-19 pandemic with a high number of hospitalized patients, our opinion was that the benefits of vaccination outweighed the possible relapse risk even in iTTP patients with a risk of relapse. Thus, in order to early detect relapses, we chose to monitor our patients with iTTP in clinical remission with weekly CBC, ADAMTS13 and anti-ADAMTS13 testing following each mRNA vaccination for COVID-19. Serial biological monitoring was not considered because that there was no indication for treatment in patients suffering from biochemical relapse alone, and patients were therefore monitored at prescheduled controls every 3 months. This strategy allowed us to detect five cases of relapse (clinical or biochemical) following at least two doses of Pfizer-BioNTech. Interestingly, three of the eleven patients with ADAMTS13 <40% suffered from clinical relapse following the second or third vaccine dose, whereas only 9% of the patients with ADAMTS13 >40% had clinical and/or biochemical relapses (Figure 1). Two patients were treated early and successfully with steroids alone at a time when thrombocytopenia was not severe (platelet count > 20.000/mmc) and in the absence of hemolytic anemia. Of the two patients who received PEX and caplacizumab together with steroids, one had an early relapse and was re-treated with the same regimen, followed by weekly rituximab for a total of four doses. Furthermore, there was a case who had only a biochemical relapse with normal hemoglobin and platelet count following the second vaccination dose. Of note, three of four patients who had a clinical relapse are recurrent TTP patients (with at least one prior relapse in their clinical history) and one of them had low prevaccination ADAMTS13 activity (<10%). Thus, we acknowledge that these patients were at high risk of relapse irrespective of vaccination, although the temporal relationship between the two events suggests that vaccination was the trigger of the event, but not necessarily the cause.[20]

Since the beginning of the global COVID-19 vaccination various cases of autoimmune activations, both as new-onset and disease flares, were reported.[16] Watad and colleagues described 27 subjects with different autoimmune reactions that occurred on average 4 days following SARS-CoV-2 vaccination, including 17 flares and 10 new onsets. Twenty-three of 27 cases had received Pfizer-BioNTech, while Moderna and ChAdOx1 vaccines were received in two cases each.[19] Furthermore, the development of venous thrombosis at unusual sites was described in association with the vaccine-induced immune thrombotic thrombocytopenia (VITT) syndrome caused by adenovirus-based COVID-19 vaccines such as ChAdOx1 and INN-Ad26.COV2-S.[21] Cases of new onset of both immune thrombocytopenic purpura (ITP) and iTTP following COVID-19 vaccination have been also described, including our experience of three cases of the former and two of the latter.[15,22]

In the case of VITT syndrome and newly diagnosed ITP and iTTP seen at our center, disease onset was detected following the first vaccine dose in the majority of instances, at variance with our experience in the relapse setting. Unlike the two cases described in the literature following the first vaccine dose, in the present study all relapsed patients had received at least two doses of Pfizer-BioNTech and the association between vaccination and clinical relapse is supported by the short latency period between COVID-19 vaccine dose and changes of both hemoglobin and platelets.

Although the benefits of vaccination outweigh potential risks, clinicians should be aware that iTTP relapse might follow COVID-19 vaccination. Considering the important morbidity and mortality of iTTP, the importance of an early diagnosis of clinical relapse and prompt treatment initiation with weekly CBC controls following vaccination can be of aid both for patient outcome and the burden on the health system in the period of COVID-19 pandemic.

Disclosures

No conflicts of interest to disclose.

Contributions

GG was responsible for project administration; UM, AC and MC interpreted the data and drafted the article; AC, MC, SG, AD and ACP selected patients, acquired and analyzed the data; GG and FDR revised the article for important intellectual content and approved the final version for submission. All authors contributed to the article and approved the submitted version.

Acknowledgments

The authors are thankful to all patients and families and nurses who accepted to participate.

Funding

This work was supported by "Associazione Italiana contro le Leucemie, Linfomi e Mielomi" (A.I.L.) Catania.

Data-sharing statement

The data that support the findings of this study are available upon documented request.

References

1. Miesbach W, Menne J, Bommer M, et al. Incidence of acquired thrombotic thrombocytopenic purpura in Germany: a hospital level study. Orphanet J Rare Dis. 2019;14:260.
2. Sukumar S, Lämmle B, Cataland SR. Thrombotic thrombocytopenic purpura: pathophysiology, diagnosis, and management. J Clin Med. 2021;10(3):536.
3. Kremer Hovinga JA, Vesely SK, Terrell DR, Lämmle B, George JN. Survival and relapse in patients with thrombotic thrombocytopenic purpura. Blood. 2010;115(8):1500-1511.
4. Sun L, Mack J, Li A, et al. Predictors of relapse and efficacy of rituximab in immune thrombotic thrombocytopenic purpura. Blood Adv. 2019;3(9):1512-1518.
5. 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(2):232-239.
6. Bresin E, Gastoldi S, Daina E, et al. Rituximab as pre-emptive treatment in patients with thrombotic thrombocytopenic purpura and evidence of anti-ADAMTS13 autoantibodies. Thromb Haemost. 2009;101(2):233-238.
7. Jestin M, Benhamou Y, Schelpe AS, et al. Preemptive rituximab prevents long-term relapses in immune-mediated thrombotic thrombocytopenic purpura. Blood. 2018;132(20):2143-2153.
8. Miyata T, Fan X. A second hit for TMA. Blood. 2012;120(6):1152-1154.
9. Dias PJ, Gopal S. Refractory thrombotic thrombocytopenic purpura following influenza vaccination. Anaesthesia. 2009;64(4):444-446.
10. Hermann R, Pfeil A, Busch M, et al. Schwerste thrombotisch-thrombozytopenische Purpura (TTP) nach H1N1-Vakzinierung. Med Klin. 2010;105(9):663-668.
11. Kojima Y, Ohashi H, Nakamura T, et al. Acute thrombotic thrombocytopenic purpura after pneumococcal vaccination. Blood Coagul Fibrinolysis. 2014;25(5):512-514.
12. Brodin-Sartorius A, Guebre-Egziabher F, Fouque D, et al. Recurrent idiopathic thrombotic thrombocytopenic purpura: a role for vaccination in disease relapse? Am J Kidney Dis. 2006;48(3):e31-e34.
13. Kadikoylu G, Yavasoglu I, Bolaman Z. Rabies vaccine-associated thrombotic thrombocytopenic purpura. Transfus Med. 2014;24(6):428-429.
14. Yocum A, Simon EL. Thrombotic thrombocytopenic purpura after Ad26.COV2-S vaccination. Am J Emerg Med. 2021;49441.e3-441.e4.
15. Giuffrida G, Condorelli A, Di Giorgio MA, et al. Immune-mediated thrombotic thrombocytopenic purpura following Pfizer-BioNTech COVID-19 vaccine. Haematologica. 2022;107(4):1008-1010.
16. Mannucci PM. Thrombotic thrombocytopenic purpura and other immune mediated blood disorders following SARS-CoV-2 Vaccination. Haematologica. 2022;107(4):785-786.
17. Cuker A, Cataland SR, Coppo P, et al. Redefining outcomes in immune TTP: an international working group consensus report. Blood. 2021;137(14):1855-1861.
18. Kivity S, Agmon-Levin N, Blank M, Shoenfeld Y. Infections and autoimmunity – friends or foes? Trends Immunol. 2009;30(8):409-414.
19. Watad A, De Marco G, Mahajna H, et al. Immune-mediated disease flares or new-onset disease in 27 subjects following mrna/dna sars-cov-2 vaccination. Vaccines. 2021;9(5):435.
20. Causality assessment of an adverse event following immunization (AEFI): user manual for the revised WHO classification (Second edition). Geneva: World Heal Organ; 2018.
21. Gresele P, Momi S, Marcucci R, Ramundo F, De Stefano V, Tripodi A. Interactions of adenoviruses with platelets and coagulation and the vaccine-associated autoimmune thrombocytopenia thrombosis syndrome. Haematologica. 2021;106(12):3034-3045.
22. Condorelli A, Markovic U, Sciortino R, Di Giorgio MA, Nicolosi D, Giuffrida G. Immune thrombocytopenic purpura cases following COVID-19 vaccination. Mediterr J Hematol Infect Dis. 2021;13(1):e2021047.