TO THE EDITOR:

SARS-CoV-2 vaccination and immune thrombotic thrombocytopenic purpura

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SARS-CoV-2 infection and COVID-19 vaccines have been associated with concerns about the new onset or recrudescence of autoimmune hematologic disorders. Cases of immune thrombocytopenia (ITP) following messenger RNA (mRNA) vaccines (Pfizer-BioNTech and Moderna) were reported soon after vaccines became available. Although subsequent analyses suggested that the incidence of ITP is not increased after mRNA vaccines,[1] there may be an association with the AstraZeneca ChAdOx1 vaccine.[2] Patients with ITP may have exacerbations after vaccination.[3,4] Vaccine-induced thrombotic thrombocytopenia (VITT) has also been reported after adenoviral COVID-19 vaccines.[5] These reports led to vaccine hesitancy among patients with thrombocytopenic disorders, including immune thrombotic thrombocytopenic purpura (iTTP), a relapsing thrombotic microangiopathy caused by antibody-mediated severe ADAMTS13 deficiency. These concerns were further compounded by reports of de novo and relapsed iTTP following mRNA vaccines.[6-10] Whether SARS CoV-2 vaccination is associated with iTTP recurrence has significant clinical implications; however, this has not been systematically investigated. We conducted a multicenter retrospective cohort study to evaluate the safety of SARS-CoV-2 vaccination in patients with preexisting iTTP. To estimate the incidence of iTTP (de novo and relapsed) after vaccination, we examined cases of iTTP after COVID-19 vaccination reported in the Vaccine Adverse Event Reporting System (VAERS), the US passive surveillance system for adverse events after immunization.[11]

Patients with confirmed iTTP (based on documented ADAMTS13 activity <10% during an acute episode of thrombotic microangiopathy) and documented SARS-CoV-2 vaccination, who were followed at Johns Hopkins Hospital, The Ohio State University, and the University of Minnesota, were included. Details about iTTP and SARS-CoV-2 vaccination, as well as available laboratory data, including platelet counts and ADAMTS13 activity before and after vaccination, were extracted from the medical record. The primary outcome was iTTP relapse characterized by a platelet count $<150 \times 10^9$/L and microangiopathic hemolysis with ADAMTS13 activity <10% occurring within 4 weeks of vaccination, the typical window for postvaccine autoimmune hematologic complications.[12] We report iTTP relapses occurring at >4 weeks after vaccination separately. We also examined changes in ADAMTS13 activity and platelet counts before and after vaccination.

Additionally, we searched the VAERS database for reports of adults (age >18 years) who developed iTTP after receiving SARS-CoV-2 vaccines. Individual reports were reviewed by 2 independent investigators to determine whether these were consistent with iTTP. We categorized cases as definite iTTP (documented severe ADAMTS13 deficiency), probable iTTP (presentation and treatment compatible with iTTP but ADAMTS13 not reported), and possible iTTP (presentation and treatment possibly compatible with iTTP but inadequate information to make a definitive determination). Cases that were more compatible with alternative diagnoses, such as ITP or VITT, were excluded.

Between December of 2020 and December of 2021, 79 patients with iTTP received COVID-19 vaccines (52 at Johns Hopkins University, 20 at The Ohio State University, and 7 at the University of Minnesota) (Table 1); 47 received the Pfizer vaccine, 27 received the Moderna vaccine, and 5 received the Johnson &

Table 1. Demographics and clinical characteristics of patients with iTTP who received SARS CoV-2 vaccines at 3 university hospitals in the United States

Characteristic	N = 79
Age, median (IQR), y	54 (42.5-66)
Females	61 (77.2)
Males	18 (22.8)
Race	
Black	45 (57.0)
White	33 (41.8)
Asian	1 (1.2)
Number of iTTP episodes, median (IQR)	1 (1-3)
Time from last iTTP episode to first vaccine dose, median (IQR), mo	68.5 (29.7-144.1)
Vaccine type	
Pfizer	47 (59.5)
Moderna	27 (34.2)
Johnson & Johnson	5 (6.3)
Prior rituximab therapy	52 (65.8)
Time from most recent dose of rituximab to first dose of vaccine, median (IQR), mo	10.5 (0.57-50.28)
ADAMTS13 activity prevaccination, median (IQR), % (n = 66)	79.2 (47.2-100)

Unless otherwise noted, data are n (%).

Table 2. Characteristics of iTTP cases after mRNA COVID-19 vaccines reported in VAERS

Variable	All cases (N = 37)	Certainty of diagnosis of iTTP		
		Definite (n = 16)	Probable (n = 8)	Possible (n = 13)
Age, median (IQR), y (n = 32)	49.5 (25.5-63.0)	60.5 (26.0-69.0)	52.5 (26.8-68.0)	37.0 (25.3-60.8)
Females	19 (51.4)	3 (18.8)	7 (87.5)	9 (69.2)
Males	17 (45.9)	13 (81.3)	1 (12.5)	3 (23.1)
Type of vaccine				
Pfizer	18 (48.6)	7 (43.8)	4 (50.0)	7 (53.8)
Moderna	15 (40.5)	7 (43.8)	4 (50.0)	4 (30.8)
Johnson & Johnson	4 (10.9)	2 (12.5)	0 (0.0)	2 (15.4)
Vaccine dose				
First dose	15 (40.5)	6 (37.5)	3 (37.5)	6 (46.2)
Second dose	18 (48.7)	9 (56.3)	3 (37.5)	6 (46.2)
Third dose	1 (2.7)	0 (0.0)	1 (12.5)	0 (0.0)
Not reported	3 (8.1)	1 (6.3)	1 (12.5)	1 (7.7)
Time since vaccination, median (IQR), d (n = 32)	13.5 (3.3-27.8)	12.5 (3.8-35.7)	8.5 (0.25-25.0)	22.0 (5.8-45.5)
De novo iTTP	32 (86.5)	15 (93.8)	5 (62.5)	12 (92.3)
Recurrent iTTP	5 (13.5)	1 (6.2)	3 (37.5)	1 (7.7)

Johnson vaccine. Thirty patients also received a booster dose. Time between the most recent iTTP episode and the first vaccine dose was 68.5 months (interquartile range [IQR], 29.7-144.1). Median follow-up after the first vaccine dose was 6.7 months (IQR, 4.9-8.7 months). Median ADAMTS13 activity in the 3 months prior to vaccination (evaluated in 66 patients) was 79.2% (IQR, 47.2%-100%). iTTP relapse within 4 weeks of vaccination occurred in 1 patient (1.3%), a 28-year-old female at 1.5 years from her initial iTTP episode who did not recover ADAMTS13 activity at all (<2%) during remission. Six days after the first dose of the Pfizer vaccine, she developed bruising, petechiae, ataxia, and slurred speech. Laboratory testing revealed thrombocytopenia, schistocytes, and undetectable ADAMTS13 activity. She was successfully treated with caplacizumab, rituximab, and corticosteroids without plasma exchange based on our prior experience treating early relapse with this regimen.[13] She received the second dose of the Pfizer vaccine uneventfully after ADAMTS13 activity was >20%. Three other patients were treated for iTTP recurrences between 35 and 143 days after vaccination, which are less likely to be associated with vaccination (supplemental Table 1, available on the *Blood* Web site). Over the entire observation period, the incidence of iTTP relapse after vaccination was 0.095 per patient-years.

We next examined the VAERS database for de novo and relapsed iTTP after COVID-19 vaccination. As of 17 December 2021, 37 cases of TTP after SARS-CoV-2 vaccines (18 Pfizer, 15 Moderna, and 4 Johnson and Johnson) were reported (Table 2): 16 were classified as confirmed iTTP, 8 were classified as probable iTTP, and 13 were classified as possible iTTP (supplemental Table 2). Five cases were recurrences in patients with a prior history of iTTP. The majority (n = 18, 48.6%) of cases occurred after the second dose of an mRNA vaccine, and the median time from vaccine dose to presentation was 13.5 days (IQR, 3.3-27.8). During this period, 188 893 626 adults were fully vaccinated (excluding individuals who received a single dose of an mRNA vaccine).[14] Thus, the calculated incidence rate of postvaccination iTTP is 0.195 per million. Fifteen cases were reported for 73 283 928 adults fully vaccinated with the Moderna vaccine (0.245 per million), 18 cases were reported for 115 691 156 adults fully vaccinated with the Pfizer BNT162b2 vaccine (0.155 per million), and 4 cases were reported for 16 409 558 individuals who received the Johnson & Johnson vaccine (0.244 per million). Although the temporal relationship of several cases occurring within a month of vaccination is concerning for an association, the estimated incidence is not higher than the incidence of iTTP in the United States (1.7-3.7 per million).[15,16]

De novo and relapsed iTTP have been reported after various vaccines,[17-19] including SARS-CoV-2 vaccines,[6-10] where the association is supported by the absence of another proximate cause and a temporal relationship, with most cases occurring between 5 and 15 days after vaccination. Most cases of iTTP following COVID-19 vaccination in VAERS occurred within 14 days after vaccination, which is concerning for a possible association. In our cohort, 3 of 4 patients with iTTP recurrence presented >30 days after vaccination, arguing against vaccine-induced autoimmunity in these cases, although it must be noted that VITT has been reported up to 48 days after vaccination[5]; therefore, an association with iTTP relapse after 30 days is plausible and may apply to the patient who had a relapse 35 days after the second vaccine dose (supplemental Table 1). Vaccination could precipitate acute iTTP in patients who already have low ADAMTS13. This is supported by the observation that ADAMTS13 deficiency is necessary, but not sufficient, for TTP and that the only relapses in our cohort occurred in individuals with low/unknown ADAMTS13 activity within 3 months prior. Our combined cohort is relatively mature, and we offer preemptive rituximab to patients with

ADAMTS13 activity <20% during clinical remission, which may explain the high prevaccination ADAMTS13 activity and corresponding low relapse rate. Patients in clinical remission without ADAMTS13 remission[20] might be at increased risk for relapse[21,22] following COVID-19 vaccination. We check ADAMTS13 activity every 3 months in all patients to estimate the risk of recurrence (including postvaccination). We recommend checking the platelet count and ADAMTS13 activity weekly for 2 to 4 weeks after vaccination in patients with low ADAMTS13 activity (<20%).

Acute iTTP is life-threatening, and we expect that all recurrences were documented in the medical record. However, we are unable to report other vaccine-associated adverse events because these were not consistently documented. A limitation of VAERS data is that some cases have limited clinical and laboratory information (including ADAMTS13).[23] To address this challenge, we categorized cases based on certainty of the TTP diagnosis. Finally, VAERS is a passive surveillance system, and iTTP after vaccination may be underreported,[23] which is a limitation. To avoid underestimating incidence, we included all reported cases of iTTP (rather than only ADAMTS13 cases) and used only fully vaccinated individuals as the denominator.

In summary, data from a large multicenter cohort and VAERS appear to be reassuring that COVID-19 vaccination does not increase the risk of de novo or relapsed iTTP, except in individuals with extremely low ADAMTS13 activity (<20%) in remission. Prospective studies to confirm this finding are needed. Until then, these data may help individuals with iTTP and their physicians to make informed decisions about vaccination.

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Authorship

Contribution: H.S. and A.K collected data, performed analyses, and wrote the manuscript; S.S. and M.M. collected data and critically reviewed the manuscript; R.K. reviewed VAERS data and wrote the manuscript; E.M.B, R.A.B., and S. Cataland interpreted the data and critically reviewed the manuscript; S. Chaturvedi designed the research, verified all outcomes, reviewed VAERS data, interpreted the analyses, and wrote the manuscript; and all authors read and approved the final version of the manuscript.

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Footnotes

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Requests for data sharing may be submitted to Shruti Chaturvedi (schatur3@jhmi.edu).

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