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Short communication

Thrombocytopenia including immune thrombocytopenia after receipt of mRNA COVID-19 vaccines reported to the Vaccine Adverse Event Reporting System (VAERS)

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ABSTRACT

Background: The objective of this study is to assess cases of thrombocytopenia, including immune thrombocytopenia (ITP), reported to the Vaccine Adverse Event Reporting System (VAERS) following vaccination with mRNA COVID-19 vaccines.
Methods: This case-series study analyzed VAERS reports of thrombocytopenia after vaccination with Pfizer-BioNTech COVID-19 Vaccine or Moderna COVID-19 Vaccine.
Results: Fifteen cases of thrombocytopenia were identified among 18,841,309 doses of Pfizer-BioNTech COVID-19 Vaccine and 13 cases among 16,260,102 doses of Moderna COVID-19 Vaccine. The reporting rate of thrombocytopenia was 0.80 per million doses for both vaccines. Based on an annual incidence rate of 3.3 ITP cases per 100,000 adults, the observed number of all thrombocytopenia cases, which includes ITP, following administration of mRNA COVID-19 vaccines is not greater than the number of ITP cases expected.
Conclusions: The number of thrombocytopenia cases reported to VAERS does not suggest a safety concern attributable to mRNA COVID-19 vaccines at this time.

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1. Introduction

FDA issued an Emergency Use Authorization (EUA) for the Pfizer-BioNTech COVID-19 Vaccine on December 11, 2020 as a two dose series administered 21 days apart [1]. Shortly after, on December 18, 2020, an EUA was issued for the Moderna COVID-19 Vaccine for administration as two doses given one month apart [2]. Both vaccines use a lipid-nanoparticle encapsulated mRNA platform that encodes the SARS-CoV-2 viral spike (S) glycoprotein. Interim recommendations for use were published by the Advisory Committee on Immunization Practices [3]. Prior to the issuance of the EUA for these vaccines, FDA and CDC planned for monitoring of their safety utilizing passive and active surveillance, which included enhanced surveillance for adverse events of special interest such as thrombocytopenia [4]. In addition, the EUA for both vaccines required reporting of serious adverse events (irrespective of attribution to vaccination) to the Vaccine Adverse Event Reporting System (VAERS), the national spontaneous reporting (passive surveillance) system for monitoring vaccine safety [1,2]. Shortly after authorization, FDA received reports of immune thrombocytopenia (ITP) in close temporal proximity to COVID-19 vaccination to VAERS. ITP is characterized by a platelet count less than 100 $x10^9$/L and immune-mediated destruction of platelets or impaired megakaryocytopoiesis [5]. Given that ITP has been associated with measles-mumps-rubella (MMR) vaccine and natural measles and rubella infection [6], it was considered biologically plausible to consider an association with COVID vaccines since ITP has also been associated with SARS-CoV-2 infection [7]. Thrombocytopenia was rarely reported in the clinical trial experience for mRNA COVID-19 vaccines with no imbalances between the vaccinated and placebo groups [8,9]. This report assesses thrombocytopenia cases, which includes ITP, reported to VAERS after vaccination against COVID-19 disease with the Pfizer-BioNTech or Moderna COVID-19 Vaccine.

2. Materials and methods

VAERS was searched for reports from the time of authorization of the first mRNA COVID-19 vaccine to the data lock point of February 4, 2020 for the following Medical Dictionary for Regulatory

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Activities (MedDRA) preferred terms: autoimmune thrombocytopenia, idiopathic thrombocytopenic purpura, immune thrombocytopenia, immune thrombocytopenic purpura, thrombocytopenia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, platelet count abnormal, platelet count decreased, platelet transfusion, and petechiae. FDA physicians assessed these reports using the Brighton Collaboration definition for thrombocytopenia [10]. Briefly, a Level 1 (confirmed thrombocytopenia) of diagnostic certainty according to the Brighton definition of thrombocytopenia consists of a platelet count of less than 150×10^9/L AND confirmed by blood smear examination OR presence of signs and symptoms of spontaneous bleeding; Level 2 of diagnostic certainty (unconfirmed thrombocytopenia) is defined as a platelet count of less than 150×10^9/L; and Level 3 of diagnostic certainty is n*ot applicable*. Cases with symptom onset or thrombocytopenia identified on the same day of vaccination were excluded, as onset of less than 24 h was deemed to not be biologically attributable to vaccination given that an immune-mediated response is the hypothesized mechanism of ITP post-vaccination [11]. FDA chose to include all potential thrombocytopenia cases presenting $\geq$1 day after vaccination because spontaneous reports may not always have sufficient information for precise classification of the etiology of thrombocytopenia, and to evaluate all cases that may be plausibly consistent with a vaccine etiology.

Empirical Bayesian data mining techniques [12] were used to identify MedDRA preferred terms that occurred more often than expected compared to all other vaccines in VAERS. Data mining analysis calculates the Empirical Bayes Geometric Mean and a 90% confidence interval (EB05, EB95). An EB05 $\geq$2 indicates a vaccine-event pair occurs at least twice as often as expected, which is used as a threshold for further evaluation of an adverse event [13].

3. Results

As of February 4, 2021, there were 18,841,309 doses of Pfizer-BioNTech COVID-19 Vaccine and 16,260,102 doses of Moderna COVID-19 Vaccine administered in the United States [14]. FDA identified 15 cases of thrombocytopenia after Pfizer-BioNTech COVID-19 Vaccine and 13 cases after Moderna COVID-19 Vaccine (Table 1) corresponding to reporting rates of 0.80 per million doses for both vaccines. All cases were reported from the United States. Of the 28 cases of thrombocytopenia after COVID-19 vaccines, 15 were female, 11 were male, and in two the sex was not reported. The median age of cases was 48.5 years (range 22–82 years, unreported for two cases). The reported onset of thrombocytopenia after COVID-19 vaccination ranged from 1–23 days (median 5.5 days) after vaccination, although the onset time relative to vaccination was unreported for four cases. Most reports described patients who presented for medical evaluation due to signs and symptoms of bleeding such as petechiae or bruising. There was one patient who experienced a pulmonary embolism and was reported to have thrombocytopenia; however, minimal case details were available. One report described an asymptomatic patient with thrombocytopenia discovered 15 days after vaccination by laboratory work performed for a routine physical examination. Two cases occurred following the second COVID-19 vaccination; the remaining cases were after dose one or did not specify the dose number in the report. Two patients in this case series died, one of whose death was attributed to intracranial hemorrhage secondary to ITP. The second patient who died reportedly experienced acute myocardial infarction, a pulmonary embolism, and thrombocytopenia although minimal additional case details are available.

Of the 28 cases of thrombocytopenia after mRNA COVID-19 vaccination, 12 cases after the Pfizer-BioNTech COVID-19 Vaccine and 12 cases after the Moderna COVID-19 Vaccine were assessed as Brighton Level 1 or 2. Three cases reported a prior history of ITP, which is often a chronic disorder in adults [5]. One patient had a history of Crohn's disease, another had type 1 diabetes, another reported a history of Hashimoto's thyroiditis (positive anti-thyroglobulin antibodies, euthyroid, and not on thyroid hormone replacement), and a fourth case reported having psoriasis, all of which are conditions that indicate an underlying inflammatory state that may have contributed to ITP development [15]. The remaining cases did not report other conditions that predispose to thrombocytopenia such as recent viral infection, other autoimmune disorders, or a family history of thrombocytopenia. As of February 26, 2021, data mining did not reveal any MedDRA preferred terms with an EB05 $\geq$2 for either mRNA COVID-19 vaccine.

4. Discussion

ITP has been reported after several vaccines, including MMR, Haemophilus influenza, hepatitis B virus, human papilloma virus, diphtheria-tetanus-acellular pertussis, varicella-zoster, pneumococcus, and polio [16]. However, only the MMR vaccine has been linked to ITP, with a risk window of six weeks [6,16]. The etiology of vaccine-related thrombocytopenia is considered immune related because antibodies can be detected on platelets in approximately 79% of cases [11]. Of note, COVID-19 infection has been linked to thrombocytopenia and ITP possibly due to immune-mediated destruction, direct infection of megakaryocytes or platelets, decreased thrombopoietin production related to liver damage, and consumption due to a coagulopathic state [7]. The median time to onset from symptoms of COVID-19 to presentation with ITP in one review was 13 days, with most patients presenting after two to three weeks, although approximately 20% of COVID-19 patients presented with ITP in $\leq$7 days [7]. In comparison, in this case series the median onset time from vaccination to presentation with thrombocytopenia was 5.5 days for cases where the onset time frame was reported (range 1–23 days). The mechanism by which thrombocytopenia could plausibly be related to vaccination in these cases is unclear, as an immune-mediated mechanism would be expected to have a longer onset interval than observed in most cases in this series, unless these patients had been previously sensitized by prior SARS-CoV-2 infection. It is unknown if these patients had a prior history of COVID-19. It is also possible that the temporal proximity to vaccination was coincidental.

The annual incidence of ITP is approximately 1 to 6 cases per 100,000 adults per year [17]. If an incidence rate of 3.3 ITP cases per 100,000 adults is assumed [17], among 27,905,197 people who have received at least one dose of vaccine [14], one would expect 921 cases of ITP over the course of a year. Assuming December 21, 2020, as the date of initiation of mass vaccinations for a risk period of 45 days (December 21, 2020 to February 4, 2021) and that each vaccinee contributes 22.5 days (mid-point of the risk period), approximately 57 cases of ITP are expected in the risk interval. In comparison, VAERS received 28 cases of thrombocytopenia. As all of these reports of thrombocytopenia may not be ITP, reports of ITP were not higher than expected.

Recent reports have emerged of thrombotic events, including cerebral venous sinus thrombosis and splanchnic thrombosis, following use of COVID-19 Vaccine AstraZeneca and the Johnson & Johnson COVID-19 Vaccine [18,19]. These thrombotic events have frequently occurred in the presence of thrombocytopenia, with most cases occurring in women less than 60 years of age and within two weeks of vaccination. However, this issue is still under evaluation at this time and other risk factors may be identified as

Table 1
Characteristics of reported thrombocytopenia cases following receipt of Pfizer-BioNTech COVID-19 Vaccine or Moderna COVID-19 Vaccine through February 4, 2021.

Case	Age (yrs)	Sex	Past medical history	Onset after vaccination (days)	Signs and symptoms	Initial platelet count (10^9/L)	Brighton level	Treatment	Outcome or disposition
a) Cases of thrombocytopenia reported after Pfizer-BioNTech COVID-19 Vaccine									
1	56	M	None	2	Generalized purpura and petechiae, gingival bleeding, scleral hemorrhage, intracranial hemorrhage	<1	1	Prednisone, platelet and RBC transfusion, eltrombopag, dexamethasone, cyclosporine, rituximab, IVIG, emergent craniectomy, splenectomy	Death
2	22	M	None	3	Diffuse petechiae, epistaxis, gingival bleeding, hematuria, scleral hemorrhage	2	1	Dexamethasone, platelet transfusion, IVIG	Discharged home
3	73	M	HTN, DM	1	Diffuse petechiae and purpura	1	1	Prednisone, IVIG, platelet transfusion	Discharged home
4	Unk	Unk	Unk	Unk	Reported decrease in platelets after vaccination	Unk	3	Not reported	Not reported
5	36	F	None	5	Weakness, increased menstrual bleeding, blood blisters in mouth, diffuse petechiae, epistaxis	9	1	Not reported	Not reported
6	41	M	Type 1 DM, ITP in 2012, GERD	2	Epistaxis, petechiae	2	1	Platelet transfusion, IVIG, prednisone, rituximab	Discharged home
7	53	M	Hyperlipidemia, HTN	15	None, platelet count performed as part of routine physical	10	2	Platelet transfusion, IVIG, dexamethasone	Discharged home
8	82	F	Unk	Unk	Reported as thrombocytopenia, pulmonary embolism, neutropenia, dyspnea, and myocardial infarction	Unk	3	Not reported	Death
9	59	M	None	Unk	None, case reported as thrombocytopenia	Unk	3	Not reported	Not reported
10[a]	39	F	Depression, PCOS	2	Diffuse petechiae, increased menstrual bleeding	1	1	Platelet transfusion, solumedrol, prednisone, IVIG	Admitted at time of report
11	80	M	Diverticulosis, aortic stenosis, HTN, hyperlipidemia, DM	6	GI bleed	60	1	RBC and platelet transfusion	Not reported
12	53	M	Crohn's disease, HTN, GERD, prediabetes, nephrolithiasis	7	Hemorrhagic oral bullae, diffuse petechiae	2	1	Dexamethasone, IVIG	Discharged home
13	39	F	HBV	12	Intracranial hemorrhage, bruising	36	1	Platelet and RBC transfusion, unspecified brain surgery	Discharged to rehabilitation facility
14	78	F	Afib, essential tremor, thyroid nodule	6	Petechiae	6	1	IVIG, dexamethasone, platelet transfusion	Discharged to home
15	55	F	HTN, DM, arthritis	4	Petechiae, gum sores	2	1	Dexamethasone, IVIG, platelet transfusion	Admitted at time of report
b) Cases of thrombocytopenia reported after Moderna COVID-19 Vaccine									
1	25	F	Anxiety, positive Hashimoto's thyroiditis	10	Oral mucosal bleeding, diffuse petechiae and ecchymoses	1	1	Dexamethasone, IVIG	Discharged to home
2	43	F	GERD	8	Diffuse petechiae, bruising	2	1	IVIG, prednisone	Discharged to home
3	26	F	None	2	Diffuse bruising	2	1	IVIG, platelet transfusion, unspecified steroids	Recovered
4	50	F	HTN	23	Diffuse petechiae	2	1	Platelet transfusion, IVIG, dexamethasone	Admitted at time of report
5	36	F	ITP	16	Diffuse petechiae, bruising	3	1	Dexamethasone, IVIG	Recovered
6	Unk	Unk	Not reported	1	Reported as "blister in head officially Shingles"	29	2	Unspecified steroids	Not reported
7	72	F	Not reported	1	Blood blisters in mouth, diffuse bruising	3	1	Unspecified steroids	Not reported
8	48	F	HTN, obesity	13	Heavy vaginal bleeding	1	1	Platelet transfusion, IVIG, unspecified steroids	Admitted at time of report
9	36	M	Epilepsy	15	Not reported	1	2	Not reported	Not reported
10	63	M	DM, HTN, hyperlipidemia	11	Not reported	1	2	Not reported	Admitted at time of report
11[a]	38	F	ITP, positive for anti-platelet antibodies	2	Diffuse petechiae	<1	1	IVIG, dexamethasone	Discharged to home

(*continued on next page*)

Table 1 (*continued*)

Case	Age (yrs)	Sex	Past medical history	Onset after vaccination (days)	Signs and symptoms	Initial platelet count (10^9/L)	Brighton level	Treatment	Outcome or disposition
12	37	M	Not reported	Unk	Reported as thrombocytopenia	Unk	3	Platelet transfusion	Recovered
13	49	F	Migraines, psoriasis	1	Petechiae, shortness of breath	66	1	Not reported	Not reported

[a] Thrombocytopenia developed after 2nd dose.

the investigation on thrombotic events after COVID-19 vaccination proceeds. A hypothesized mechanism for thrombosis in the presence of thrombocytopenia is an immune-mediated response similar to heparin-induced thrombocytopenia [18,19]. Most of the patients in this case series did not have a reported thrombotic event in the presence of thrombocytopenia.

There are limitations in interpreting these data. As a passive safety surveillance system, VAERS relies on submission of reports that describe adverse reactions after vaccination. Although mandatory reporting requirements exist, underreporting and delayed reporting are known to occur. The absence of an unvaccinated control group prohibits calculation of relative risks. Data mining analyses are limited by focusing on one MedDRA preferred term and vaccine pair which may not capture related events that are coded with different preferred terms, and are subject to the same limitations of underlying VAERS data. Medical records were not always available to assess for underlying etiologies that may be associated with thrombocytopenia and ITP. It is not possible to exclude other causes of thrombocytopenia due to the potential for incomplete reports with passive surveillance systems. Given that COVID-19 vaccines will continue to be administered in increasingly diverse populations, and new vaccines for COVID-19 may be authorized in the future, continuing surveillance for thrombocytopenia including ITP is warranted. In addition to VAERS, thrombocytopenia, thrombotic events, and other adverse events of special interest are monitored by active surveillance studies conducted by CDC and FDA using v-safe, Vaccine Safety Datalink, the FDA Biologics Effectiveness and Safety System, and the Center for Medicare and Medicaid Services databases [4,20]. This analysis found fewer thrombocytopenia cases were reported to VAERS than expected when considering the background rate of ITP and the number of individuals vaccinated. In the context of heightened vigilance and robust reporting to VAERS, the number of post-vaccination ITP cases do not suggest a safety concern attributable to COVID-19 vaccination at this time. FDA continues to monitor reports of thrombocytopenia, including ITP in VAERS, along with other outcomes.

All authors attest they meet the ICMJE criteria for authorship.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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