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Vaccine 40 (2022) 4116–4120

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Thrombocytopenia after Ad.26.COV2.S COVID-19 vaccine: Reports to the vaccine adverse event reporting system

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ARTICLE INFO

Article history:
Received 30 March 2022
Received in revised form 24 May 2022
Accepted 25 May 2022
Available online 30 May 2022

Keywords:
Thrombocytopenia
VAERS
Ad.26.COV2.S COVID-19 vaccine
Coronavirus
SARS-CoV2

ABSTRACT

Background: On February 27, 2021, the Food and Drug Administration (FDA) issued an Emergency Use Authorization for Ad.26.COV2.S COVID-19 vaccine. As part of post-authorization safety surveillance, the FDA has identified a potential safety concern for thrombocytopenia following receipt of Ad.26.COV2.S COVID-19 vaccine.

Methods: Reports of thrombocytopenia were identified in a passive reporting system (Vaccine Adverse Event Reporting System; VAERS) February-December 2021. Demographics, clinical characteristics, laboratory values, and relevant medical history were reviewed. The reporting rate was analyzed, including calculation of the observed-to-expected ratio based on vaccine administration data and the background rate of thrombocytopenia in the general (unvaccinated) population.

Results: As of December 31, 2021, 100 reports of thrombocytopenia were identified in VAERS following vaccination with Ad.26.COV2.S. The median platelet count was 33,000 per μL (interquartile range 8,000–86,000). Fifteen reports (15%) documented a platelet count of 5,000 per μL or lower. The median time to onset of thrombocytopenia was 9 days (interquartile range 3–18.5), with most cases (69; 69%) beginning within 14 days after vaccination. A large majority of cases (84; 84%) were serious, including six deaths. With approximately 16,292,911 doses of Ad.26.COV2.S administered to adults in the US, the crude reporting rate was 0.61 cases of thrombocytopenia per 100,000 doses administered. The overall estimated observed-to-expected rate ratio was 2.43 (95% CI 1.97, 2.95).

Conclusions: These findings suggest an increased risk of thrombocytopenia following receipt of Ad.26.COV2.S.

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1. Introduction

On February 27, 2021, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for Janssen COVID-19 Vaccine [1], followed by interim recommendations for use by the Advisory Committee on Immunization Practices [2]. Ad.26.COV2.S uses a replication-incompetent human adenoviral type 26 vector platform and is indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 18 years of age and older [1,3]. The FDA's EUA review focused on a randomized, double-blind, placebo-controlled trial; safety was assessed in 21,895 vaccine recipients and 21,888 individuals who received placebo [4].

Post-authorization safety surveillance in the Vaccine Adverse Event Reporting System (VAERS) identified reports of cerebral venous sinus thrombosis (CVST) and thrombosis with thrombocytopenia syndrome (TTS) after Ad.26.COV2.S [5,6]. On April 13, 2021, use of the vaccine in the US was paused because of concerns about a potential association with the vaccine [7]. Upon review by the FDA, CDC, and ACIP, the pause was lifted on April 23, 2021 [8] and the product Fact Sheets were updated to include a Warning about TTS [3].

As part of continual, routine safety surveillance, FDA has identified VAERS reports of thrombocytopenia, with or without thrombosis, following Ad.26.COV2.S. The objective of the case series described herein is to review reports of thrombocytopenia after Ad.26.COV2.S vaccination and to assess whether the risk of thrombocytopenia is greater than would be expected, based on a background rate from the published literature.

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https://doi.org/10.1016/j.vaccine.2022.05.078
0264-410X/Published by Elsevier Ltd.

2. Methods

VAERS is a national passive surveillance system for monitoring vaccine safety [9,10]. Established in 1990, VAERS is jointly managed by the U.S. Food and Drug Administration (FDA) and Centers for Disease Control and Prevention and, in recent years, has received more than 50,000 reports per year. Reports are submitted by clinicians, vaccine recipients or their parents or guardians, vaccine manufacturers, and other interested parties. FDA physicians review all reports of serious events, defined as events that are fatal, disabling, or life-threatening; require or prolong hospitalization; result in congenital anomalies; require medical intervention to prevent such outcomes; or are deemed to be other medically important conditions [11].

VAERS was searched for US reports received February 27, 2021 through December 31, 2021, stating that the patient had received Ad.26.COV2.S. Reports of possible thrombocytopenia were identified by two complementary methods: daily review of serious reports by an FDA physician, and automated query of VAERS for Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs): PT search: *autoimmune thrombocytopenia, idiopathic thrombocytopenic purpura, immune thrombocytopenia, immune thrombocytopenic purpura, thrombocytopenic purpura,* and *thrombocytopenia.* Reports with any of these terms were identified as cases of potential thrombocytopenia, and were then individually reviewed by a physician. Any available medical records were also reviewed. Demographics, clinical characteristics, concomitant exposures, and relevant medical history were reviewed and summarized. Duplicates were consolidated.

In the main analysis, cases were retained as thrombocytopenia based on a platelet count below 150,000 per μL or diagnosis of thrombocytopenia (in case of a missing platelet count). The narrow analysis included cases with a documented platelet count below 100,000 per μL. The expanded analysis included cases with a platelet count below 150,000 per μL or a diagnosis of thrombocytopenia, including cases that had undergone expert adjudication and were confirmed to be TTS [5,6]. All three analyses were limited to cases that began within 28 days after Ad.26.COV2.S vaccination.

The reporting rate was estimated and observed-to-expected (O/E) analyses were performed using the observed number of cases from spontaneous reporting, vaccine administration data [12], and published background rates [13]. The person-time at risk was calculated based on the cumulative vaccine administration data (Table 2). The expected number of cases was calculated as Exp_{cases} = (person-years) × (BR/100,000), where person-years was the accumulated person-time in years and BR was the background rate per 100,000 person-years. The respective Rate Ratio (RR) was then estimated as RR = N_{cases}/Exp_{cases}, where N_{cases} was the number of reported (observed) cases. The 95% confidence intervals (i.e., assuming a two-sided type 1 error of 0.05) for the RRs were provided. These were based on the exact confidence intervals for the number of observed cases, assumed to be a Poisson random variable, and were given as:

$$\left(\frac{1}{2}\chi^2_{2c;\frac{\alpha}{2}}, \frac{1}{2}\chi^2_{2(c+1);1-\frac{\alpha}{2}}\right)$$

where c was the observed number of cases, $\chi^2_{2c;\frac{\alpha}{2}}$ was the $\frac{\alpha}{2}$-th quantile of the χ^2 distribution with 2c degrees of freedom [14]. The respective CI for the RR was derived by dividing the above CI's limits by the expected number of cases Exp_{cases}. No adjustment of the type 1 error for multiple testing was conducted. The calculations were done in R (version 3.6.1).

This work was conducted as part of routine vaccine safety activities [i] and public health surveillance [ii]. No Institutional Review Board approval was required. Data are deidentified, and patient informed consent was not required.

3. Results

3.1. Overview

As of December 31, 2021, FDA identified 100 reports of thrombocytopenia after Ad.26.COV2.S (Table 1). The median platelet count was 33,000 per μL (interquartile range 8,000–86,000). Fifteen reports (15%) documented a platelet count of 5,000 per μL or lower. The median time to onset of thrombocytopenia was 9 days (interquartile range 3–18.5), with most cases (69; 69%) beginning within 14 days after vaccination. The median patient age was 56 years (interquartile range 43.5–66), and 52 individuals (52%) were female. A large majority of cases, 84 (84%) were serious [11], including six deaths. Six reports mentioned a history of thrombocytopenia. No reports listed concomitant vaccines.

3.2. Death reports

Of the six individuals who died, the median age was 73.5 years (interquartile range 49–79), and four patients were female. Median platelet count was 41,000 per μL (interquartile range 10,000–86,000). Median onset time was 15 days after vaccination (interquartile range 1–19). One person had COVID-19 infection at the time of death, and one was incidentally found to be positive for SARS-CoV2. In addition to thrombocytopenia, five people had experienced clinically significant thrombotic or thromboembolic

Table 1
Demographics of patients and characteristics of thrombocytopenia reports after Ad.26.COV2.S vaccine.

Demographic and Report Characteristics	
Age (years)	
n	100
Mean	54.6 (15.55)
Median (interquartile range)	56 (43.5–66)
Sex	
Female	52 (52%)
Male	48 (48%)
Platelet count per μL	
n	82
Mean (standard deviation)	48,543 (47,122)
Median (interquartile range)	33,000 (8,000–86,000)
platelets < 10,000	29 (29%)
10,000 ≤ platelets < 20,000	8 (8%)
20,000 ≤ platelets < 50,000	12 (12%)
50,000 ≤ platelets < 100,000	15 (15%)
platelets ≥ 100,000	18 (18%)
platelet count missing[a]	18 (18%)
Time to onset (days) of thrombocytopenia after vaccination	
n	100
Mean (standard deviation)	10.6 (8.25)
Median (interquartile range)	9 (3–18.5)
Onset ≤ 7 days	41 (41%)
Onset ≤ 14 days	69 (69%)
Onset ≤ 21 days	90 (90%)
Onset ≤ 28 days	100 (100%)
Seriousness[b]	
Serious (including deaths)	84 (84%)
Died	6 (6%)

[a] For 18 reports, the platelet count was missing, but the diagnosis or clinical impression was thrombocytopenia.

[b] Serious: events that are reported as resulting in death, life-threatening adverse experience, hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, or congenital anomaly/birth defect [11]. These designations are defined by the reporter's input. Serious criteria are not mutually exclusive.

events: bilateral ovarian vein thrombi; 4-cm thrombus in the right atrium and mural thrombus in the femoral artery; cerebrovascular accident; deep vein thromboses; and bilateral pulmonary embolism with thrombi in the right atrium, right ventricle, left ventricle, ovarian vein, and inferior vena cava. These cases did not meet the case definition of TTS [5,6].

At the time of this review, one autopsy report was available. The cause of death was a vertebral fracture (preceded vaccination) complicated by fat embolism syndrome. For one fatal case, hospital records included a death summary; the cause of death was intracerebral hemorrhage. For the remaining four cases, information about the cause of death was pending.

3.3. Observed-to-expected analysis

From the date of EUA [1] through January 1, 2022, approximately 16,292,911 doses of Ad.26.COV2.S were administered to adults in the US (Table 2). The crude reporting rate for thrombocytopenia was approximately 0.61/100,000. O/E analyses revealed elevated RRs in the main (RR 2.43, 95% CI 1.97, 2.95), narrow (RR 1.55, 95% CI 1.20, 1.98), and expanded analyses (RR 4.10, 95% CI 3.51, 4.77) (Table 3, Supplemental Table 1, and Supplemental Table 2, respectively). The reported events for all risk windows that were considered, i.e. 7, 14, 21, and 28 days, were statistically significantly elevated (Table 3, Supplemental Table 1, and Supplemental Table 2, respectively).

Table 2
Vaccine administration data by week, as of 1/4/2022 [a] [12].

MMWR Week	Dose 1	Dose 2	Dose 3
1	464	22	0
2	475	32	0
3	395	41	0
4	333	50	0
5	1,710	123	0
6	1,116	118	0
7	1,144	203	0
8	1,550	315	0
9	375,343	1,446	0
10	1,561,090	3,855	0
11	965,348	2,895	0
12	724,234	2,475	0
13	1,246,512	3,429	0
14	3,091,929	7,729	0
15	661,736	2,417	0
16	10,451	572	0
17	374,750	1,561	0
18	621,412	2,284	0
19	547,536	2,297	0
20	597,853	2,439	0
21	478,438	1,926	0
22	357,182	1,416	0
23	360,047	1,494	0
24	321,439	1,401	0
25	260,792	1,119	0
26	207,554	949	0
27	201,151	979	0
28	187,321	891	0
29	187,836	936	0
30	212,329	1,044	0
31	216,710	1,136	0
32	202,328	1,319	0
33	192,176	2,292	676
34	175,470	2,397	685
35	150,187	1,975	546
36	122,331	1,594	474
37	137,600	1,858	448
38	111,131	1,862	419
39	107,999	1,964	630
40	100,039	1,507	446
41	102,410	1,542	467
42	100,369	12,270	792
43	127,340	102,930	3,446
44	139,908	125,010	4,329
45	123,146	117,247	4,812
46	124,092	125,381	6,230
47	84,183	81,522	4,737
48	122,423	138,999	9,419
49	103,828	125,588	11,014
50	89,963	98,264	7,574
51	52,002	48,915	3,140
52	47,806	42,762	2,085
Total	16,292,911	1,084,792	62,369

[a] Data are updated weekly and are subject to delay.

4. Discussion

Our findings suggest an increased risk of thrombocytopenia following receipt of Ad.26.COV2.S vaccine. In this VAERS review, O/E analyses based on broad and narrow approaches demonstrated an elevated RR in the 7-, 14-, 21-, and 28-day risk windows. The lower bound of the 95% confidence interval suggests that the risk of thrombocytopenia is at least doubled. However, the absolute risk of thrombocytopenia, both in the background population of adults (3.3/100,000 [13]) and following Ad.26.COV2.S vaccination (100 reports per ~16.3 million vaccinations), is extremely small and far lower than the risk of COVID-19, which as of December 31, 2021 has led to 54,839,778 cases in the US, including 824,174 deaths [12].

In the main analysis, we included cases with a diagnosis of thrombocytopenia, even in the absence of a confirmatory platelet count. Medical records acquisition is an ongoing process; additional laboratory reports might become available, particularly for patients who were treated at multiple facilities. To improve specificity, we performed a narrow analysis that required not only a documented platelet count, but imposed the further restriction of a count below 100,000 per μL. That analysis revealed a lower—but statistically significant—relative risk. Thus, even the most conservative evaluation suggests an elevated risk of thrombocytopenia following Ad.26.COV2.S.

To address the possibility of a broad spectrum of coagulopathy, in which thrombocytopenia might be the "tip of the iceberg," we performed an expanded analysis that included confirmed cases of TTS [5,6]. Although such analysis is likely to suffer from lower specificity, it may be more sensitive ("canary in a coal mine"). It is not yet known whether TTS is completely distinct from other clinical syndromes that include thrombocytopenia, or whether it lies on a continuum. Thrombocytopenia and TTS might represent different stages or manifestations of a protean syndrome that has not yet been fully characterized. In our review, almost all of the deaths involved thrombocytopenia paired with severe clot burden. That finding suggests that, even among cases that are not confirmed as TTS, there may be similar elements that represent a common pathophysiologic mechanism involving decreased platelet counts in the presence of thrombosis. Consumption, destruction, or reduced production of platelets can each cause thrombocytopenia, and these processes can (and likely do) co-exist in some individuals. We included cases of thrombocytopenia that began within 28 days following Ad.26.COV2.S. We chose that time window based on post-authorization experience in Europe. Cases of ITP following receipt of Ad.26.COV2.S or the AstraZeneca COVID-19 vaccine have been reported to EudraVigilance, the adverse event reporting system for the European Union [15]. (The AstraZeneca COVID-19 vaccine, which uses a replication-incompetent chimpanzee adenoviral vector, is not authorized or licensed for use in the US at this time.) The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) performed an assessment and recommended adding a warning statement that cases of very low levels of platelets have been reported very rarely, usually within the first four weeks following vaccination with

Table 3
Observed/Expected analysis of thrombocytopenia after Ad.26.COV2.S vaccine Cases are included based on platelet count below 150,000 per μL or diagnosis of thrombocytopenia, with onset time within 28 days after Ad.26.COV2.S vaccination.

	n	Person-years[a]	Expected Cases[b]	Rate Ratio (95% CI)
Onset ≤ 7 days	41	312,253	10.3	3.98 (2.86, 5.40)
Onset ≤ 14 days	69	624,506	20.6	3.35 (2.61, 4.24)
Onset ≤ 21 days	90	936,759	30.9	2.91 (2.34, 3.58)
Onset ≤ 28 days	100	1,249,012	41.2	2.43 (1.97, 2.95)

[a] Person-years = N × Risk Window/365.25, where N is the number of vaccine doses administered (based on cumulative vaccine administration data [12], Table 2).
[b] Based on a background rate of 3.3 cases per 100,000 person-years [13].

Ad.26.COV2.S or the AstraZeneca COVID-19 vaccine [15,16]. Data emerging from passive and active surveillance, as well as ongoing clinical studies, might suggest other risk windows (e.g., 42 days).

In our review, we identified cases of severe thrombocytopenia. Future assessments of thrombocytopenia following Ad.26.COV2.S could include a subgroup analysis of critical thrombocytopenia (e.g., platelet count < 10,000 per μL). Again, it is possible that our observations represent only one segment of a larger clinical entity, and evaluating cases of extreme thrombocytopenia might provide insight into the biological mechanism and pathophysiology of post-vaccination thrombocytopenia.

Strengths of VAERS include its national scope, size, timeliness, ability to detect events that were not observed during prelicensure trials, and surveillance among special populations [9]. FDA and CDC are also conducting active surveillance with large scale population-based studies, using claims data or electronic healthcare record data, which can provide additional information about VAERS-derived safety signals. The population-based data sources include the FDA Biologics Effectiveness and Safety System [17], the Center for Medicare and Medicaid Services databases [18], and the CDC Vaccine Safety Datalink [19]. Under the EUA [1], the manufacturer is also required to conduct post-authorization observational safety studies. FDA conducts continuous safety monitoring for adverse events after all vaccines, including Ad.26.COV2.S.

This study has several limitations. First, reports were not adjudicated by hematologists. Expert review might identify cases that should be excluded from O/E analyses. Second, spontaneous reports may contain incomplete information. The analysis was constrained by the information in the initial VAERS reports and limited medical documentation available to date. Additional medical record collection, review, and analyses are needed to evaluate comorbidities, concomitant medications/vaccines, and concurrent infections—including COVID-19—that might be associated with coagulopathy. Efforts to obtain medical records are underway. Third, our analyses compared the observed thrombocytopenia rates to the expected rates, based on background rates reported in the literature. We used the rate published by Terrell et al., which was "the strongest estimate of the incidence of [immune thrombocytopenia purpura]" in adults [13]. However, Terrell et al. cautioned that studies were from Europe and therefore might not be generalizable to other populations [13], i.e., the vaccinated population might not have the same background rate as the population that was assessed in the literature [13]. Fourth, thrombocytopenia and immune thrombocytopenia purpura are not synonymous, and the background rate of the latter might not be the best proxy for the background rate of the former. Fifth, in this series, only one case of thrombocytopenia was reported following the second dose of Ad.COV2.S. It is possible that clinicians and/or patients avoided Ad.COV2.S as a booster dose because of an adverse event after the first dose or because of public awareness of TTS. Although few people are likely to know their PF4 status, many individuals may be aware that they have common risk factors for coagulopathy (e.g., oral contraceptives, history of DVT or ITP) and opted to delay a booster or to receive an mRNA vaccine as a booster dose. Sixth, in our search strategy for identifying potential cases of thrombocytopenia, we excluded PTs that were too non-specific (e.g., *platelet count abnormal* and *platelet disorder*) because they might have captured reports of thrombocytosis, and PTs for conditions in which thrombocytopenia is likely related to different pathophysiological mechanisms (e.g., thrombotic thrombocytopenic purpura and hemolysis, elevated liver enzymes, and low platelets or HELLP syndrome). Alternative search parameters could yield different results. Finally, the type I error was not adjusted for multiple testing.

Although the EUA [1] stipulates mandatory reporting requirements for the manufacturer and clinicians, passive surveillance systems such as VAERS are subject to many limitations, including underreporting, stimulated reporting, incomplete information, and lack of direct and unbiased comparison groups [9,10]. Because of these and other limitations, it is usually not possible to verify causal associations between vaccines and adverse events from spontaneous reports to VAERS. Nevertheless, VAERS data are used to describe a range of potential vaccine adverse events and to look for unexpected patterns in demographics and clinical characteristics that might lead to hypotheses that can be tested with epidemiologic studies [20].

5. Conclusions

FDA has continually monitored the post authorization safety of COVID-19 vaccines through both active and passive surveillance, as well as review of safety data submitted by the manufacturers. These findings suggest an increased risk of thrombocytopenia following receipt of Ad.26.COV2.S. Based on an analysis with broader search parameters, FDA determined that the Fact Sheet for vaccination providers should be revised to include immune thrombocytopenia in Warnings and Precautions [21]. FDA also determined that Fact Sheet for vaccine recipients and their caregivers should be revised to include information on the occurrence of immune thrombocytopenia following administration of Ad.26.COV2.S vaccine, instructions for potential vaccine recipients to inform vaccination providers of a history of thrombocytopenia, and instructions for vaccine recipients to seek medical attention for symptoms of immune thrombocytopenia [21].

Funding

The work was completed as part of routine postmarketing surveillance by the Food and Drug Administration, and funding came from the agency's budget.

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.

Acknowledgements

The authors thank Drs. Meghna Alimchandani, Karen Farizo, Richard Forshee, Adamma Mba-Jonas, Narayan Nair, and Alisha Thomas for critical review of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.05.078.

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