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BRIEF REPORT

Comparison of adverse drug reactions among four COVID-19 vaccines in Europe using the EudraVigilance database: Thrombosis at unusual sites

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Abstract

Background: Real-world experience with adenoviral vector vaccines against COVID-19 raised some safety concerns. Cases of cerebral vein thrombosis (CVT) associated with thrombocytopenia have been observed after the first dose of the adenoviral vector vaccines CHADOX1 NCOV-19 and AD26.COV2.S.

Objectives: To assess the reporting rate of CVT as adverse drug reaction (ADR) for the COVID-19 vaccines authorized in Europe.

Patients and Methods: This observational study assessed the CVT reporting rate attributed to four COVID-19 vaccines authorized in Europe, namely Tozinameran (Pfizer-Biontech), CX-024414 (Moderna), CHADOX1 NCOV-19 (AstraZeneca), and AD26.COV2.S (Janssen). Data on thrombotic ADRs reported on EudraVigilance database between January 1, 2021 and July 30, 2021, were collected. ADRs referring to CVT were identified. The reporting rate of CVT was expressed as 1 million individual vaccinated-days with 95% confidence interval. Finally, an observed-to-expected (OE) analysis was performed.

Results: The reporting rate of CVT per 1 million person vaccinated-days was 1.92 (95% confidence interval [CI], 1.71–2.12) for Tozinameran, 5.63 (95% CI, 4.74–6.64) for CX-024414, 21.60 (95% CI, 20.16–23.11) for CHADOX1 NCOV-19, and 11.48 (95% CI, 9.57–13.67) for AD26.COV2.S. CVT occurred alongside thrombocytopenia for the four vaccines. The OE ratio was greater than one for all four vaccines, both with the lowest and the highest CVT background incidence.

Conclusions: This report on EudraVigilance data strengthens anecdotal findings on CVT following COVID-19 vaccinations. Although the European Medicines Agency released an alert only for CHADOX1 NCOV-19 and AD26.COV2.S, Tozinameran and CX-024414 also are complicated by CVT, albeit to lesser extent.

KEYWORDS
adverse drug reaction, cerebral vein thrombosis, COVID-19, thrombocytopenia, vaccine

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1 | BACKGROUND

The current pandemic of coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2) stimulated rapid vaccine production against the disease. The European Medicines Agency (EMA) has approved so far four COVID-19 vaccines, namely the mRNA Tozinameran (Pfizer-Biontech), the mRNA CX-024414 (Moderna), chimpanzee adenoviral vector CHADOX1 NCOV-19 (AstraZeneca), and adenoviral vector type 26 AD26.COV2.S (Janssen). Although no major warnings emerged from the authorization trials, post-marketing real-world experience raised safety concerns. A few cases of rare thrombotic manifestations such as cerebral vein thrombosis (CVT) were observed, alongside thrombocytopenia, mainly after the first dose of the CHADOX1 NCOV-19 and AD26.COV2.S vaccines.[1–3] An immune response, similar to heparin-induced thrombocytopenia, has been suggested as a possible explanation for the association between thrombotic events and low platelet count.[4] This syndrome, called vaccine-induced immune thrombotic thrombocytopenia, is characterized by the development of high-titer antibodies to platelet factor 4-polyanion complexes despite no heparin exposure. Recently, EMA finalized two signal evaluations on the adenoviral vector vaccines CHADOX1 NCOV-19[5] and AD26.COV2.S,[6] with blood clots and thrombocytopenia listed as very rare side effects. The aim of this study was to assess, using the EudraVigilance database, the reporting rate of CVT among the thrombotic adverse drug reactions (ADRs) attributed to the four COVID-19 vaccines authorized by EMA.

Essentials

- Cases of cerebral vein thrombosis (CVT) occurred mainly after COVID-19 adenoviral vaccines.
- Cases of CVT adverse drug reactions for the four COVID-19 vaccines were retrieved from the EudraVigilance database.
- Cases of CVT did occur with the four vaccines, albeit at different rates.
- Cases of CVT was accompanied by thrombocytopenia for the four vaccines.

2 | METHODS

The EudraVigilance is a public pharmacovigilance database, available at www.adrreports.eu, that allows managing and analyzing the ADRs, thus enabling post-marketing surveillance in Europe. We collected ADRs (access date July 30, 2021) for Tozinameran, CX-024414, CHADOX1 NCOV-19, and AD26.COV2.S. Individual case safety reports (ICSRs) submitted from all the European Member States from January 1, 2021 to July 30, 2021 (210 days) were exported to an internal database. ADRs related to thrombotic events were selected from the total using the following filtering conditions: (1) *Reported suspected reaction* contains "thrombosis"; (2) *Gateway date* "01/01/2021--30/07/2021." Cases were reviewed and CVT defined if at least one among "cerebral thrombosis," "cerebral venous/vein thrombosis," "cerebral venous sinus thrombosis," "jugular vein thrombosis," or "sagittal/transverse sinus thrombosis" was present in the reaction list. Splanchnic vein thrombosis (SVT) was attributed if at least one among "splanchnic/splenic vein thrombosis," "portal vein thrombosis," "mesenteric vein thrombosis," or "portosplenomesenteric venous thrombosis" was listed. In addition, multiple unusual sites were determined if CVT, SVT, and/or terms such as "renal/ovarian/retinal/subclavian vein thrombosis" were reported together in the same ICSR. Otherwise, reports containing at least "thrombosis" among suspected reactions were considered as "common sites," either arterial or venous. Thrombocytopenia was declared with "thrombocytopenia," "low platelet count," or "platelet count decreased" listed among suspected reactions.

The reporting rate of CVT during the study period was estimated using the following formula: number of thrombotic ADRs reported in the study period divided by the number of individuals who received their first dose of vaccine in the same period, 1 Jan 2021--30 Jul 2021 (retrieved from the European Center for Disease Prevention and Control, ECDC, public database available at https://www.ecdc.europa.eu/en/publications-data/data-covid-19-vaccination-eu-eea). Each estimate was expressed as 1 million individual vaccinated-days with the respective 95% confidence interval (CI). An observed-to-expected (OE) analysis within 28 days post first vaccine dose was also performed, considering the estimated lowest CVT background incidence rates and the highest CVT background incidence rates of 0.2 and 1.5 per 100,000 person-years, respectively. The person-time at risk was calculated as number of first doses x 28/365.2425 x 1/100,000. The OE ratio was expressed as standardized morbidity ratio (SMR) with 95% CI.

3 | RESULTS AND DISCUSSION

We identified for each vaccine the total number of ADRs reported in the study period and selected those related to thrombotic events, from now on "thrombotic ADRs." For Tozinameran we identified 2926 thrombotic ADRs out of 311,364 total ADRs (0.9%), for CX-024414 1878 out of 80,428 (2.3%), for CHADOX1 NCOV-19 4752 out of 337,712 (1.4%), and for AD26.COV2.S 761 out of 18,744 (4.1%). Table 1 shows the distribution of thrombotic ADRs according to the age group and sex. Overall, the age group <65 was more prevalent among the thrombotic ADRs of adenoviral vector vaccines than among those of mRNA vaccines and the prevalence of female sex was approximately 55% for the four vaccines. CVT events were observed for all vaccines, a lower reporting rate of unusual site thrombosis ADRs was observed for the mRNA compared to the adenoviral vaccines (Table 2). CVT events alongside with thrombocytopenia have been reported for all vaccines, ranging from 3–5% to 31–44% for mRNA and adenoviral vaccines, respectively.

TABLE 1 All thrombotic adverse drug reactions stratified by age group and sex

Vaccine name, *n* of total ADRs (1 Jan 2021–18 Apr 2021)	Age group (years)	Sex, *n* (%)			Thrombotic ADRs, *n* (%)
		Female	Male	NS	
COVID–19 mRNA vaccine Tozinameran *N* = 311 364	<65	659	597	15	1271 (43)
	65–85	617	602	9	1228 (42)
	>85	202	82	5	289 (10)
	Not specified	79	50	9	138 (5)
	Total	1557 (53)	1331 (45)	38 (1)	2926
COVID–19 mRNA COVID–19 mRNA vaccine CX–024414 *N* = 80 428	<65	567	449	3	1019 (54)
	65–85	359	340	0	699 (37)
	>85	60	40	0	100 (5)
	Not specified	25	21	14	60 (3)
	Total	1011 (54)	850 (45)	17 (1)	1878
COVID–19 vaccine CHADOX1 NCOV–19 *N* = 337 712	<65	1495	1219	23	2737 (58)
	65–85	796	776	13	1585 (33)
	>85	103	55	2	160 (3)
	Not specified	130	118	22	270 (6)
	Total	2524 (53)	2168 (46)	60 (1)	4752
COVID–19 vaccine AD26.COV2.S *N* = 18 744	<65	287	258	2	547 (72)
	65–85	91	71	0	162 (21)
	>85	17	4	0	21 (3)
	Not specified	14	11	6	31 (4)
	Total	409 (54)	344 (45)	8 (1)	761

Abbreviations: ADRs, adverse drug reactions; NS, not specified.

The number of individuals in Europe who received the first dose in the study period was 183,288,011 (Tozinameran), 25,038,569 (CX-024414), 38,664,988 (CHADOX1 NCOV-19), and 10,972,234 (AD26.COV2.S). The reporting rate of CVT per 1 million individual vaccinated-days in the study period was 1.92 (95% CI, 1.72–2.13) for Tozinameran, 5.63 (95% CI, 4.74–6.64) for CX-024414, 21.60 (95% CI, 20.16–23.11) for CHADOX1 NCOV-19, and 11.48 (95% CI, 9.57–13.67) for AD26.COV2.S. In Table 3 the OE analysis showed SMR greater than one for all four vaccines, both with the lowest and the highest known background incidence, suggesting an excess of risk. However, when the highest background incidence was considered, the SMR was lower for both the mRNA vaccines than for adenoviral vector ones.

This study employed the EudraVigilance data to evaluate the reporting rate of CVT after COVID-19 vaccination, with the goal to provide a comprehensive look at thrombotic complications with the available vaccines. Rare thromboses at unusual sites, with or without thrombocytopenia, have been reported in EudraVigilance for the four vaccines, even though thrombocytopenia appeared to be more prevalent in patients who developed thrombosis after the adenoviral vector vaccines. Moreover, a higher prevalence of CVT was observed in the <65 years old group for adenoviral vector vaccines than for the others. However, this observation should be interpreted cautiously considering the different target populations who did benefit from each vaccine. Adenoviral vaccines have been mostly used in the young and AD26.COV2.S was only recently introduced, so we cannot exclude that the observed different reporting rates are due to a selection bias. Moreover, the reporting rate of CVT for AD26.COV2.S was likely to be affected by the low number of individuals who did benefit from this vaccine.

Concerning the extent of the CVT disease burden, CVT incidence increased in the general population over the past decade, from 2–5 to 13.2–15.7 annual cases per million, owing to growing awareness and improved imaging techniques.[7,8] Yet, these figures are likely to be underestimated because of lack of dedicated epidemiological studies and variability of ethnic groups with different degree of exposure to infectious diseases, well-known triggers of CVT. Moreover, the reporting rate of CVT could not be directly compared to the incidence rate in the general population, these being different measures that use different definitions of the time at risk. Therefore, whether the incidence of CVT is higher in vaccinated people than in the general population is beyond the scope of this study. However, the OE analysis showed an SMR greater than one suggesting an excess of risk for all four vaccines, but particularly for the adenoviral vector ones considering the highest background incidence rate. These data should be critically interpreted because they are based on several assumptions[9] and we do not know the exact background incidence rates, which could widely differ among the vaccine target populations. In addition, a possible underestimation of the ADRs' registration should be considered.

This study has the typical limitations of a study based upon pharmacovigilance data. First, the possibility of underreporting should

TABLE 2 Frequency of thrombocytopenia, younger age group, sex, and fatality among thrombotic adverse drug reactions in common sites, cerebral vein thrombosis and splanchnic vein thrombosis

Characteristics		Common sites	CVT	SVT	Multiple unusual sites	Thrombotic events
		N, (% on thrombotic ADRs) % on total ADRs				*N*, (%)
COVID–19 mRNA vaccine Tozinameran	Thrombocytopenia	41 (2)	19 (5)	13 (13)	1 (100)	2926
	No. of cases <65Y	1037 (42)	175 (50)	59 (57)	0	
	No. of female	1305 (53)	207 (59)	44 (42)	1 (100)	
	Fatal	81 (3)	29 (8)	12 (12)	1 (100)	
	Tot No. of eventsit	2470 (84%)	351 (12%)	104 (3.5%)	1 (0.03%)	
		0.8%	0.1%	0.03%	0.0003%	0.9%
COVID–19 mRNA vaccine CX–024414	Thrombocytopenia	19 (1)	4 (3)	0	0	1878
	No. of cases <65Y	897 (53)	82 (58)	38 (67)	2 (100)	
	No. of female	911 (54)	70 (50)	30 (53)	1 (50)	
	Fatal	72 (4)	11 (8)	4 (7)	0	
	Tot No. of events	1678 (89%)	141 (8%)	57 (3%)	2 (0.1%)	
		2%	0.2%	0.07%	0.002%	2.3%
COVID–19 vaccine CHADOX1 NCOV–19	Thrombocytopenia	338 (9)	370 (44)	93 (40)	37 (84)	4752
	No. of cases <65Y	1931 (53)	608 (65)	159 (69)	39 (89)	
	No. of female	1852 (51)	519 (62)	122 (53)	31 (70)	
	Fatal	128 (4)	148 (18)	28 (12)	12 (27)	
	Tot No. of events	3642 (77%)	835 (18%)	231 (5%)	44 (1%)	
		1%	0.2%	0.07%	0.01%	1.4%
COVID–19 vaccine AD26. COV2.S	Thrombocytopenia	40 (7)	39 (31)	15 (58)	7 (100)	761
	No. of cases <65Y	423 (70)	97 (77)	22 (85)	5 (71)	
	No. of female	297 (49)	93 (74)	14 (54)	5 (71)	
	Fatal	13 (2)	16 (13)	1 (4)	2 (29)	
	Tot No. of events	602 (79%)	126 (17%)	26 (3%)	7 (1%)	
		3%	0.7%	0.1%	0.04%	4.1%

Abbreviations: ADRs, adverse drug reactions; CVT, cerebral vein thrombosis; SVT, splanchnic vein thrombosis.

TABLE 3 Observed-to-expected analysis

Vaccine name	Person-time at risk (100,000 person-years)	Lowest highest background incidence	Expected CVT	Observed CVT	SMR (95% CI)
COVID–19 mRNA vaccine Tozinameran	140.51	0.2	28.10	351	12.49 (11.23–13.85)
		1.5	210.77		1.67 (1.57–1.78)
COVID–19 mRNA COVID–19 mRNA vaccine CX–024414	19.19	0.2	3.84	141	36.73 (33.17–40.60)
		1.5	28.79		4.9 (4.42–5.41)
COVID–19 vaccine CHADOX1 NCOV–19	29.64	0.2	5.93	835	140.85 (135.07–146.77)
		1.5	44.46		18.78 (18.02–19.58)
COVID–19 vaccine AD26.COV2.S	8.41	0.2	1.68	126	74.9 (63.35–83.42)
		1.5	12.62		9.99 (8.97–11.10)

Abbreviations: CI, confidence interval; CVT, cerebral vein thrombosis; SMR, standardized morbidity ratio.

be mentioned. The incidence of CVT for each vaccine could not be estimated lacking information on the extent of underreporting and exact time of occurrence. Only a minority of data are missing for sex and age group, but other strong thrombotic risk factors are not available (e.g., oral contraceptive use, thrombophilia abnormalities). Therefore, no causal inference should be done from these data due

to missing information on possible confounders. Moreover, we fail to provide reporting rates standardized for age and countries due to missing data. Considering that the safety profile of a vaccine may differ within each target population (i.e., higher risks in the youngest age groups), comparison between different reporting rates for age categories or countries should be avoided, because they will include many biases and lack of appropriateness. In addition, we lacked information for performing a stratified OE analysis.

In conclusion, although EMA released an alert only for adenoviral vector vaccines (CHADOX1 NCOV-19 and AD26.COV2.S), mRNA vaccines (Tozinameran and CX-024414) also are complicated by CVT, albeit to a lesser extent. In accordance with the EMA statements, the benefits of vaccination against COVID-19 continue to outweigh the risks of side effects, including rare life-threatening thrombotic manifestations that appear to occur with all four vaccines but with possible differences in frequency and mechanism that need further investigation. Therefore, we prompt more awareness on the pivotal role of pharmacovigilance, especially for those events that remain unnoticed during the clinical trials and urge spontaneous reports.

CONFLICTS OF INTEREST

F.P. has received honoraria for participating as a speaker at satellite symposia organized by Roche, Sanofi, Sobi, and Takeda; and is a member of advisory boards of Roche, Sanofi, Sobi, and Takeda. I.M. reports personal and non-financial support from Bayer, Roche, Rovi, and Novo Nordisk outside of the submitted work. M.A. has nothing to disclose.

AUTHOR CONTRIBUTIONS

All authors had full access to all study data and take responsibility for their integrity and for the accuracy of the data analysis. M.A. acquired, analyzed, and interpreted the data, and drafted the manuscript. I.M. interpreted the data and critically revised the manuscript. F.P. conceived the study, interpreted the data, and critically revised the manuscript. F.P. and I.M. supervised the study.

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