

Title: Comparison of vaccine-induced thrombotic events between ChAdOx1 nCoV-19 and Ad26.COV.2.S vaccines

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Abstract

Cerebral venous thromboses (CVT) events have been reported after vaccination with adenoviral COVID-19 vector vaccines. This study aimed to compare the clinical presentations and courses of vaccine-induced thrombotic thrombocytopenia (VITT) between the two adenoviral vector vaccines, Ad26.COV.2.S (Janssen/Johnson & Johnson) and ChAdOx1 nCoV-19 (Astra-Zeneca). We found that CVT after Ad26.COV.2.S vaccination presents later with similar symptoms compared to CVT after administration of ChAdOx1 nCoV-19, albeit with more thrombosis and intracerebral hemorrhage, lower D-dimer and aPTT levels but similar mortality. These findings could help guide clinical assessment and management of CVT after COVID-19 vaccination.

Keywords: vaccine-induced thrombotic thrombocytopenia, thrombotic thrombocytopenia syndrome, adenoviral vector vaccine, COVID-19 vaccine, cerebral venous thrombosis.

1. Introduction

Reports of rare thrombotic events such as cerebral venous thromboses (CVT) have been accumulating after COVID-19 vaccination¹⁻⁵. Severe vaccine-induced thrombotic thrombocytopenia (VITT) following vaccine administration was initially reported after ChAdOx1 nCoV-19 vaccination (Astra-Zeneca)¹⁻⁴, causing the European Medicine Agency (EMA) to issue a report on March 18, 2021⁶. In the meantime, reports of CVT after another adenoviral vector-based vaccine, the Ad26.COV.2.S vaccine (Janssen/Johnson & Johnson), resulted in the US Food and Drug Administration (FDA) recommending a pause in the use of the Ad26.COV.2.S vaccine as well⁷. Although the clinical course of VITT has been postulated to be similar to autoimmune heparin-induced thrombocytopenia^{1,2,5}, the exact pathogenesis of VITT has not been fully elucidated, nor whether there are any differences in VITT events after the two adenoviral vector-based vaccines. Therefore, this study aimed to perform a rapid review to compare the clinical presentations of CVT cases between Ad26.COV.2.S and ChAdOx1 nCoV-19 vaccines.

2. Methods

2.1. Study design and data source

We conducted a rapid review to capture case reports of VITT after adenoviral vector-based COVID vaccine administration. We searched PubMed ePubs, Scopus, Embase, and Web of Science databases to include articles published up to April 28, 2021, and related to COVID-19 vaccine-associated CVT after adenoviral vector-based COVID-19 vaccine administration. Case series with more than five cases were considered. We only included cases with CVT documented by clinical and radiologic findings after vaccination with the ChAdOx1 nCoV-19 or Ad26.COV.2.S vaccine. After reviewing individual abstracts and full texts, we identified 5 case series that met the inclusion criteria for this systematic review¹⁻⁵. Laboratory measurements presented were either those obtained at time of admission or peak/nadir values.

2.2. Statistical analysis

Basic demographic and clinical information were presented as the median and interquartile range (IQR) for continuous variables and the percentage for categorical variables. Variables were compared with the Mann-Whitney U-test for continuous variables and Fisher's exact test for categorical variables. Statistical significance was defined as two-tailed $p < 0.05$. Statistical analyses were performed with R version 4.0.4 (R Core Team, Vienna, Austria).

3. Results

Demographic and clinical characteristics of 40 patients (ChAdOx1 nCoV-19, $n=28$; Ad26.COV.2.S,

n=12) are shown in Table 1 and Supplementary Table S1. Patients who received the Ad26.COV.2.S vaccine tended to have clinical manifestations later than those administered ChAdOx1 nCoV-19, with a median of 16 days post-vaccination compared to 10 days ($p=0.004$). D-dimer levels were significantly lower in the Ad26.COV.2.S group (16.3 vs. 74.2 times the upper limit of normal, $p=0.036$), and aPTT levels were also lower in the Ad26.COV.2.S group with borderline significance (28.0 vs. 34.0 sec, $p=0.086$). Other clinical characteristics were similar, with no significant differences in age or sex distribution, platelet counts, prothrombin time, fibrinogen levels. In both groups, almost all patients had positive tests for HIT antibody enzyme-linked immunosorbent assay (ELISA) (96.0% vs. 100.0%, $p=1.000$). However, while 92.9% of patients administered ChAdOx1 nCoV-19 had positive platelet function tests, only 11.1% had positive tests in the Ad26.COV.2.S group ($p<0.001$).

Interestingly, patients with CVT after Ad26.COV.2.S administration were more likely to also have intracerebral hemorrhage (58.3% vs. 17.9%, $p=0.021$). They were also more likely to have additional thrombosis other than CVT, with borderline significance (66.7% vs. 32.1%, $p=0.063$). Notably, patients with CVT after Ad26.COV.2.S administration were more likely to also have internal jugular vein (IJV) thrombosis (2.2% vs. 50%, $p<0.001$). However, there was no statistically significant difference in mortality (25.0% vs. 56.5%, $p=0.152$). There were no significant differences in presenting symptoms, most commonly being headache, visual disturbance, hemiparesis, and fever.

4. Discussion

The current study is the first to directly compare CVT profiles after COVID-19 vaccine administration between the two adenoviral vector-based vaccines, Ad26.COV.2.S and ChAdOx1 nCoV-19. Although the main presenting symptoms were similar, with the majority reporting headaches and neurologic manifestations, patients who received Ad26.COV.2.S tended to present CVT later, with a median time to admission of 16 days post-vaccination compared to 10 days after ChAdOx1 nCoV-19. Therefore, it is essential to educate patients to be vigilant for neurologic symptoms for a longer period after Ad26.COV.2 vaccination.

Patients with CVT after the Ad26.COV.2.S vaccine had lower D-dimer and aPTT levels, even though there was a greater likelihood of other thrombosis or intracerebral hemorrhage in this group. From the findings of our study, it can be inferred that the Ad26.COV.2.S vaccine, even with a seemingly adverse radiologic profile, has a milder, more insidious clinical course. This could be due to the differential immunogenic profiles of ChAdOx1 nCoV-19 and Ad26.COV.2.S vaccines in stimulating interferon-gamma levels, which is a known mediator in diffuse intravascular coagulation⁸⁻¹⁰.

Even though the mortality of patients with CVT after Ad26.COV.2.S administration was 25.0%, lower than the 56.5% from cases after ChAdOx1 nCoV-19, there was no statistically significant difference. However, as the sample size was relatively small, additional data for higher statistical power is required to better assess differences in mortality.

We found that anti-PF4/heparin antibodies were overwhelmingly present in most patients with either vaccine, whereas the platelet function assay results were strikingly different between the Ad26.COV.2.S and ChAdOx1 nCoV-19 vaccines. Typically, anti-PF4/heparin ELISA is regarded as a sensitive screening tool, but platelet function assays are the gold standard for the diagnosis of heparin-induced thrombocytopenia^{11,12}. The discrepancy of anti-PF4/heparin ELISA and platelet function tests adds a question mark regarding the previously hypothesized heparin-induced thrombocytopenia-like mechanism. The results also need to be interpreted with caution, however, as platelet function tests tend to vary by testing center, and different testing methods were used between studies^{1-3,5}.

There are some limitations to our study. First, the sample size was small, considering the relatively recent, rare nature of VITT. Second, cases of CVT after Ad26.COV.2.S vaccination were based in the United States, whereas cases associated with ChAdOx1 nCoV-19 were all based in Europe, which may have contributed to differences in management. Lastly, as this study was a systematic review of case reports, the timing of laboratory measurements differed between studies. Therefore, it should be stated that our study is intended to provide descriptive information for future, more definitive studies, and not to confirm any hypothesis. However, understanding these different characteristics between vaccines could help guide further investigations and clinical management as both Ad26.COV.2.S and ChAdOx1 nCoV-19 vaccines are being distributed worldwide.

5. Conclusions

This study found that CVT after Ad26.COV.2.S vaccination presents later with similar symptoms compared to CVT after administration of ChAdOx1 nCoV-19, albeit with more thrombosis and intracerebral hemorrhage, lower D-dimer and aPTT levels but similar mortality. Understanding different characteristics between vaccines could help guide future clinical management of VITT.

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Tables

Table 1. Different clinical characteristics of patients with CVT after COVID-19 vaccination according to vaccine type.

Characteristic	Total (n=40)	ChAdOx1 nCoV-19 / Astra- Zeneca (n=28)	Ad26.COV.2.S / Janssen (n=12)	P-value
	Number of patients (%) / Median [IQR]	Number of patients (%) / Median [IQR]	Number of patients (%) / Median [IQR]	
Days to admission	11.0 [9.0; 16.0]	10.0 [8.0; 13.5]	16.0 [12.0;18.0]	0.004
D-dimer (ratio to upper limit of normal range)	52.0 [15.7; 124.7]	74.2 [32.6; 140.0]	16.3 [12.2; 61.7]	0.036
Functional HIT assay positive	14/23 (60.9%)	13/14 (92.9%)	1/9 (11.1%)	< 0.001
Presence of intracerebral hemorrhage	12/40 (30.0%)	5/28 (17.9%)	7/12 (58.3%)	0.021
Internal jugular vein thrombosis	7 (12.3%)	1 (2.2%)	6 (50.0%)	< 0.001

IQR: interquartile range; HIT: heparin-induced thrombocytopenia

Supplementary Tables

Supplementary Table S1. Demographic and clinical characteristics of patients with CVT after COVID-19 vaccination according to vaccine type.

Characteristic	Total (n=40)	ChAdOx1 nCoV-19 / Astra- Zeneca (n=28)	Ad26.COV.2.S / Janssen (n=12)	P-value
	Number of patients (%) / Median [IQR]	Number of patients (%) / Median [IQR]	Number of patients (%) / Median [IQR]	
Demographic information				
Age > 60 years	1/31 (3.2%)	1/19 (5.3%)	0/12 (0.0%)	1.000
Age > 40 years	13/31 (41.9%)	9/19 (47.4%)	4/12 (33.3%)	0.484
Female	27/31 (87.1%)	15/19 (78.9%)	12/12 (100.0%)	0.139
Days to admission*	11.0 [9.0; 16.0]	10.0 [8.0; 13.5]	16.0 [12.0;18.0]	0.004
Laboratory Findings				
Platelet count	22,500 [14,000; 64,500]	23,000 [15,000; 62,000]	19,000 [12,500; 79,500]	1.000
Platelet count < 25×10 ³ /μL	18/40 (45.0%)	15/28 (53.6%)	7/12 (58.3%)	1.000
PT				
PT INR	1.2 [1.1; 1.4]	1.2 [1.1; 1.4]	1.2 [1.1; 1.2]	0.438
PT, abnormal value [†]	23/34 (67.6%)	16/23 (69.6%)	7/11 (63.6%)	1.000
aPTT				
aPTT sec	30.6 [25.7; 35.0]	34.0 [26.7; 41.6]	28.0 [25.2; 31.1]	0.086
aPTT, abnormal value ^{††}	13/34 (38.2%)	10/23 (43.5%)	3/11 (27.3%)	0.465
Fibrinogen				
Fibrinogen (mg/dL)	129.0 [80.0; 210.0]	120.0 [80.0; 210.0]	145.0 [87.5; 222.5]	0.528
Fibrinogen < 200mg/dL	24/34 (70.6%)	16/22 (72.7%)	8/12 (66.7%)	1.000
Fibrinogen < 150mg/dL	21/34 (61.8%)	14/22 (63.6%)	7/12 (58.3%)	1.00
D-dimer				
D-dimer (ratio to upper limit of normal range)	52.0 [15.7; 124.7]	74.2 [32.6; 140.0]	16.3 [12.2; 61.7]	0.036
D-dimer, abnormal value (>500mg/L, FEU)	34/34 (100.0%)	22/22 (100.0%)	12/12 (100.0%)	-
HIT ELISA (n=42) [‡]				
HIT ELISA (OD)	2.3 [1.4; 3.0]	2.4 [1.4; 3.3]	2.3 [1.9; 2.7]	0.883
HIT ELISA positive	35/36 (97.2%)	24/25 (96.0%)	11/11 (100.0%)	1.000
Functional HIT assay positive	14/23 (60.9%)	13/14 (92.9%)	1/9 (11.1%)	< 0.001
Thromboses and Hemorrhages				
Number of thrombosis sites	1.0 [1.0; 2.5]	1.0 [1.0; 2.0]	2.0 [1.0; 3.0]	0.063
Additional thrombosis other than CVT	17/40 (42.5%)	9/28 (32.1%)	8/12 (66.7%)	0.079
Number of hemorrhage sites				0.063
0	27/40 (67.5%)	22/28 (78.6%)	5/12 (41.7%)	
1	12/40 (30.0%)	6/28 (21.4%)	6/12 (50.0%)	
2	1/40 (2.5%)	0/28 (0.0%)	1/12 (8.3%)	

Presence of intracerebral hemorrhage	12/40 (30.0%)	5/28 (17.9%)	7/12 (58.3%)	0.021
Mortality	16/35 (45.7%)	13/23 (56.5%)	3/12 (25.0%)	0.152
Symptoms	(n=40)	(n=28)	(n=12)	
General condition				
Fever	5 (27.8%)	2 (33.3%)	3 (25.0%)	1.000
Gastrointestinal				
Abdominal pain	4 (22.2%)	2 (33.3%)	2 (16.7%)	0.569
Nausea	4 (22.2%)	1 (16.7%)	3 (25.0%)	1.000
Vomiting	4 (22.2%)	0 (0.0%)	4 (33.3%)	0.245
Epigastric discomfort	1 (5.6%)	1 (16.7%)	0 (0.0%)	0.333
Bleeding tendency				
Petechial rash	1 (5.6%)	0 (0.0%)	1 (8.3%)	1.000
Hematoma	1 (5.6%)	1 (16.7%)	0 (0.0%)	0.333
Bruising	1 (5.6%)	0 (0.0%)	1 (8.3%)	1.000
Neurologic				
Headache	18 (100.0%)	6 (100.0%)	12 (100.0%)	-
Hemiparesis	5 (27.8%)	2 (33.3%)	3 (25.0%)	1.000
Visual disturbance	6 (33.3%)	1 (16.7%)	5 (41.7%)	0.600
Dysphasia	4 (22.2%)	1 (16.7%)	3 (25.0%)	1.000
Seizure	3 (16.7%)	0 (0.0%)	3 (25.0%)	0.515
Thrombosis sites other than CVT	(n=57)	(n=45)	(n=12)	
Lung				
Pulmonary embolism	11 (19.3%)	8 (17.8%)	3 (25.0%)	0.879
Other thrombosis in the lung	1 (1.8%)	1 (2.2%)	0 (0.0%)	1.000
Gastrointestinal				
Portal vein thrombosis	7 (12.3%)	5 (11.1%)	2 (16.7%)	0.979
Hepatic vein thrombosis	2 (3.5%)	1 (2.2%)	1 (8.3%)	0.889
Splenic vein thrombosis	2 (3.5%)	1 (2.2%)	1 (8.3%)	0.889
Other thrombosis in the liver	4 (7.0%)	4 (8.9%)	0 (0.0%)	0.663
Mesenteric vein thrombosis	1 (1.8%)	0 (0.0%)	1 (8.3%)	0.474
Other thrombosis in the bowel	2 (3.5%)	2 (4.4%)	0 (0.0%)	1.000
Heart				
Intraventricular thrombosis	1 (1.8%)	1 (2.2%)	0 (0.0%)	1.000
Large vessels				
Aortoiliac	4 (7.0%)	3 (6.7%)	1 (8.3%)	1.000
Internal jugular vein (IJV)	7 (12.3%)	1 (2.2%)	6 (50.0%)	< 0.001
Inferior vena cava (IVC)	1 (1.8%)	1 (2.2%)	0 (0.0%)	1.000

SD: Standard deviation [†] PT (Prothrombin time) / PT sec normal range: 10.0-12.0 sec / PT INR normal range: 0.9-1.1

^{††} aPTT (activated Partial thromboplastin time) / aPTT sec normal range: 25.0-35.0 sec / aPTT ratio normal range: 0.8-1.2

[‡] PF4/heparin enzyme-linked immunosorbent assay for heparin-induced thrombocytopenia. ^h cut off was varies between 0.28~0.5 by the articles. ^e 500mg/L was used as upper limit of normal range.