Progress in Cardiovascular Diseases 67 (2021) 105–107

Contents lists available at ScienceDirect

Progress in Cardiovascular Diseases

journal homepage: www.onlinepcd.com

Covid-19 vaccine- induced thrombosis and thrombocytopenia-a commentary on an important and practical clinical dilemma

Aashish Gupta *, Partha Sardar, Michael E. Cash, Richard V. Milani, Carl J. Lavie

John Ochsner Heart and Vascular Institute, Ochsner Clinical School-The University of Queensland School of Medicine, New Orleans, LA, United States of America

On February 27, 2021, the United States (US) Food and Drug Administration (FDA) issued an emergency use authorization (EUA) of coronavirus disease 2019 (COVID-19) vaccine manufactured by Johnson and Johnson's vaccine division Janssen (Beerse, Belgium) for use in individuals 18 years of age or older.[1] This was the 3rd vaccine to receive EUA for prevention of COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the US following COVID-19 vaccines from Moderna (Moderna TX, Inc., Massachusetts, US) and Pfizer-BioNTech (New York, US; Rhineland-Palatinate, Germany). As of April 12, 2021 6.8 million doses of Janssen's COVID-19 vaccine have been administered in the US.[2] The Janssen's COVID-19 vaccine is a recombinant vaccine that uses replication-incompetent human Adenovirus 26 (Ad26) as a vector to express the SARS-CoV-2 Spike (S) protein. Vector adenoviruses are able to accommodate large genetic payloads and can be modified so they do not initiate an infection. Vector vaccines have been studied and utilized most recently against the Ebola virus. On April 13, 2021, a joint statement issued by FDA and Centers for Disease Control and Prevention (CDC) confirmed 6 cases of cerebral venous thrombosis (CVT) reported in the US and halted further use of Janssen's COVID-19 vaccines. These cases were all associated with thrombocytopenia and were seen in women aged 18–48 years occurring 6–13 days after vaccination.[2] Vaccine induced Thrombosis and Thrombocytopenia (VITT) have not been reported as a side effect of Ebola vaccines, however, scale of vaccinations has been significantly lower.[3]

These reports come after similar cases of possible VITT were identified in Europe after administration of Vaxzevria (Covishield in India), the COVID-19 vaccine developed by AstraZeneca and Oxford group that is also an adenovirus vector vaccine with Chimpanzee Adenovirus (ChAdOx1) as a vector encoding the spike protein antigen of the SARS-CoV-2. Vaxzevria received conditional marketing authorization in the European Union (EU) by European Medicines Agency (EMA) for immunization against COVID-19 in individuals 18 years of age or older on January 29, 2021. On March 7, 2021, the Austrian National competent authority suspended use of one batch of Vaxzevria after reports of thromboembolic events following vaccination. This was followed by other countries from EU following suit among reports of more thromboembolic events. A signal assessment report on embolic and thrombotic events found 269 cases in EudraVigilance (EU drug safety database) with cerebrovascular accidents (CVA), myocardial infarction and pulmonary embolism being the most common reported events (see Table 1). More than 60% of these events occurred in women. EMA's safety committee, the Pharmacovigilance Risk Assessment Committee (PRAC) carried out an in-depth review of 62 cases of CVT and 24 cases of Splanchnic Vein Thrombosis (SVT) that have been reported by March 22, 2021, and concluded that overall benefits outweigh the risks. As of April 4, 2021 the number of cases of CVT stood at 169 and SVT at 53 with 34 million vaccinations administered.[4]

There are no reports of suspected VITT from India where around 80–85 million doses of Covishield vaccines have been administered, and the adverse events following immunization (AEFI) report dated March 17, 2021 lists only 3 deaths with a possible temporal relationship to vaccine administration. One of these patients had a CVA and thrombocytopenia which is highly suspicious for VITT. However, there was insufficient evidence for classification as a vaccine related event. Six other deaths were deemed coincidental, 1 death unclassifiable and 1 death due to anaphylaxis.[5] A non-robust AEFI reporting system is the more likely explanation than a genetic makeup that protects Indian population from prothrombotic events.

There are two other COVID-19 vaccines that use the adenovirus vector route - Sputnik V (Gamaleya research institute, Moscow, Russia) and Convidecia (CanSino biologics-Beijing Institute of Biotechnology, Tianjin, China; Beijing, China) Adenovirus-5(Ad-5) based vaccine. Sputnik V is unique as it uses two different serotypes as vectors -Ad 26 and Ad 5, which are given 21 days apart to overcome any pre-existing adenovirus immunity in the population. Heterologous vector regimens, like Sputnik V, can elicit distinct phenotypes of cellular immune responses resulting in a potent prime boost vaccine regimen. Interim analysis of a Phase 3 trial on patients who received the Sputnik V vaccine showed 1 patient who developed deep vein thrombosis, 1 incidence of cerebral circulatory failure, 1 patient with transient ischemic attack, and 1 patient with vascular encephalopathy (n = 16, 427). Details regarding the adverse effects have not been published at the time of the writing of this article.[6] There have been no reports of thrombosis with Convidecia based on interim analysis of its phase III clinical trial but no data has been published in a peer-reviewed medical journal (n = 40,000).[7]

In comparison, there have been no reports of suspected VITT with Moderna and Pfizer-BioNTech COVID-19 vaccines, both of which are composed of m-RNA encapsulated in lipid nanoparticles.

* Corresponding author at: Department of Interventional Cardiology, John Heart and Vascular clinic Institute, Ochsner Clinic, 1514 Jefferson Highway, New Orleans, LA 70121, United States of America.

E-mail address: aashish.gupta@ochsner.org (A. Gupta).

https://doi.org/10.1016/j.pcad.2021.05.001

Table 1
Adenovirus vector vaccines - reported events and current status.

Manufacturer	Vaccine	Vector	Doses	Events	Current status
AstraZeneca-Oxford vaccine group	Vaxzevria	ChAdOx1	2	Signal assessment report (March 12, 2021) CVA (n = 57), MI (n = 34), PE (n = 22), monoplegia (n = 31), DVT (n = 15), Ischemic stroke (n = 11), CVT (n = 4), DIC (n = 1) 169 CVT 53 SVT (until 4th April 2021)	Suspended in Denmark. Recommended for only older age groups in UK, Belgium, Italy, Spain, Germany, France, Netherlands, Finland, Sweden.
Janssen (Johnson and Johnson)	Janssen	Ad26	1	6 CVT	Currently suspended in EU, South Africa and USA.
AstraZeneca-Oxford vaccine group	Covishield	ChAdOx1	2	None confirmed-3 deaths with possible temporal relationship (1 death associated with thrombocytopenia and stroke)	Unrestricted use in India.
Gamaleya research institute of epidemiology and microbiology	Sputnik V	Ad26 and Ad5	2	DVT (1) Cerebral circulatory failure (1) TIA (1) vascular encephalopathy (1)	Approved for emergency use In 62 countries, Rolling review in EU. Currently in use in Russia, Armenia, Belarus, Guinea, Hungary, Iran, Kazakhstan, Kenya, Laos, Lebanon, Nicaragua, Pakistan, Paraguay, Serbia, Syria, Tunisia, UAE, Venezuela.
CanSino biologics-Beijing Institute of biotechnology	Convidecia	Ad5	1	None reported from interim analysis of Phase-III trial	Approved for use in China, Hungary, Mexico, Chile and Pakistan. Currently in use in China, Mexico.

CVA = Cerebrovascular Accident, MI = Myocardial Infarction, PE = Pulmonary Embolism, DVT = Deep Vein Thrombosis, CVT = Cerebral Vein Thrombosis, DIC=Disseminated Intravascular Coagulation, SVT = Splanchnic Vein Thrombosis, TIA = Transient Ischemic Attack, Ad = Adenovirus.

Cerebral venous thrombosis (CVT) is a rare occurrence and reported at an incidence of 0.22–1.57 per 100,000. It is more common in women and in a younger patient population than typical for other types of strokes. Presence of a prothrombotic condition is one of the most common risk factors for development of CVT.

The possibility of immune response to the vector resulting in a heparin induced thrombocytopenia (HIT)-like syndrome has been suggested. HIT, a prothrombotic thrombocytopenic disorder, develops in response to exposure to heparin products resulting in formation of autoantibodies referred to as "HIT antibodies" directed against platelet factor 4 (PF4) complex with heparin. PF4 is a small chemokine protein released by activated platelets in response to trauma or infections. Other polyanions like hypersulfated chondroitin sulfate, DNA, RNA, polyphosphates and bacterial wall components can result in a conformational change in PF4 and exposure of HIT antigen in the absence of heparin resulting in spontaneous or autoimmune HIT.[8] In a recent study, 28 patients who developed thrombosis and thrombocytopenia after receiving Vaxzevria showed presence of antibodies against PF4-heparin as well as a positive platelet-activation assay in presence of PF4 independent of heparin.[9] Another study on 23 patients who developed thrombosis and thrombocytopenia post Vaxzevira found evidence of antibodies to PF4 in 22 out of 23 patients.[10] Laboratory analysis of a patient presenting with thrombocytopenia and disseminated intravascular coagulation like syndrome along with splanchnic and cerebral venous thrombosis after receiving Janssen COVID-19 vaccine showed a strongly positive enzyme-linked immunosorbent assay for antibodies for PF4-plyanion.[11] The Vaxzevria and Janssen vaccines rely on different adenoviruses, but the occurrence of the HIT-like symptoms among recipients of these two vaccines but not with other types of mRNA based vaccine has raised concerns that the problem could be related to adenovirus vector.

An undiagnosed COVID-19 infection in a vaccine recipient is a plausible but less likely explanation of these findings. Thrombosis and thrombocytopenia, as well as many coagulation disorders, have been well documented with COVID-19 infections.[12] In the study by Scully et al., all patients reported to have suspected VITT had a negative SARS-CoV2 polymerase-chain-reaction at presentation.[10] Also, one would expect a signal of thrombosis and thrombocytopenia after mRNA COVID-19 vaccines which has not been the case.

Another hypothesis is a pre-existing hypercoagulable or auto immune condition with the vector vaccine serving as a trigger resulting in cascade of thrombosis and thrombocytopenia. In a detailed analysis of 11 patients with suspected VITT, only one patient was found to have preexisting von Willebrand disease, anticardiolipin antibodies and factor V Leiden.[9] Moreover, Scully et al. found no previous prothrombotic medical condition in the 23 patients presenting with possible VITT.[10]

Certain EU countries have restricted the use of vector vaccines to older age groups. The U.K.'s vaccines advisory body recommended AstraZeneca vaccine should preferably not be given to people under 30 year. Individuals who have received the first dose already may be receiving a different vaccine for the 2nd dose with no data available on the efficacy of this approach. The current situation should have been foreseen months ago when the COVID-19 vaccines were under development. All currently available COVID-19 vaccines were approved by emergency authorizations under pandemic conditions and rightly so. There was bound to be the possibility of signals not initially noticed in Phase III clinical trials at the scale of vaccinations that have been administered. Nevertheless, the incidence of VITT is similar to the incidence of thrombosis that would be expected in the general population. Adenovirus based vaccines are cheaper and easier to store than mRNA based vaccines, which is critical to global immunization campaigns and the main component of the United Nations-backed COVAX program that aims to vaccinate some of the world's poorest countries. Benefits of utilizing limited supply of vaccines in the face of an ongoing pandemic might outweigh the risks involved, especially in countries where the non-vector COVID-19 vaccines are not readily available. Countries with limited resources, surging infections and no non-vector COVID-19 vaccine alternatives may be better off continuing their vaccination campaign with the current stockpiles in spite of ethical considerations and slight potential risks. We do hope that production of non-vector vaccines will soon be able to meet this new heightened demand.

References

1. FDA. *Janssen COVID-19 Vaccine.* EUA. 2021.Available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/janssen-covid-19-vaccine-frequently-asked-questions.
2. FDA and CDC. FDA and CDC Joint Statement Janssen COVID-19 Vaccine. Available at: https://www.fda.gov/news-events/press-announcements/joint-cdc-and-fda-statement-johnson-johnson-covid-19-vaccine 2021.
3. WHO. WHO-Safety of Two Ebola Virus Vaccines. Available at: https://www.who.int/groups/global-advisory-committee-on-vaccine-safety/topics/ebola-virus-vaccines 2020.

4. EMA. European Medicines Agency AstraZeneca's COVID-19 Vaccine Analysis. Available at: https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood 2021.
5. MOHFW. Adverse Event Following Immunization Report India Covishield Vaccine. Available at: https://main.mohfw.gov.in/Organisation/Departments-of-Health-and-Family-Welfare/immunization/aefi-reports 2021.
6. Logunov DY, Dolzhikova IV, Shcheblyakov DV, et al. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. Lancet 2021;397:671-681.
7. ClinicalTrials. Convidecia-Phase III Trial of A COVID-19 Vaccine of Adenovirus Vector in Adults 18 Years Old and Above. Available at: https://clinicaltrials.gov/ct2/show/NCT04526990 2021.
8. Greinacher A, Selleng K, Warkentin TE. Autoimmune heparin-induced thrombocytopenia. J Thromb Haemost 2017;15:2099-2114.
9. Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. N Engl J Med 2021.
10. Scully M, Singh D, Lown R, et al. Pathologic antibodies to platelet factor 4 after ChAdOx1 nCoV-19 vaccination. N Engl J Med 2021.
11. Muir K-L, Kallam A, Koepsell SA, Gundabolu K. Thrombotic thrombocytopenia after Ad26.COV2.S vaccination. N Engl J Med 2021.
12. Lippi G, Sanchis-Gomar F, Favaloro EJ, Lavie CJ, Henry BM. Coronavirus disease 2019–associated coagulopathy. Mayo Clin Proc 2021;96:203-217.