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

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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.

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