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Thrombotic complications of Covid 19 vaccines: The nuances of PV

Introduction

In response to the Coronavirus Disease of 2019 (COVID-19) pandemic, the successful genome sequencing of SARS-CoV-2 was done, and a frantic race towards the development of vaccines against COVID-19 was initiated. Following the results of the phase 3 clinical trials on vaccines demonstrating extremely high efficacy rates in symptomatic and serious COVID-19 cases, international drug regulation agencies issued emergency use authorization for several novel vaccines, between December 2020 and March 2021, and thus resulting in the world-wide distribution of these vaccines[1-3].

Four vaccine preparations were granted marketing authorization by the European Medicines Agency (EMA)[4]. National vaccination programs of remarkable speed and carefulness were implemented worldwide, resulting in vaccinations of several millions of individuals from all age adult groups. Slowly cases of rare but serious and potentially lethal complication of vaccine induced thrombotic thrombocytopenia (VITT) began to be observed. This term has been used interchangeably with thrombosis-thrombocytopenia-syndrome (TTS).

By March 2021, EMA's Pharmacovigilance Risk Assessment Committee (PRAC) began an assessment on signals of increased incidence of thrombotic events, including splanchnic vein and cerebellar sinus thrombosis (SVT and CVST respectively) accompanied by thrombocytopenia, especially seen among females aged less than 60 years, within the 2 weeks following the 1st dose of adenoviral vector ChAdOx1 vaccine Vaxzevria (Oxford/AstraZeneca) [4].

On April 7, 2021, the committee concluded that a causal link between this rare side-effect and the vaccination could not be ruled out. Till then, 169 CVST and 53 SVT cases had been reported among around 34 million vaccinated individuals in the European Economic Area and the United Kingdom [3]. Because of concerns regarding ChAdOx1 safety, temporary cessation, which were followed by permanent stoppings of its administration were done in some countries (Norway, Denmark). Restriction of its usage in older age groups were followed by other countries (e.g., Iceland, France, Germany)[4].

In a similar course of events, on April 13th, 2021, the Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC) in the USA also recommended a pause of the administration of another adenovirus vector vaccine, Ad26.COV2·S (Johnson & Johnson/ Janssen)[5].

As of May 16, 2021, there had been no cases of TTS associated with the mRNA-based vaccines from Moderna or Pfizer-BioNTech [6, 7, 8, 9]. There is limited data on the safety profile of the Sputnik V vaccine. Based on all these reports, the safety of these recombinant adenovirus vector vaccines has been put under the spotlight.

Vaccines of this category, use recombinant, non-replicative adenoviruses which act as shells for the carriage of the DNA strand that codes for the SARS-CoV-2 spike protein[6, 7, 10], which is necessary for its pathogenicity. The AstraZeneca vaccine uses a chimpanzee adenovirus; the Johnson & Johnson vaccine uses human adenovirus 26; Sputnik V uses two different human adenoviruses; 26 for the priming dose and 5 for booster dose. Several mechanisms have been proposed implicating the adenoviral vectors as main triggers of the prothrombotic state in these cases.

The striking clinical and laboratory similarities between VITT/TTS and HIT (Heparin induced thrombocytopenia) imply that a similar autoimmune mechanism may underly both conditions. In HIT/ a HIT (autoimmune HIT) the pathogenic autoantibodies target PF4 complexes with any variety of large polyanions[11]. These PF4-polyanion-autoantibody complexes then activate platelets through their Fcγ-receptors resulting in an increased risk of thrombosis. In the case of VITT/TTS, the adenoviral DNA content or other currently unaccounted for polyanionic vaccine contents could bind to PF4, and hence induce autoantibody production and a subsequent platelet activation could take place. This would essentially render VITT/TTS as a subtype of aHIT. This mechanism was supported by Greinacher et al. and in support of this mechanism the circulating PF4/Polyanion autoantibodies have also been demonstrated [12].

Platelets also express CAR [13], so it can be hypothesized that they may be susceptible to recombinant adenovirus infection. A subsequent SARS-CoV-2 spike protein expression, therefore could contribute to platelets being the primary antibody targets or even enhance thromboxane A2 production [14].

Following intravenous administration, adenoviruses may bind to circulating platelets, causing their activation and sequestration in the reticuloendothelial system [15,16]. Furthermore, injection through this route induces endothelium which may further contribute to the establishment of a prothrombotic atmosphere[15]. Though it is not expected after intramuscular administration, an exceptional case in intravenous injection cannot be outrightly excluded.

Apart from platelets, anti-PF4 antibodies may also bind to and activate various other cell types, such as neutrophils[17], monocytes [18,19], as well as endothelial cells[20], therefore further promoting a thrombotic presentation.

Greinacher et al. have proposed that the Ethylenediaminetetraacetic acid (EDTA) contained in the vaccine preparation may increase local vascular permeability in the injection site and cause the systematic dissemination of vaccine components which may interact with preformed natural antibody. This inflammatory state may act as a co-signal to augment the antibody production of anti PF4-antibody-producing B-cells[21].

Evaluation

TTS is characterized by exposure to the ChAdOx1 nCoV-19 or AD26. COV2 ·S vaccine around 4–30 days before the presentation, followed by arterial or venous thrombosis along with mild-to-severe thrombocytopenia (<150 × 109/L) and a positive platelet factor-4 (PF4)-heparin enzyme-linked immunosorbent assay (ELISA)[6, 7, 10]. The common post-vaccination symptoms include systemic symptoms such as fever, myalgias, fatigue, and headache, often seen in the first 24–48 hours[6, 7]. These symptoms do not suggest TTS, but rather a normal immune response. TTS should only be suspected in those patients with severe, persistent symptoms (more than 3 days), or recurrent headache, abdominal pain, vomiting, dyspnoea, chest pain, leg pain, or leg swelling which have been presented 4–30 days after receiving either vaccine [6, 7, 22, 23].

The initial recommended evaluation for TTS includes complete blood count (CBC), peripheral smear, D-dimer, fibrinogen, coagulation panel, and PF4-heparin ELISA [6, 7, 9, 22, 23]. In most cases reported, almost all patients have demonstrated high levels of PF4-heparin ELISA levels, with a low platelet count (median platelet count 20–30 × 109/L) [7, 9, 23]. Fibrinogen levels are typically decreased while D-dimer levels are elevated [6, 7]. With a reasonable clinical suspicion of TTS in patients with exposure to any one of the vaccines and who have thrombocytopenia, an elevated D-dimer or low fibrinogen, it is mandatory to initiate therapy rather than waiting for the results of PF4-heparin.

Scientific questions and future directions

There are certainly many unanswered questions regarding the occurrence of VITT particularly in association with the SARS-CoV2 vaccination. Further research is required to define the incidence of VITT, potential contributing factors, any early risk factors, and management for this rare condition. Identification of the specific component of the adenoviral vaccines that may trigger this syndrome is a vital component of this condition. One key unsolved question is why this syndrome appears to cause CVT and abdominal thromboses out of proportion as to its effect on limb and pulmonary thrombosis, which are more often involved in other forms of spontaneous venous thrombosis[26].

Treatment

Treatment includes intravenous immunoglobulin (IVIG), anticoagulation therapy, along with avoidance of heparin and platelet transfusion[11, 12, 20, 21,2 4, 25]. Prior to administration of IVIG, confirmatory testing should be obtained, as IVIG may cause false-negative test results [7, 10]. IVIG should be given 1–2 g per kilogram daily for 2 days[6, 7, ,22, 23, 24, 25]. As of now, treatment with corticosteroids has not been recommended, though several medical societies agree that they can be considered in patients with platelet counts <50 × 109/L or if IVIG therapy will be delayed[7, 22, 23]. Fibrinogen should be corrected to >1.5 g/L with fibrinogen concentrate or cryoprecipitate[6, 7, 22, 23]. Once platelet levels are >30 × 109/L and fibrinogen >1.5 g/L, non-heparin anticoagulation should be started. First-line agents include argatroban or bivalirudin, provided activated partial thromboplastin clotting time (aPTT) is normal[6, 7, 22, 23]. Apixaban or rivaroxaban may also be considered[6, 7, 23]. The American Society of Hematology states fondaparinux or danaparoid may also be used[7]. Treatment duration for provoked venous thromboembolism (VTE) is 3 months. Patients on oral anticoagulant medications for conditions such as atrial fibrillation or previously diagnosed VTE should continue their medication during and after the vaccination[6, 7]. Heparin may be used to treat VTE if the PF4-heparin ELISA and disseminated intravascular coagulation (DIC) testing are negative and the platelet count is

normal. Antiplatelet agents are not recommended[6, 7, 22, 23]. Due to the potential severity of TTS, patients with suspected or confirmed TTS should be admitted to the hospital for monitoring and further evaluation.

Conclusion

Ongoing close monitoring and reporting of conditions by frontline clinicians is crucial for the national and international public health agencies. Strategies for rapid treatment of VITT and VITT-CVT are necessarily required. With an improved understanding of the pathophysiology, there would be a better guidance towards the management of these cases. Working groups in several professional societies and public health agencies, including the World Health Organization, have gathered experts to provide further guidance rapidly. A particular challenge will be around assessment, monitoring, and management for VITT in resource-limited settings, where specialized clinical services, laboratory, and imaging capacity, as well as treatments,

are very much limited. Beyond diagnosis and management, public health specialists and implementation scientists should explore ways to enhance public and professional education to reduce the impact of VITT on the individual's health and vaccination efforts.

It is important to recognize the risk of VITT from COVID-19 vaccines, and to understand that the benefits greatly outweigh the risk from COVID-19 vaccines, which are overall safe, very effective, and critical to end the acute phase of this global pandemic.

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