COVID-19 Vaccine Astrazeneca, a Boon or Bane: Thrombocytopenia, a Probable Consequence

Aswin Sarath¹, Senthil Madasamy²*, R. Kameswaran²

¹Department of Pharmacy Practice, ²Department of Pharmacy Practice, J.K.K.Nattraja College of Pharmacy, Kumarapalayam-638183, Tamil Nadu

*Corresponding Author:
Aswin Sarath
Department of Pharmacy Practice, J.K.K.Nattraja College of Pharmacy, Kumarapalayam-638183, Tamil Nadu

Type of Publication: Original Research Paper
Conflicts of Interest: Nil

Abstract
As the Novel SARS-CoV-2 carry on to infect people all over the world, immunization against COVID-19 is the most effective ways to combat the wide-ranging health disaster. Vaccination with ChAdOx1 nCov-19 (produced by Oxford and AstraZeneca) has been linked to a vaccine-induced catastrophic thrombotic thrombocytopenia disease, according to updated reports. This condition is characterised by serious thrombosis in unusual locations, primarily the cerebral venous, along with thrombocytopenia and the release of auto-antibodies towards platelet-factor 4. (PF4). This uncommon side effect closely mirrors the clinical manifestations of the classic immune-mediated HIT illness, which occurs post heparin exposure. Shockingly, no patients had been exposed to heparin prior to the development of the sickness, supporting the theory that a viral antigen from the vaccine provoked the response. COVID-19 has been associated to a variety of autoimmune symptoms, including the formation of pathogenic autoantibodies and the advent of novel autoimmune illnesses and disorders. As the ChAdOx1 nCov-19 vaccination leads to the synthesis of specific SARS-CoV-2-proteins, they may stimulate a production of PF4 auto-antibody though molecular mimicry phenomenon, on the other hand vaccination compounds pave way to a rigorous bystander stimulation of immune cells. If present, eliminating such homological sequences from the vaccine may counteract this phenomenon.

Keywords: ChAdOx1 nCoV-19, Thrombosis, AstraZeneca, Thrombocytopenia, PF4, Hypercoagulation, Heparin-induced thrombocytopenia, Molecular mimicry

Introduction
Globally, as of mid-July 2021, there have been 188,655,968 confirmed cases of COVID-19, including 4,067,517 deaths, reported to WHO and a total of 3,402,275,866 vaccine doses have been administered1. Vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are the most important counter-measure to fight the coronavirus 2019 (Covid-19) pandemic2. As of 9 July 2021, 12% (933.88 million) of the people have been fully vaccinated against COVID-19 where as 13% (1.02 billion) of people are only partly vaccinated against COVID-19. In India, as of on July 08 2021 5.1% (70.31 million) of the people have been fully vaccinated against COVID-19 where as 17% (228.37 million) of people are only partly vaccinated against COVID-19. The European Medicines Agency (EMA) authorised a COVID-19 vaccine produced by Oxford University and AstraZeneca on January 29, 2021. (AZD1222, ChAdOx1 nCov-19, COVID-19 vaccine AstraZeneca, Vaxzevria, Covishield).

Cerebral Venous Thrombosis Associated with SARS-CoV-2 Vaccination
The vaccination prepared by Oxford and AstraZeneca, the ChAdOx1 nCoV-19, is made of a recombinant chimpanzee adenoviral vector which...
encodes the spike protein of SARS-CoV-2 that has the ability to insert artificial DNA into human cells. The goal is to get inoculated cells to make spike protein of SARS-CoV-2, which will cause immune cells to go into overdrive bystander activation. While the vaccination protects against COVID-19's severe course and death, reports of lung, abdominal, and cerebral venous thromboembolic incidents have caused worry. Intracranial venous sinus thrombosis (IVST) is a fatal illness that affects roughly 15 people per million in Western region of the world each year. A total of nine patients seemed to have thrombocytopenia and IVST post vaccination with AstraZeneca's "COVID-19 vaccine" were seen in Germany in early March 2021 (Paul Ehrlich Institute, communication on March 19, 2021).5 Moreover, since the beginning March 2021, a growing number of case reports from Austria, Norway, Denmark, Germany, the United Kingdom, and other nations have revealed that ChAdOx1.nCoV-19 is related to a possibly different thrombotic syndrome. 5 to 24 days post vaccination there were reports that uncommon anatomical locations such as the cerebral venous sinus thrombosis, or thrombosis of the portal, splanchnic, or hepatic veins were observed to have venous thrombosis along with severe thrombocytopenia, bleeding, arterial thrombosis and a few [patients were also seen to have developed lower limb venous thrombosis or pulmonary embolism.

CVT is related with traditional risk factors.

The traditional risk factors that are associated with the occurrences of CVT are mainly categorised into four types. 1. Genetic and acquired thrombophilia involves, factor V Leiden thrombophilia, Prothrombin Gly20210A1a mutation, Anti-thrombin deficiency, Protein S deficiency, Protein deficiency. 2. Systemic conditions that Malignancy/myeloproliferative disorders, Neuro-inflammatory conditions (ie Sarcoidosis, Behcet, SLE), Antiphospholipid syndrome, Thyroid disease, Obesity. 3. Gender & Sex-specific risk factors includes Oral contraceptives, Pregnancy and puerperium, Hormone replacement therapy. 4. Miscellaneous consists of Dural arteriovenous fistula, Head or neck infections, anaemia, head trauma. Previous incidences of vaccine induced thrombocytopenia

In the setting of adenovirus replication, thrombocytopenia has been described. Thrombocytopenia, commonly known as IVST, has been linked to a number of different vaccines:

1. Mittelmeier (1959): A 15-month-old boy died two days after receiving his second diphtheria vaccine; autopsy revealed widespread endothelial damage and thrombosis of the superior sagittal and straight sinuses;
2. Nieminen et al. (1993): Vaccination against measles, mumps, and rubella (MMRV), incidence 23/700,000, benign course, and no thromboembolic consequences;
3. Hamiel et al. (2016): three paediatric case occurrences;
4. Yamamoto et al. (2020): Following influenza vaccination, alveolar bleeding occurs within one day of exposure.

Mechanism of vaccine induced thrombocytopenia

The clinical picture of moderate-to-severe thrombocytopenia and thrombotic consequences at unexpected locations commencing 1 to 2 weeks following immunization with ChAdOx1 nCoV-19 against SARS-CoV-2 implies a disease that clinically mimics severe heparin-induced thrombocytopenia. Platelet-activating antibodies detect multimolecular complexes between cationic PF4 and anionic heparin, resulting in HIT, a well-known prothrombotic disease.

HIT is an acquired prothrombotic disorder characterized by thrombocytopenia, coagulopathy, and a high risk of thrombosis, that is induced by antibodies targeting neoepitopes formed by the binding of PF4 to heparin. Binding of these immune complexes to platelet FcγIIA receptors leads to platelet activation, degranulation, NE-Tosis, and endothelial activation, further aggravated by activation of the complement system. Autoimmune HIT, or spontaneous HIT, refers to a disorder clinically and serologically indistinguishable from HIT, but without prior exposure to heparin. The pathophysiological background is incompletely understood, but it is hypothesized to be caused by other polyanions complexing with PF4-forming antigens to which anti-PF4/polyanion antibodies can bind. Several case reports have described a HIT caused by non-heparin triggers.
In general, autoimmune manifestations associated with SARS-CoV-2 infection are thought to occur in genetically predisposed individuals through two main mechanisms: [1] molecular mimicry between human and SARS-CoV-2 components, resulting in antigenic cross-reactivity, and [2] SARS-ability CoV-2’s to induce immune hyper-stimulation.

The formation of the PF4 autoantibody, which binds to the human FcγRIIA receptor on platelets and leads to their aggregation, may be aided by molecular mimicry. There may be one of the several homologous sequences of SARS-CoV-2 that can cause the formation of PF4 autoantibody. This method was hypothesised to start the formation of PF4 autoantibodies in some COVID-19 cases who had not been exposed to heparin before. The existence of molecular mimicry between SARS-CoV-2 vaccine-induced proteins and human components might lead to possible adverse effects, such as the development of pathogenic autoantibodies and vaccine-induced autoimmunity. In this scenario, eliminating homologous sequences from the vaccine would prevent vaccinated people from producing PF4 antibodies in the near time.

**Case reports of VITT**

A 27-year-old otherwise healthy man with intermittent headaches, myodesopsia, and emesis plagued. Blood tests revealed an increased D-dimer, low platelets, and fibrinogen 48 hours post receiving the initial shot of ChAdOx1 nCoV-19 vaccine (Vaxzevria, originally AstraZeneca COVID-19 vaccine; AstraZeneca). A CT venogram revealed severe thrombosis of the cerebral venous sinus. After consulting with a haematologist, he was administered with intravenous immunoglobulins and dabigatran right away. He reported a growing headache and new homonymous hemianopia the succeeding day. Idarucizumab and high-dose steroids were given after a repeat CT of the head revealed an acute parenchymal bleed along subdural extension. His intracranial pressures were sternous to regulate, so he received emergency decompressive craniotomy and an external ventricular drain. Even after the comprehensive medical and surgical treatment, his intracranial pressures continued to escalate, and brain injury was too severe to survive.

A 37-year-old lady with headaches that began one week getting receiving ChAdOx1 nCoV-19 immunization. She complained fever and persistent headaches when she reached the emergency room the succeeding day. Her thrombocytopenia was discovered to be severe. The left transverse and sigmoid sinuses were presented to be thrombosed on a computed tomography (CT) scan of the head. A smaller dose of dalteparin (2500IU) was given as there was reduced platelet count. Her health worsened the succeeding day, and another CT scan indicated a significant cerebellar haemorrhage and edema in the posterior fossa. Platelet transfusions and a decompressive craniectomy were used to treat her. Massive and unmanageable edema developed during surgery. On the second day patient died post-surgery.

**Treatment**

Despite only a small number of vaccine-induced catastrophic thrombotic thrombocytopenia patients along with treatments have been reported, adequate treatment seems comparable to that given to a conventional HIT disease case. Most importantly, though thrombocytopenia, platelet transfusions are unnecessary and should be steer clear of to avoid further immune-mediated platelet activation and hypercoagulation. Intravenous immunoglobulin (IVIg) has been demonstrated to significantly enhance patient coagulative stability and escort to a consistent increase in platelet count because PF4 is an autoantibody that causes platelet activation. If IVIg is not available, plasma trade-off may be an effective treatment for eliminating PF4 autoantibodies. Nonetheless, the long-term consequences of PF4 autoantibodies are unknown. Anticoagulation therapy may be hazardous in some situations, especially in individuals with cerebral venous thrombosis, because of the potential of haemorrhagic brain injury. By reason of the high mortality rates, treatment should be started as soon as feasible, especially in individuals with cerebral venous thrombosis. As a result, in patients who present with thrombosis, thrombocytopenia, or an elevated D-dimer level after receiving the ChAdOx1 nCoV-19 vaccination, urgent IVIg treatment should be thought about considered. Treatment should not be postponed in order to do an ELISA test for the existence of PF4 autoantibodies.
During early to mid-March 2021, vaccination against COVID-19 with the Oxford-AstraZeneca vaccine ChAdOx1-S was stopped in several European countries because of spontaneous reports of severe and sometimes fatal thromboembolic events among vaccinated people. The MHRA and the Joint Committee on Vaccination and Immunization (JCVI) have made clear that the benefits of SARS-CoV-2 vaccination far outweigh the risk of VITT. “The thromboembolic events among vaccinated patients is no higher than the amount seen among general population,” the EMA later concluded. The European Medicines Agency recently raised “embolic and thrombotic events” as a new signal for the adenovirus vector based vaccine from Janssen and its use was put on temporary hold by the Centers for Disease Control and Prevention.
for Disease Control and Prevention and the Food and Drug Administration in the United States while further investigations were ongoing

**Conclusion**

Local and national public health organisations require continuous attentive monitoring and reporting of problems by frontline practitioners. Though information is developing, and increased understanding of the pathophysiology will further guide future guidance, strategies for quick treatment of CVT and VITT-CVT are given below. Experts have been collected by working groups in numerous professional organisations and public health authorities, including the World Health Organization, to provide more guidance quickly. In resource-constrained environments, where specialist clinical services, laboratory and imaging capabilities, as well as treatments, are severely restricted, assessing, monitoring, and managing CVT will be a particular difficulty. Beyond diagnosis and management, public health experts and implementation scientists should look into ways to improve public and professional knowledge in order to lessen the impact of CVT on individual health and vaccination efforts. It’s key to remember that the risk of COVID-19-related CVT far surpasses the risk of COVID-19 immunizations, which are generally safe, highly effective, and essential for terminating the pandemic's acute phase.

**References:**