Review article

Concerning the unexpected prothrombotic state following some coronavirus disease 2019 vaccines

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Currently, the world is coping with the COVID-19 pandemic with a few vaccines. So far, the European Medicine Agency has approved four of them. However, following widespread vaccination with the recombinant adenoviral vector-based Oxford-AstraZeneca vaccine, available only in the United Kingdom and Europe, many concerns have emerged, especially the report of several cases of the otherwise rare cerebral sinus vein thrombosis and splanchnic vein thrombosis. The onset of thrombosis particularly at these unusual sites, about 5–14 days after vaccination, along with thrombocytopenia and other specific blood test abnormalities, are the main features of the vaccine side effects. The acronym vaccine-induced prothrombotic immune thrombocytopenia (VIPIT) has been coined to name this new condition, with the aim of highlighting the difference from the classic heparin-induced thrombocytopenia (HIT). VIPIT seems to primarily affect young to middle-aged women. For this reason, the vaccine administration has been stopped or limited in a few European countries. Coagulopathy induced by the Oxford-AstraZeneca vaccine (and probably by Janssen/Johnson & Johnson vaccine as well in the USA) is likely related to the use of recombinant vector DNA adenovirus, as experimentally proven in animal models. Conversely, Pfizer and Moderna vaccines use mRNA vectors. All vaccine-induced thrombotic events should be treated with a nonheparin anticoagulant. As the condition has some similarities with HIT, patients should not receive any heparin or platelet transfusion, as these treatments may potentially worsen the clinical course. Aspirin has limited rational use in this setting and is not currently recommended. Intravenous immunoglobulins may represent another potential treatment, but, most importantly, clinicians need to be aware of this new unusual postvaccination syndrome.

J Cardiovasc Med 2021, **22**:000–000

Keywords: coagulation, coronavirus, endotheliitis, immunity, thrombocytopenia, vaccine

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Received 16 April 2021 **Revised** 8 June 2021
Accepted 27 June 2021

Introduction

Since its first report, the coronavirus disease 2019 (COVID-19) pandemic has been presenting as an aggressive disease responsible for patients' admission to ICU and high mortality rates worldwide.[1]

There is increasing evidence that COVID-19 is by far a systemic illness involving multiple organs. It affects the elderly the most.[2,3] Recent reports suggest that also a minority of children may develop COVID-19 with features mimicking Kawasaki disease and its complications.[4]

Vascular endothelium, the largest organ in the body, is at the interface between the circulating blood and body tissues and displays a series of antiaggregatory, anticoagulant and anti-inflammatory properties. Endothelial cells form the front line in host defence against pathogens, thus sending warning signals of concomitant infection, invasion, or injury to the immune system.[5]

On endothelial cells, transmembrane angiotensin-converting enzyme 2 (ACE-2) receptors and host type 2 transmembrane serine protease (TMPRSS2) are widely expressed. These two enzymes allow the coronavirus to enter the cells.[6] It then spreads quickly through the vascular tree and can involve the lungs, heart and nervous system, kidneys, and gastrointestinal tract. Endothelial dysfunction may quickly result in life-threatening platelet aggregation and intravascular clot formation because of an inflammatory milieu.[7]

A plausible mechanism underlying these clinical manifestations involves endothelial dysfunction/damage as well as haemostasis derangement. It is known that COVID-19 triggers a prothrombotic state with some unique characteristics.[8] The concept that COVID-19 is primarily an endothelial disease provides a unifying pathophysiological explanation for the multiorgan involvement and forms the basis for a rational management strategy, even though the current scientific evidence to guide the therapy against COVID-19 is still under debate.[9]

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) triggers endotheliitis resulting in reduced

DOI:10.2459/JCM.0000000000001232

antithrombotic activity. The features of COVID-19-associated coagulopathy are significantly different from those of bacterial sepsis-induced coagulopathy and disseminated intravascular coagulation (DIC). In fact, COVID-19-induced coagulopathy usually shows low platelet count, increased D-dimer, low fibrinogen, and initially minimal abnormalities in prothrombin time.[8,9] Venous thromboembolism and arterial thrombosis are much more frequent in COVID-19-associated coagulopathy than in the above-described coagulopathies.[10,11]

From endotheliopathy to endotheliitis

The resulting thrombo-inflammatory phenotype, characterized by endothelial cell injury and dysfunction, is responsible for microvascular dysregulation with vasoconstriction, ischaemia, inflammation, and hypercoagulable state. COVID-19 usually results in venous thromboembolism, but arterial thrombosis is often observed, unlike other infection-associated coagulopathies.[10,12]

Arterial and venous thromboembolic complications are a hallmark of COVID-19 disease.[11] Platelets give the impression of being 'hyperactive' in COVID-19 and this may contribute to massive clotting. It is unclear if platelets serve as a cellular reservoir for coronavirus replication as well.[13]

Vaccines

Currently, there are several treatments that have been shown to be effective against COVID-19, such as monoclonal antibodies in patients with mild-to-moderate disease to hamper disease progression and dexamethasone in hospitalized patients.[14,15] In order to cope with the COVID-19 pandemic with millions of cases around the world, hope lies in vaccinating a large number of people. From December 2020 to March 2021, the European Medicine Agency (EMA) approved four vaccines based on randomized, blinded, and controlled trials: two of them are m-RNA-based vaccines, that is BNT162b2 (Pfizer-BioNTech) and mRNS-1273 (Moderna). They encode the spike protein of SARS-CoV-2 encapsulated in lipid nanoparticles. Another vaccine, which is named ChAd0x1 nCov-19 (Oxford-AstraZeneca), is a recombinant chimpanzee adenoviral vector encoding the spike glycoprotein of the coronavirus. The last vaccine is Ad26.CoV2.S (Janssen/Johnson & Johnson), based on the recombinant adenovirus type 26 vector encrypting the viral spike protein as well (https://www.healthcareit-news.com/news/emea/four-types-covid-19-vaccine-snapshot, accessed on 11 April 2021). Both the Oxford-AstraZeneca and Janssen/Johnson & Johnson vaccines are produced using inactivated virus to deliver the spike protein to recipients and trigger an immune response.

Following widespread vaccination using the AstraZeneca vaccine, available only in the United Kingdom and Europe, many concerns have emerged. In fact, apart from quite common postvaccine reactions involving soreness at the site of injection, chills, tiredness, and aching muscles in about 10% of recipients, some uncommon and harmful symptoms have been noted (https://www.bbc.com/news/world-europe-56397157, accessed on 15 March 2021).

Updated data released by the European regulators on 11 April 2021 reported a total of 222 cases of a rare blood clotting: 106 were because of cerebral sinus vein thrombosis (CVST); the remaining 53 were the otherwise rare splanchnic vein thrombosis. Clotting is less likely to be reported after the second dose of the vaccine. In fact, the risk of a blood clot formation after a second dose is about one in 600 000, which is 1/10th the risk of clotting after an initial dose (https://brighterworld.mcmaster.ca/articles/second-dose-of-astrazeneca-covid-19-vaccine-faqs-about-blood-clots-safety-risks-and-symptoms, accessed on 05 June 2021).

About 20% of patients with these thrombotic episodes in the UK and European Economic Area (30 European Union countries plus Iceland, Norway, and Liechtenstein) died. Some of the cases were associated with DIC. As around 34 million individuals received the Oxford-AstraZeneca vaccine in these countries, the clotting problems have an occurrence rate of about 1 : 100 000 recipients (https://www.meconomictimes.com/news, accessed on 11 April 2021).

CVST is a rare neurovascular disorder with a highly variable presentation and clinical course. Its low incidence and confounding symptoms often lead to a delay in diagnosis. CVST is characterized by local clot formation and occlusion of intracranial venous structures, including the dural venous sinuses, cortical veins, and the proximal part of the jugular veins. The consequent large variety of symptoms and signs make the diagnosis difficult.[16]

Recently, the Johnson & Johnson COVID-19 vaccine has been suspended in the United States after six people, one death, experienced blood clot formation, out of 6.8 million who received the vaccine in that country.[17] The cases were similar to those seen in recipients of the Oxford/AstraZeneca vaccine, which has caused some countries to restrict its use.

Of note, COVID-19 can at times itself trigger CVST.[18]

Clotting has been reported mainly in healthy people under the age of 60 years, and more often in women than men, in Germany, Italy, and the United States. However, the sex difference in part might be because more women have been vaccinated, as they constitute more healthcare workers and home care staff.

Why younger people seem to be more at risk is not known but the age distribution can be partly explained as some countries have declared that this vaccine should be given only to those above a certain age. In fact, several European countries stopped the Oxford-AstraZeneca

vaccination or limited it to people older than 55–66 years. Similarly, the Joint Committee on Vaccination and Immunisation (JCVI) in the United Kingdom is now recommending healthy people under 30 years be offered a different vaccine. Another possible explanation for the age predilection is that older people are more at risk from COVID-19 itself, so that the benefit of the vaccine should outweigh the risk (https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting, accessed on 05 June 2021; https://www.ema.europa.eu/en/news/covid-19-vaccine-astrazeneca-benefits-still-outweigh-risks-despite-possible-link-rare-blood-clots, accessed on 18 March 2021; https://www.theguardian.com/society/2021/apr/07/under-30s-in-uk-should-be-offered-alternative-covid-vaccine-to-astrazeneca-jab-says-regulator, accessed on 08 April 2021).[19]

The thrombosis and thrombocytopenia occurred 5–14 days after vaccination with the AstraZeneca COVID-19 vaccine. This observation suggests that an immunological event may be the cause of the tendency for thrombosis. The term vaccine-induced prothrombotic immune thrombocytopenia (VIPIT) was recently coined for this new and rare condition. The vaccination is likely to induce the formation of antibodies against platelet antigens as part of the inflammatory reaction and immune stimulation. These antibodies then cause massive platelet activation via the Fc receptor similarly to that seen with heparin-induced thrombocytopenia (HIT). VIPIT and HIT are similar and different at the same time.[20]

Pathophysiologic basis of thrombosis

Human DNA adenovirus is remarkably efficient in infecting and replicating in human cells. These features make human adenovirus-based vectors a promising platform for developing novel therapeutics to combat genetic diseases, cancer, and COVID-19 now. Natural adenovirus infections in humans rarely cause severe disorders. Conversely, in animal models, intravenous administration of high doses of DNA adenovirus-based vectors may trigger a quick activation of the innate immune system, leading to cytokine storm syndrome, DIC, thrombocytopenia, and hepatotoxicity, which taken together may be life-threatening.[21]

Specifically, after intravenous injection, the DNA adenoviral vector quickly binds to circulating platelets, thus inducing their activation/aggregation, which in turn leads to cytokine release, binding of platelets to endothelial cells, and subsequent endothelial cell activation by VCAM-1 expression. The interplay between activated platelets and endothelial cells then promotes platelet aggregation and thrombus formation. Clumps of these aggregates end up and are trapped in liver sinusoids. Virus-platelet aggregates are finally taken up by Kupffer cells and degraded (accelerated platelet clearance).[21,22] A combination of clots and low platelet count is one of the features of VIPIT. But there is a lot more that needs to be understood about the process. Of note, vaccination with DNA ChAdOx1 nCov-19 results in antibodies which may react with a molecule released by platelets, that is, the protein PF4 (PF4–polyanion complexes). Interaction with PF4 is likely to trigger the prothrombotic process.[23]

Conclusion

The mechanism of coagulopathy induced by the Oxford-AstraZeneca (and probably Janssen/Johnson & Johnson) vaccine is likely to be related to the use of a recombinant vector DNA adenovirus as experimentally proven in animal models. Conversely, the Pfizer and Moderna vaccines, which use mRNA vectors, seem to be exempt from this harmful side effect.

The onset of venous and arterial thrombosis, particularly at unusual sites, such as the brain or abdomen, approximately from 5 to 14 days after vaccination, along with thrombocytopenia and specific abnormalities at blood tests, are the main features of the side effect induced by the vaccine.[24]

In the cases associated with the Oxford-AstraZeneca vaccine, many patients have tested positive for antibodies that bind to PF4, suggesting that the vaccine may somehow trigger the production of these antibodies. In our opinion, the first test to make a diagnosis of VIPIT should be a screening for HIT, which is based on the immunological detection of antibodies against PF4.[25] As, nowadays, there is no scientific evidence of any condition predisposing to the development of VIPIT, we believe that testing the coagulation profile of patients who are candidates for the AstraZeneca or Janssen/Johnson & Johnson vaccines is not indicated, irrespective of the cost to the healthcare systems.

It is still unclear whether the other COVID-19 vaccines approved in Europe (Pfizer, Moderna) are linked to clot formation. A few cases of clotting and immune thrombocytopenia have been reported in people getting these vaccines as well.[26]

If there are no specific contraindications, all thrombotic events in patients who have recently received COVID vaccination should be treated with a nonheparin anticoagulant (i.e. fondaparinux or DOAC – apixaban or rivaroxaban). Consultation with a sub-specialist haematologist is recommended as well. As the condition has some similarities with HIT, patients with this suspected condition should not receive heparin or platelet transfusion, as these treatments may potentially worsen the clinical course. Aspirin has limited rational use in this setting.[27,28] Intravenous immunoglobulins may be another potential treatment.[29]

In the trade-off between the extended protection offered by vaccines and the significant but remote risks of clot formation, the first outweighs the second. Not taking any

vaccine, AstraZeneca or Janssen/Johnson & Johnson included, is certainly riskier than getting the same, in terms of general health. We need clinical awareness of this new unusual postvaccination syndrome.[30]

Conflicts of interest

There are no conflicts of interest.

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