Covid-19 and Vaccine-Induced Thrombosis

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1. Overview

The COVID-19 pandemic is an ongoing global healthcare crisis, which can lead to systemic multi-organ complications. In particular, the risk of both venous and arterial thromboembolism is significantly increased. (1) (2) (3) Venous thrombosis, comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), occurs with an incidence of approximately 1 per 1000 annually in adult populations. (4) Venous thromboembolism (VTE) occurs in 22.7% of patients with COVID-19 in the ICU, and 8% in non-ICU hospitalized patients. Studies evaluating thromboprophylaxis strategies in patients with COVID-19 are needed to improve the prevention of VTE. (3) VTE is the most commonly reported thrombotic complication, with higher incidence rates among critically ill patients. A 2020 systematic review estimated that 28% of critically ill patients with COVID-19 had VTE. (5) (6)

Several vaccines have been licensed and are currently being used to combat the COVID-19 pandemic. Several cases have been reported to the European Medicines Agency, including at least 169 possible cases of cerebral venous sinus thrombosis and 53 possible cases of splanchnic vein thrombosis among 34 million recipients of the ChAdOx1 nCoV-19 (Astrazeneca) vaccine, 35 possible cases of central nervous system thrombosis, associated with low blood platelets, among 54 million recipients of the BNT162b2 (Pfizer–BioNTech mRNA) vaccine, and 5 possible (but unvetted) cases of cerebral venous sinus thrombosis among 4 million recipients of the mRNA-1273 (Moderna mRNA) vaccine. Six possible cases of cerebral venous sinus thrombosis have been reported among the more than 7 million recipients of the Ad26.COV2.S adenoviral vector (Johnson & Johnson/Janssen) vaccine. It must be emphasized that all of these case reports haven’t been subject to rigorous central review, and these numbers may be underestimates since reporting is voluntary. Nevertheless, they indicate the need for maintaining

a high level of concern when patients present with the central nervous system or abdominal symptoms after receiving any SARS-CoV-2 vaccine. (7)

Greinacher and colleagues wrote that the thrombosis mechanism resembles severe heparin-induced thrombocytopenia (HIT), but unlike the usual situation none of these patients were exposed to heparin during the previous days. They concluded that the vaccines can result in a rare syndrome that clinically mimics autoimmune heparin-induced thrombocytopenia (aHIT), and proposed using the term vaccine-induced immune thrombotic thrombocytopenia (VITT) for the first time to avoid confusion. In a past publication, they had referred to this syndrome as vaccine-induced prothrombotic immune thrombocytopenia (VIPIT). These blood clots were found to occur in approximately 1 in 100,000 people who received the vaccine. (8)

2. **Thrombosis prevalence and incidence after the first or second dose of Covid-19**

VTE prevalence in COVID-19 patients in the ICU, and non-ICU hospitalized patients is 22.7% and 8%, respectively. (3) The UK's Medicines and Healthcare Products Regulatory Agency had received 79 reports of thrombosis associated with low platelets by 31 March, of which 44 were CVST. Of these 79 cases, 51 (13 fatal) were in women and 28 (six fatal) in men. So far all of the UK cases have occurred after the first dose. (7)

In the 513284 patients with a covid-19 diagnosis, the incidence of cerebral venous thrombosis was 39.0 per million people, and in the 489871 patients who had received covid-19 vaccination, the incidence was 4.1 per million (1.1 to 14.9 million). (9) Till now, at least 1,809,239,524 doses of coronavirus vaccines have been administered around the world, in 230 locations. (10)

3. **Mortality rate after vaccination-induced thrombosis**

Based on CDC report, over 285 million doses of COVID-19 vaccines were administered in the United States from December 14, 2020, through May 24, 2021. During this time, Vaccine Adverse Event Reporting System (VAERS) received 4,863 reports of death (0.0017%) among people who received a COVID-19 vaccine. (CDC and FDA physicians review each case report of death as soon as notified and CDC requests medical records to further assess reports**.** (11)

Based on another report, one to two percent mortality and potential long-term sequelae must be emphasized because of the very low prevalence of thrombosis after vaccination. (7)

4. Vaccination-induced thrombosis signs and symptoms

The syndrome likely begins in 5 to 10 days post-vaccination, leading to the identification of cases typically between 5 to 30 days post-vaccination. If there is a delay in recognizing the symptoms and/or in seeking medical attention, the identification can be later. Symptoms of thrombosis include severe unremitting headache, backache, abdominal pain, chest pain.

A DIC-like picture can happen in VITT and although bleeding predominates in acute DIC, thrombosis predominates in VITT. However, bleeding complications have been reported in VITT, especially intracerebral bleeding.

Isolated thrombocytopenia (without thrombosis) with hemorrhage has also been reported. Thrombocytopenia may be suspected based on the presence of petechiae or minor bleeding (bruising). (12)

5. Locations of thrombosis

Often thrombi are present at multiple sites, frequently with thrombosis in unusual locations.

❖ ***Venous***

•Cerebral venous thrombosis also called cerebral venous sinus thrombosis, which may present as intra cerebral hemorrhage.

•Splanchnic vein thrombosis includes mesenteric vein, portal vein, splenic vein, hepatic vein.

•Adrenal vein thrombosis, which may present as adrenal hemorrhage. If bilateral, the patient is at risk for acute adrenal failure.

•Pulmonary embolism is more common than DVT.

•In a series of 22 individuals with VITT, 13 (60 percent) had CVT. Other unusual sites of thrombosis such as the ophthalmic vein have also been reported.

❖ ***Arterial***

•Ischemic stroke, especially middle cerebral artery territory

•Acute limb ischemia

•Sudden death (diagnosis of VITT established post-mortem) may reflect any number of thrombotic complications including coronary thrombosis, pulmonary embolism, or intra cerebral hemorrhage. (12)

6. Lab data suggesting post-vaccination thrombosis

Individuals with VITT have a high frequency of overt, decompensated disseminated intravascular coagulation (DIC), which manifests the following abnormalities:

●Moderate to severe thrombocytopenia (Normal platelet count in adults ranges from 150,000 to 450,000 platelets per microliter of blood)

●Elevated D-dimer (The reference concentration of D-dimer is < 250 ng/ml)

Elevations in D-dimer are very nonspecific and may reflect ongoing thrombosis, chronic inflammatory states, and/or DIC. (12)

●Decreased fibrinogen (approximately half have a fibrinogen level below the normal range; many of the remainders are in the low-normal range)

●Normal or mildly increased prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (aPTT)

7. Risk factors of vaccination-induced thrombosis

Risk factors for VITT are unknown. Female sex and younger age were proposed as possible risk factors based on initial reports:

Initial reports suggested a female predominance. However, this may reflect the demographics of the first wave of individuals (young female health care workers) to receive the vaccine. In a series from the United Kingdom, 14 of 23 (61 percent) were female. In the first three cases from Canada, two were males, and all were over the age of 60 years; this was during the period when the ChAdOx1 nCoV-19 vaccine was being avoided in younger women.

Initial reports appeared to suggest that individuals with VITT were younger (<55 or 60 years). One study has highlighted three independent descriptions of 39 persons with a newly described syndrome characterized by thrombosis and thrombocytopenia. These persons were healthy, and very few were known to have had previous thrombosis or a preexisting prothrombotic condition.

Most of them included in these reports were women younger than 50 years of age, some of whom were receiving estrogen replacement therapy or oral contraceptives. (7) Despite the combined oral contraceptive pill also increases the risk of blood clots, these clots are likely formed by a different mechanism. (13)

8. **Prophylaxis of vaccine-induced thrombosis**

Routine pharmacological thromboprophylaxis with anticoagulants or antiplatelet agents to prevent atypically located thrombosis resulting from the specific immunological response following vaccination is not indicated. (14)

Especially, there is no role for taking aspirin before or following vaccination as a strategy to reduce the risk of VITT. (15)

9. **Covid 19 vaccine injection in people with a history of thrombosis or hypercoagulable state**

Due to the immunogenetics of thrombosis, patients with a positive history of thrombosis do not have an increased risk of developing this specific and very rare complication after vaccination.

Also, having a blood-clotting tendency such as Factor V Leiden may put the patient at higher risk of blood clots, but this is not increased by the vaccine. People who have COVID-19 are at higher risk of developing blood clots. So, because COVID-19 disease often causes blood clots, the vaccine will provide you with protection against developing another blood clot. (8)

10. **Covid 19 vaccine injection in people on blood thinners (ASA, Warfarin, Clopidogrel, NOAC)**

Individuals taking novel oral anticoagulation (apixaban, dabigatran, edoxaban, and rivaroxaban), warfarin in therapeutic INR range, full-dose heparin, or fondaparinux injections, for any indications, can all receive the COVID-19 vaccination. Vaccinating before the next dose of anticoagulant may be considered rather than immediately after taking the blood thinner. There is a risk of bruising at the injection site, but serious effects are not anticipated. Prolonged pressure

(for at least 5 minutes) should be applied to the injection site; patients on warfarin with supra-therapeutic INR should wait until their INR is <4.0. (14) (16)

11. Management of vaccine-induced thrombosis

Consulting a hematologist or other hemostasis and thrombosis expert is critical to assist with the evaluation and management of VITT. Many individuals are hospitalized due to the severity of their clinical condition, except individuals with isolated thrombocytopenia who can be treated with a novel oral anticoagulant (NOAC) with very close follow-up.

❖ ***Anticoagulation:*** Therapeutic anticoagulation is one of the primary treatments for VITT and is used unless there is a contraindication such as expanding intracerebral hemorrhage.

In addition to patients with confirmed VITT-associated thrombosis, therapeutic anticoagulation is also indicated in individuals with a strong clinical suspicion for VITT who are awaiting confirmatory testing, and those with positive laboratory testing for VITT who have not had a thrombosis.

Early reports in which VITT patients were treated with heparins described clinical worsening, including death, although it is unknown whether heparin exposure contributed to poor outcomes. Because of the similarity to HIT and aHIT, most experts caring for the initial patients suggest using a non-heparin anticoagulant.

The choice of non-heparin anticoagulant depends on the patient's clinical status based on the risk of bleeding, need for an invasive procedure, and/or anticipated need to stop anticoagulation. In individuals who can take oral medications, anticoagulants in order of preference are:

•NOAC: Options include a factor Xa inhibitor (apixaban, edoxaban, or rivaroxaban); the oral direct thrombin inhibitor dabigatran may also be an option, although it is less studied.

•Fondaparinux or danaparoid

•A parenteral direct thrombin inhibitor (argatroban or bivalirudin).

Standard full-therapeutic dosing is appropriate, provided there is no active bleeding, with appropriate adjustments for body weight and kidney function.

The appropriate duration of anticoagulation is unknown. Analogous with spontaneous HIT following orthopedic surgery, thrombocytopenia can be prolonged. A reasonable approach for VITT with thrombosis would be to continue anticoagulation for three months after normalization of the platelet count, as long as no further thrombosis occurs. For VITT without thrombosis, anticoagulation until platelet count recovery and perhaps longer if tolerated (four to six weeks after platelet count recovery) appears prudent, by analogy with the duration of anticoagulation for classic HIT. It should be noted that the course of the initial patients is as yet unknown, there are no data to guide decision-making, and this advice is likely to be amended as further data accrue.

Individuals who are discharged from the hospital and were taking a parenteral anticoagulant can be switched to a NOAC. Warfarin and other vitamin K antagonists (VKAs) should be avoided while the patient is thrombocytopenic, due to lack of efficacy during ongoing hemostatic activation, but for an individual who is unable to receive a NOAC, a VKA might be an option following platelet count recovery, as long as appropriate bridging is used.

- ***IVIG***: As a means of interrupting VITT antibody-induced platelet activation, high-dose intravenous immune globulin (IVIG) is recommended along with anticoagulation. A typical dose is 1 gm/kg intravenously once per day for two days.

It is important to continue to monitor the platelet count during hospitalization and following discharge from the hospital; because after IVIG administration, thrombocytopenia can recur within a few days after IVIG is completed.

- ***Minimize platelet transfusions:*** Platelet and/or a source of fibrinogen (fibrinogen concentrate, plasma, or cryoprecipitate) transfusions should be provided to patients with life-threatening complications including bleeding or the need for emergency surgery, depending on

the platelet count and fibrinogen level. Hematology and/or transfusion medicine input may be especially helpful in these cases.

❖ ***Treatment of bleeding:*** Management of bleeding in VITT is especially challenging due to the competing goals of stopping bleeding and preventing thrombosis. General principles of managing concurrent bleeding and thrombosis should be followed, with input from the consulting hemostasis specialist.

❖ ***Monitoring:*** Clinical and platelet count monitoring for signs of thrombosis is critical. Platelet count monitoring is important in VITT because thrombocytopenia can recur after the effects of IVIG wear off. Other monitoring may include PT, aPTT, fibrinogen, D-dimer, especially if abnormal.

We would continue inpatient management until the platelet count is >50,000/microL and improving for at least two to three days, the patient is on stable anticoagulation with no new or progressive thrombosis, there is no bleeding for at least two to three days, and appropriate follow-up has been assured.

❖ ***Discharge***: The duration of acute illness in VITT is unknown. The monitoring interval can be extended according to the patient's clinical status and platelet count. (17)

12. Selection of vaccine:

The importance of vaccination should be emphasized and the primary criterion for the selection of vaccines is availability. For individuals who have access to more than one vaccine, the choice is individualized based on values and preferences. For individuals who have received one dose of the ChAdOx1 nCoV-19 vaccine, there are no good data to support omitting the second dose or switching to a different vaccine; completion of the two-dose series is encouraged. (17)

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