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Editorial commentary: COVID-19 and COVID-19 vaccination: Observations on thrombosis and thrombocytopenia

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When the world was shaken by the coronavirus disease 2019 (COVID-19) pandemic, millions of people lost their lives. As recently reported by the WHO in February 2022, there have been 430,257,564 confirmed cases of COVID-19 globally, including 5,922,047 deaths

[1]. It was early on during the pandemic that the world recognised the need for vaccination as a mean of reducing the risk of transmission and the risk of developing serious clinical forms of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Various vaccines of different types using different techniques were soon developed and tested in clinical trials: whole virus, protein subunit, viral vector and nucleic acid (RNA and DNA) [2]. The most commonly used types in the mass vaccination programs worldwide include: those encoding the spike protein antigen of SARS-CoV-2 in mRNA-based technology (BNT162b2 - BioNTech/Pfizer and mRNA1273-Moderna) and adenovirus vector-based vaccines (AstraZeneca, Johnson & Johnson, Gamaleya, CanSino). Inactivated virus vaccines (Sinopharm, Sinovac, Bharat Biotech) are also used in some parts of the world [2].

We learned during the pandemic that the COVID 19 is a highly coagulopathic condition, related to 'thromboinflammation' seen with the inflammation and cytokine storm in severe disease [3] Soon after launching mass vaccination programs worldwide, unique thrombotic events with thrombocytopenia were also noted as a rare complication after vaccination with recombinant adenoviral vector vaccine (ChAdOx1 nCov-19, AstraZeneca) [4]. This unique complication is referred to as vaccine-induced immune thrombotic thrombocytopenia (VITT) or thrombosis with thrombo-

cytopenia syndrome (TTS). Unlike the adenoviral vaccines, vaccination with mRNA vaccines (Comirnaty/BioNTech/Pfizer and mRNA-1273/Moderna) was not associated with cerebral venous sinus thrombosis (CVST) and splanchnic venous thrombosis (SVT) [5].

As described in this paper by Iba et al [6], the pathogenesis of VITT is believed to resemble that of heparin-induced thrombocytopenia (HIT), where platelet-activating anti-platelet factor 4 (anti-PF4) antibodies seem to play a key role. However, antibodies in HIT are bound to aminoacids corresponding to different sites on PF4. Moreover, anti-PF4 in VITT have a stronger binding response to PF4 and PF4-heparin complexes [7].

Whereas anti-PF4 antibodies also have been detected after mRNA vaccination, their optical density tends to be low and they seem to have a poor function in terms of platelet aggregation, as detailed in the paper by Iba et al [6].

In the study by Thiele et al [8], the incidence of anti-PF4/polyanion antibodies in healthy vaccinees (after vaccination with ChAdOx1 or BNT162b2) was assessed, together with their ability to induce platelet activation. A total of 19 of 281(6.8%) participants tested positive for anti-PF4/polyanion antibodies postvaccination; ChAdOx1: 8.0%, BNT162b2: 5.6%. Optical densities were mostly low (between 0.5 and 1.0 units; reference range, <0.50), and none of the PF4/polyanion enzyme immunoassay (EIA)- positive samples induced platelet activation in the presence of PF4. Hence, it concluded that pathogenic platelet-activating antibodies that cause VITT do not routinely occur after vaccination [8].

As for the COVID 19 infection itself, the risk ratio of venous thromboembolism at 8–14 days was estimated at 13.86 (95% CI, 12.76 to 15.05), compared to risk ratio of 1.10 (95% CI, 1.02 to 1.18) after ChAdOx1 vaccine and 0.99 (95% CI, 0.90 to 1.08) after BNT162b2 vaccine. While the risk for CVST after ChAdOx1 vaccination was higher than that after BNT162b2 vaccination [4.01 (95% CI, 2.08 to 7.71 at 8–14 days) versus 2.57 (95% CI, 0.85 to

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7.78 at 15–21 days)], the risk was still the highest after COVID-19 infection per se (at 13.43 (95% CI, 1.99 to 90.59)) [9].

In summary, the morbidity and mortality associated with SARS-CoV-2 infection remain significantly higher than that seen with vaccination, and importantly, thrombosis is estimated to occur at least 100-fold more often in COVID-19 without vaccination than with vaccination [5].

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