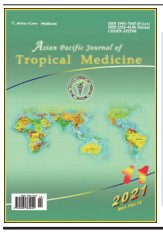

Perspective

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Vaccine induced thrombotic thrombocytopenia: Coagulation after administration of COVID-19 vaccine

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COVID-19 continues to present a daunting public health challenge globally and requires concerted efforts from multiple fronts including the development of vaccines and therapeutic agents[1,2]. To prevent the spread of COVID-19, various types of vaccines have been developed. The Moderna vaccine, is an RNA-based vaccine that encodes a protein spike to stimulate immune immunity. The Pfizer/BioNTec vaccine contains lipid nanoparticles of encapsulated mRNA to enhance immune response[3]. The AstraZeneca vaccine uses a recombinant chimpanzee adenovirus and encodes a glycoprotein of the SARS-CoV-2 spike[4]. The Sinovac vaccine is an aluminum adjuvant inactivated vaccine. Johnson & Johnson developed a vaccine with a vector of recombinant adenovirus type 26, encoding SARS-CoV-2 spike protein[3].

A vaccine can cause thrombotic events according to the WHO[5], stated thrombosis with thrombocytopenia syndrome occurs 1 case per 250 000 adults in the European Union.

Up until now, there are 5 types of COVID-19 vaccines authorized for usage, where each of them has its own advantages and limitations[3]. The first type is live attenuated vaccine (LAV) derived from virus strains, reverse genetics, and viral antigen to create vaccines[3]. LAV stimulates innate immunity through toll-like receptors 3, 7, 8 and 9 which later activates B-cells and CD4 T-cells[3]. The second type is inactivated virus vaccine which is made from purified and concentrated inactive virus[3]. Inactivated virus vaccine is more stable compared to LAVs and are already tested for its safety. However, this vaccine requires a booster dose and the producer needs to handle lots of viruses[3]. The third type is a sub-unit vaccine developed from recombinant proteins of the virus[6]. This vaccine contains a fragment of viral antigen and does not contain infectious components. Thus, the subunit vaccine is safer and have fewer side effects, but its efficacy and long-term effect remains unclear[6]. The fourth type is viral vector-based vaccine that does not contain any infectious components[6]. The vaccines made from viral vector are stable over a range of temperatures[6]. This vaccine induced humoral and cytotoxic immunity, but the amount of antibody produced through its immunogenicity is relatively low[6]. Lastly, RNA vaccines made from viral mRNA and avoid foreign DNA insertion[6].

Vaccine-induced thrombotic thrombocytopenia has been reported on the administration of adenovirus based vaccines such as AstraZeneca vaccine and Johnson & Johnson vaccine[4]. The AstraZeneca vaccine uses recombinant chimpanzee adenovirus vector encoding the SARS-CoV-2 spike glycoprotein and Johnson & Johnson vaccine based on recombinant adenovirus type 26 encoding the SARS-CoV-2 spike glycoprotein[4]. The vaccine-induced immune thrombotic thrombocytopenia (VITT) is estimated that about 1 case in 100 000 to 1 000 000 people vaccinated by adenovirus-based vaccine manifests thrombosis and thrombocytopenia possibly due to the high presence of anti-platelet factor 4 antibodies[7]. However, further study is needed to understand the pathogenesis and what affects VITT.

VITT occurs 4-28 days after AstraZeneca or Johnson & Johnson vaccines[4,7,8]. Pathogenesis may occur due to the interaction between vaccine and platelets or PF4. PF4-heparin antibodies will increase when VITT occurs. The reactiveness of PF4 is thought to be due to the presence of free DNA. Patient's DNA and RNA will form multimolecular complexes with PF4 and induce antibodies to PF4-heparin in murine form[4]. When the adenovirus vector (dsDNA) injection is carried out through the astrazeneca vaccine, PF4 together with dsDNA and TLR will form a complex. This complex will be identified by the antigen presenting cell, which identifies dsDNA and PF4 as an antigen, namely PF4 antigen (autoimmune). This will

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cause the formation of IFN continuously resulting in inflammation and coagulation. This coagulation occurs constantly, causing marked over-coagulation of biomarkers such as increase in CRP, IL-6, *D*-dimer, lactate dehydrogenase (LDH), PT, PTT, and ferritin, followed by a decrease in platelet count, fibrinogen, and WBC. VITT is mediated by platelet-activating antibodies against PF4, antibodies similar to heparin induced thrombocytopenia[8]. If the first dose of AstraZeneca vaccine shows VITT symptoms, the patient is recommended to receive a second mRNA-based vaccine such as Pfizer or Moderna[8]. It is always important to measure laboratory biomarkers that may indicate potential coagulopathy. In general, increase in CRP, IL-6, *D*-dimer, LDH, PT, PTT, and ferritin, while decrease in platelet count, fibrinogen, and WBC will be reported in patients[9].

After inoculation *via* hACE-2 receptors, SARS-CoV-2 induces IL-6, a pro-inflammatory cytokine which induces both inflammation and coagulation[10]. It was found that although SARS-CoV-2 induces less cytokine and chemokine compared to its predecessor SARS-CoV, it significantly elevates biomarkers such as IL-1B, IL-6, TNF and IL-1RA, and reduces IFN-Ⅰ and IFN-Ⅲ responses[10]. Macrophage and cytokine also produces ferritin, thus explaining the increased serum ferritin levels. Reports showed that it eludes antiviral effects of IFN-Ⅰ and IFN-Ⅲ, further activating innate response marked by cytokine production and adaptive immune response recruitment[10].

Inflammation initiates clotting, decreasing anticoagulation mechanisms and impairing fibrinolytic system as a way to compensate endothelial leakage[11]. Constant inflammation gnaws away both available and reserve thrombocytes, decreasing platelet count and fibrinogen as the coagulation cascade keeps moving[11]. Soon, PT and PTT will increase as there are less coagulation factors serving as precursor towards blood clotting[11].

After exhausting a certain amount of coagulation factor, the clot soon begins to break down, shown by an increase in *D*-dimer[12]. This may lead to formations of disseminated clots, a complication known as disseminated intravascular coagulation[12] that will disrupt oxygen supply towards areas of the body distal to the occlusion site[12]. This triggers anaerobic respiration, increasing LDH due to cellular hypoxia and damage[12].

ELISA can detect PF4-Heparin antibody which can be used to detect possible post-vaccine thrombocytopenia[4,7]. High titer intravenous immunoglobulin (IVIG)+corticosteroid (prednisolone) is considered effective to treat VITT[7]. Immunoglobulin can inhibit antibody-mediated platelets clearance and decreased platelet activation of immune complexes by inhibiting the platelet FcR γ Ⅱ A receptor[7]. In addition, IVIG also blocks antiplatelet antibodies from platelet activation to inhibit the cascading effect that produces VITT.

Various types of COVID-19 vaccines have been produced rapidly, while the emergence of side effects must continue to be studied further. VITT is a rare case but can cause death. This coagulation found in people vaccinated with an adenovirus-based vaccine is likely to be caused by an anti-platelet factor (4 PF4-heparin) antibody similar to heparin-induced thrombocytopenia. Treatment in VITT patients was carried out by administering high titer IVIG+corticosteroid (prednisolone).

Conflict of interest statement

Authors declared that there is no conflict of interest.

Authors' contributions

C.A.W.P. developed conceptualization and supervised the project. I.K.H.A. contributed to writing the original draft and resources of the manuscript. G.V.P. writing original draft and investigation. Both R.C.S. and I.G.P.W. contributed to the review and editing of the final version of the manuscript and project administration of the manuscript.

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