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Letter to the Editor

Vaccine-induced immune thrombotic thrombocytopenia: Consider IVIG batch in the treatment

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Various vaccines have been developed recently to protect the population from corona virus disease-19 (COVID-19). Although the beneficial effects of vaccines outweigh the risks associated with vaccination, unusual but life threatening thrombosis and thrombocytopenia, termed as vaccine-induced immune thrombotic thrombocytopenia (VITT) or vaccine-induced prothrombotic immune thrombocytopenia (VIPIT) have been observed in certain individuals who received recombinant adenoviral vector encoding spike protein of SARS-CoV-2 ChAdOx1 nCov-19 (AstraZeneca)[1–4]. Exploration of underlying mechanisms have identified that ChAdOx1 nCov-19 vaccine-induced platelet-activating antibodies against platelet factor 4 (PF4) are responsible for these adverse events[1-3]. Based on the *in vitro* experimental evidence that showed therapeutic potential of intravenous immunoglobulin, a pooled normal IgG, in preventing the platelet activation by anti-PF4 antibodies, and also founded on the initial experience with intravenous immunoglobulin-treatment in these patients[1,2], a recent report by Thaler et al. demonstrated a successful treatment of a vaccine-induced prothrombotic immune thrombocytopenic patient with high dose intravenous immunoglobulin therapy[5]. Considering the current knowledge on the mechanisms of action of intravenous immunoglobulin[6] and the pathogenesis of the vaccine-induced prothrombotic immune thrombocytopenia, possible mechanisms by which intravenous immunoglobulin exerts therapeutic benefits in such patients include Fcγ receptor blockade, neutralization of anti-PF4 antibodies by anti-idiotype antibodies, and enhancement of catabolism of anti-PF4 antibodies by saturation of neonatal Fc receptors. In addition, modulation of cellular immune compartment including anti-PF4 antibody-producing B cells could also play a role. Although the report by Thaler et al.[5] further expands the therapeutic potential for intravenous immunoglobulin, which is already used in the therapy of large number of autoimmune and inflammatory diseases, critical considerations should be given to the intravenous

immunoglobulin batches for the management of ChAdOx1 nCov-19-induced prothrombotic immune thrombocytopenia.

Intravenous immunoglobulin is obtained from pooled plasma of several thousand healthy donors. Therefore, depending on the geographical location, vaccination history and endemic nature of the infectious disease, intravenous immunoglobulin batches contain neutralizing antibodies to various infectious agents. Therefore, intravenous immunoglobulin lots prepared from the plasma collected from the donors before an epidemic of a particular emerging or reemerging infectious disease do not contain antibodies to those infectious agents, as shown for example during recent zika virus epidemic[7]. However, post-epidemic blood samples showed high prevalence of neutralizing IgG antibodies in the population[8]. Similarly, intravenous immunoglobulin batches prepared from the pooled plasma collected before current SARS-CoV-2 pandemic, had no neutralizing IgG antibodies to the virus[9]. However, intravenous immunoglobulin lots obtained from the plasma collected during COVID-19 pandemic (2020) have shown steadily increasing neutralizing IgG antibodies to SARS-CoV-2[10]. In addition, a significant proportion of the population in the Western countries and many Asian countries is already vaccinated against COVID-19 and have shown good seroconversion. intravenous immunoglobulin from the plasma of such donors is also expected to contain high titered neutralizing antibodies to SARS-COV-2. These reports thus raise few key issues that need to be considered while treating vaccine-induced prothrombotic immune thrombocytopenia.

The effect of pre-existing neutralizing IgG and in particular passively transferred neutralizing antibodies towards immune response to SARS-CoV-2 vaccine is not completely known. As patients with vaccine-induced prothrombotic immune thrombocytopenia receive high-dose

intravenous immunoglobulin (1-2 g/kg), if intravenous immunoglobulin batches prepared from the plasma collected during SARS-CoV-2 pandemic are used, neutralizing antibodies present in such intravenous immunoglobulin batches might neutralize SARS-CoV-2 vaccine antigens and as a consequence could reduce the vaccine efficacy. In view of this possibility, we suggest that patients with vaccine-induced prothrombotic immune thrombocytopenia should receive intravenous immunoglobulin batches prepared before current SARS-CoV-2 pandemic. This will potentially avoid vaccination failure in these patients. It is also important to note that thrombotic complications might appear between 5 to 24 days post ChAdOx1 nCov-19 vaccination[1-5] and hence intravenous immunoglobulin batch might affect immune response to the vaccine in those patients who show early thrombotic complications. Another reason for the necessity to use pre-pandemic batches of intravenous immunoglobulin is that anti-SARS-CoV-2 neutralizing IgG antibodies in the more recent batches of intravenous immunoglobulin might interfere with the accurate measurement of vaccine-induced protective IgG titers in intravenous immunoglobulin -treated patients. Nevertheless, further investigations are necessary to confirm these propositions and to understand the role of passively transferred neutralizing IgG in regulating the intensity and duration of SARS-CoV-2 vaccine-induced immune response.

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Competing interests

Authors have no competing interests to declare

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