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

Various vaccines have been developed recently to protect the population from coronavirus 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 (IVIG), a pooled normal IgG, in preventing the platelet activation by anti-PF4 antibodies, and also founded on the initial experience with IVIG-treatment in these patients,[1,2] a recent report by Thaler et al.[5] demonstrated successful treatment of a vaccine-induced prothrombotic immune thrombocytopenic patient with high-dose IVIG therapy. Considering the current knowledge on the mechanisms of action of IVIG[6] and the pathogenesis of VITT or VIPIT, possible mechanisms by which IVIG 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 IVIG, which is already used in the treatment of a large number of autoimmune and inflammatory diseases, critical considerations should be given to the IVIG 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, IVIG batches contain neutralizing antibodies to various infectious agents. Therefore, IVIG 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 the recent zika virus epidemic. However, post-epidemic blood samples showed high prevalence of neutralizing IgG antibodies in the population.[8] Similarly, IVIG batches prepared from the pooled plasma collected before the current SARS-CoV-2 pandemic, had no neutralizing IgG antibodies to the virus.[9] However, IVIG 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 Western countries and many Asian countries is already vaccinated against COVID-19 and has shown good seroconversion. IVIG 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 VIPIT.

The effect of pre-existing neutralizing IgG and in particular passively transferred neutralizing antibodies toward immune response to SARS-CoV-2 vaccine is not completely known. As patients with VITT or VIPIT receive high-dose IVIG (1–2 g/kg), if IVIG batches prepared from the plasma collected during the SARS-CoV-2 pandemic are used, neutralizing antibodies present in such IVIG 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 VITT or VIPIT should receive IVIG batches prepared before the 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 and 24 days post--ChAdOx1 nCov-19 vaccination[1-5] and hence IVIG batch might affect immune response to the vaccine in those patients who show early thrombotic complications. Another reason for the necessity of using pre-pandemic batches of IVIG is that anti-SARS-CoV-2 neutralizing IgG antibodies in the more recent batches of IVIG might interfere with the accurate measurement of vaccine-induced protective IgG titers in IVIG-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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CONFLICTS OF INTEREST

The authors have no competing interests to declare.

AUTHOR CONTRIBUTIONS

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