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Editorial: SARS-CoV-2 mRNA Vaccines and the Possible Mechanism of Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT)

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Abstract During 2020 and 2021, the global pandemic of coronavirus disease 2019 (COVID-19) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in high death rates and acute and chronic morbidity in all countries. The rapid development of new mRNA vaccines to SARS-CoV-2 brings hope that the spread of this virus can be controlled. The ChAdOx1 nCoV-19 vaccine developed by a collaboration between the University of Oxford and AstraZeneca showed efficacy in clinical trials, with a good safety profile. However, there have been recent reports of the rare development of thrombotic events in young women following vaccination with ChAdOx1 nCoV-19, particularly of the rare condition of cavernous sinus thrombosis. Studies have begun to investigate whether antibodies to the SARS-CoV-2 spike cross-react with platelet factor 4 (PF4/CXLC4) and mimic autoimmune heparin-induced thrombocytopenia. This **Medical Science Monitor** Editorial aims to briefly update the current status of studies on a possible rare complication of using new mRNA vaccines to prevent COVID-19.

Keywords: **Thrombotic Thrombocytopenia • Adverse Event • Platelet Factor 4 • Vaccine • Coronavirus Disease 2019 • COVID-19 • Severe Acute Respiratory Syndrome Coronavirus 2 • SARS-CoV-2 • Editorial**

During 2020 and 2021, the global pandemic of coronavirus disease 2019 (COVID-19) from infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in high death rates and acute and chronic morbidity in all countries [1]. In May 2020, a review article in this journal described the rationale for the development of mRNA-based SARS-CoV-2 vaccines and summarized the progress in vaccine development at that time [2]. From January 2021, SARS-CoV-2 vaccines gained emergency use authorization (EUA) in Europe, North America, South America, Australasia, and Asia, with the elderly and clinically vulnerable being given priority for vaccination.

Following clinical trial safety and efficacy data, the first two approved mRNA vaccines included the BNT162b2 Pfizer-BioNTech vaccine and the Oxford University/AstraZeneca vaccine, ChAdOx1 nCoV-19 (AZD1222) [3,4]. ChAdOx1 nCoV-19 is a recombinant adenoviral vector that encodes the spike protein antigen of SARS-CoV-2 [3,4]. However, during 2021, sporadic cases were reported of rare thrombotic events in young women who were recently vaccinated with ChAdOx1 nCoV-19, which included the rare condition of cavernous sinus thrombosis. In April 2021, Schultz et al. reported five patients who presented with venous thrombosis and thrombocytopenia between 7 days and 10 days after receiving the first dose of the ChAdOx1 nCoV-19 adenoviral vector vaccine [5]. The patients were healthcare workers who were between 32 and 54 years of age [6]. The patients were diagnosed with high levels of antibodies to platelet factor 4-polyanion complexes, but none had previous exposure to heparin [5]. Because the five cases occurred in a group more than 130,000 vaccinated individuals, this finding was reported as a rare vaccine-related variant of spontaneous heparin-induced thrombocytopenia termed vaccine-induced immune thrombotic thrombocytopenia (VITT) [5].

Recently, VITT has been identified in at least six patients who were given the AD26.COV2.S vaccine (Johnson & Johnson/Janssen), and on April 13, 2021, the US Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC) recommended pausing vaccination with AD26.COV2.S due to concerns regarding VITT [6].

For millions of people who have received the new vaccines, few side effects, if any, and vaccine development continue at an increasing pace [7]. Real-world safety monitoring and reporting is established in most countries. For example, the US has the Vaccine Adverse Event Reporting System, and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which was the first regulatory body in Europe to authorize a SARS-CoV-2 vaccine, has an established Coronavirus Yellow Card reporting system [8]. The MHRA and the Joint Committee on Vaccination and Immunisation (JCVI) have made clear that the benefits of SARS-CoV-2 vaccination far outweigh the risk of VITT [8].

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Studies have begun to investigate whether antibodies to the SARS-CoV-2 spike protein cross-react with platelet factor 4 (PF4/CXLC4) in a similar way to autoimmune heparin-induced thrombocytopenia [9]. Recently, Greinacher et al. evaluated the clinical and laboratory findings from 11 patients in Austria and Germany who developed thrombosis or thrombocytopenia after vaccination with ChAdOx1 nCov-19 [9]. Nine patients were women with a median age of 36 years (range, 22 to 49 years) [9]. Symptoms began between 5 to 16 days following vaccination [9]. Ten patients presented with one or more thrombotic event and one patient suffered from a fatal intracranial hemorrhage [9]. Nine patients had cerebral venous thrombosis, three patients were diagnosed with pulmonary embolism, three patients had splanchnic vein thrombosis, four patients had other thromboses, five patients developed disseminated intravascular coagulation (DIC), and there were six fatalities [9]. None of the patients had a history of treatment with heparin [9]. All patients had immune thrombotic thrombocytopenia and platelet-activating antibodies against PF4 [9]. The authors concluded that VITT is a clinical mimic of autoimmune heparin-induced thrombocytopenia [9].

The Society of Thrombosis and Haemostasis Research (GTH) has recently issued clinical guidelines for the diagnosis and management of VITT, which is also termed vaccine-induced prothrombotic immune thrombocytopenia (VIPIT) [10].

Conclusions

SARS-CoV-2 vaccines represent hope for reducing the prevalence and severity of acute COVID-19 and possibly 'long COVID.' Population epidemiological monitoring in countries that established early and full vaccination programs have shown reduced mortality rates from SARS-CoV-2. However rare, the mechanism for VITT requires urgent investigation to identify risk factors that may guide the use of alternative vaccines and reduce concerns that may deter compliance with global vaccination programs.

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