Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Letter to the Editor

In Response (Letter 2)

We thank Drs. Siang Kow and Shahzad Hasan for their contemporary comments on our report on Cerebral Venous Sinus Thrombosis in COVID-19 Patients: A Multicenter Study and Review of Literature.[1] We acknowledge our study period of CVST patients with COVID-19 covered March 1, 2020 to November 8, 2020, which preceded the COVID-19 vaccine roll-out in December 2020.

COVID-19 infection occurring in association with a prothrombotic state with deep venous thrombosis and pulmonary embolism are common and have been well documented.[1–3] Early reports in the first wave of the pandemic revealed thrombotic complications in as high as 49% of patients with severe, critically ill COVID-19 pneumonia. Most thrombotic events were pulmonary embolism, and associated with relatively higher mortality.[4]

In contrast, cerebral venous sinus thrombosis events in association with COVID-19 were a rare event, which we reported as 0.02% (3 /14,483) of COVID-19 patients.[5] This is in contrast with a background incidence of 2-5 cases per million in an adult population[6], which may be an underestimate of the true incidence of CVST in the general population due to the lack of well-designed populational studies. The low CVST event rate associated with COVID-19 is also in contrast to the relatively higher arterial ischemic stroke rate among COVID-19 patients which ranges between 1 to 1.5%.[7,8]

To neutralize the COVID-19 pandemic, vaccine development against SARS-CoV-2 infection was produced at warp speed. Randomized clinical trials demonstrated the high efficacy and safety of the COVID-19 vaccines, and the benefit also extended to real-world data.[9]

Late February 2021, several patients with venous thrombotic events in unusual locations with thrombocytopenia were reported after exposure to the ChAdOx1 nCov-19 (AstraZeneca) vaccine. In the United States, as of April 13, 2021, 6 thrombotic events associated with low platelets were reported out of 6.85 million people vaccinated with the Ad26.COV2.S (J&J) vaccine, or 1 thrombotic event in more than a million people. At the same time, 113.15 million people had received the BNT162b2 (Pfizer) or mRNA-1273 (Moderna) vaccine, with no signal of concern.

These clotting events with thrombocytopenia were reported in 11 patients in Germany and Austria[10] who received the ChAdOx1 (Astrazeneca) vaccine, most of which were cerebral venous sinus thrombosis events. In the United Kingdom, 22 patients with thrombosis, mostly cerebral venous thrombosis, and thrombocytopenia after exposure to the same vaccine were also reported. The mechanism appears to be related to the formation of platelet activating antibodies, similar to autoimmune heparin induced thrombocytopenia, but with none of these patients having prior exposure to heparin. This entity has been termed vaccine-induced immune thrombotic thrombocytopenia (VITT) and has been observed mainly by adenovirus-mediated rather than mRNA-mediated vaccine vectors.

It would be prudent for clinicians to have heightened awareness of CVST (severe persistent headache, focal neurological deficit, blurry visions) or other systemic symptoms (shortness of breath, chest pain, severe persistent abdominal pain, leg swelling or leg pain) in light of recent vaccine administration, with most events occurring within 28 days of vaccine administration. Evaluation with complete blood count and neuroimaging should be obtained to rule out CVST.

We agree in light of these findings and potential mechanisms implicated by Vaccine induced thrombotic thrombocytopenia, we would treat patient with non-heparin moiety initially, such as fondaparinux, danaparoid, and then transition to a novel oral anticoagulant such as dabigratran after a period of approximately 5 days if patient stable, based on RESPECT CVT trial.[11] Platelet transfusion should be avoided. In the event of a patient who presents in a moderate to severe state with extensive clot burden refractory to medical management, consideration for early venous thrombectomy should be considered.[12]

Considering the similarities of this clotting disorder to heparin induced autoimmune thrombocytopenia, intravenous immunoglobulin is recommended by the American Society of Hematology and the International Society on Thrombosis and Hemostasis.

In closing, we wish to emphasize the VITT events are very rare (approximately 1/1000,000), the importance of awareness of CVST events and appear related to VITT. We continue to advocate the importance for COVID-19 vaccinations considering the high morbidity and mortality associated with SARS-CoV2 infection and COVID-19 disease.

Once again, we thank Drs. Kow and Hasan for raising awareness of the recent VITT events and management

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paradigms. This is an area of dynamic change, and we anticipate guidance recommendations to change as the evidence evolves.

Sincerely,

Declaration of Competing Interest

None

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