Rapid Reviews COVID-19

Review 2: "A Prothrombotic Thrombocytopenic Disorder Resembling Heparin-Induced Thrombocytopenia Following Coronavirus-19 Vaccination"

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RR:C19 Evidence Scale rating by reviewer:

- **Potentially informative.** The main claims made are not strongly justified by the methods and data, but may yield some insight. The results and conclusions of the study may resemble those from the hypothetical ideal study, but there is substantial room for doubt. Decision-makers should consider this evidence only with a thorough understanding of its weaknesses, alongside other evidence and theory. Decision-makers should not consider this actionable, unless the weaknesses are clearly understood and there is other theory and evidence to further support it.

Summary of the Report:

This report summarized the clinical and laboratory features of nine patients in Germany and Austria who developed serious venous thrombosis and thrombocytopenia within 4 to 16 days after receiving the Astra Zeneca vaccine. The details of one case were presented in-depth.

Serum from four patients was tested and all were positive for anti-PF4/heparin antibodies by immunoassay as well as in the platelet activation assay in the presence of PF4 independently of heparin. Further, platelet activation was inhibited by high concentrations of heparin, Fc receptor-blocking monoclonal antibody, and intravenous immunoglobulin.

Specific Comments:

The authors present a biologically plausible mechanism that could explain a causal relationship between vaccination and the development of venous thrombosis and thrombocytopenia (pulmonary embolism, 2; cerebral vein thrombosis, 7; splanchnic vein thrombosis, 1; and arterial thrombosis, 1; some patients had more than 1 thrombotic event). Heparin-induced thrombocytopenia syndrome (HIT) is a well-described albeit rare event that strongly resembles the clinical and laboratory features of these four patients.

All four people studied had an underlying problem: Two had an autoimmune disease (multiple sclerosis; antiphospholipid antibodies) and two had a coagulopathy (von Willebrand disease; "unspecified coagulation disorder").

This was a convenience sample and observational study; it cannot give any information about the frequency of venous thrombosis and thrombocytopenia nor demonstrate causality.

Conclusions:

This is the first published research on people who had venous thrombosis and thrombocytopenia. It details the clinical course in one patient and summarizes the events in the other eight. Importantly, it studied the sera of four patients and demonstrated a consistent abnormality that would lend a biological explanation for the pathogenesis of their disease. If this is the correct pathogenesis, it hints at the possibility of a medical intervention (e.g., intravenous immunoglobulin; non-heparin anticoagulation).

The small sample size and the convenience sampling preclude saying anything about causality in general or specifically with the Astra Zeneca vaccine. According to the European Medicines Agency, as of April 4, 2021, there have been about 34 million people immunized with Astra Zeneca's Covid-19 vaccine. Central venous thrombosis (CVT) occurred in 169 people ($\sim 5/100,000$) and splanchnic venous thrombosis (SVT) in 53 ($\sim 2/100,000$). In studies done prior to 2021, the incidence of CVT is in the range of 1 to 3/100,000 person-years the incidence of SVT is less clear as most people have a predisposing factor (e.g., surgery, underlying gastrointestinal pathology). Still, estimates are in the range of 2 to 10/100,000 person-years.

I think this paper is worth publishing primarily because it is the first analysis of laboratory phenomena in patients who developed these rare forms of venous thrombosis and because it raises the possibility of effective medical interventions.