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COVID-19 vaccine safety surveillance and emerging concerns of vaccine-induced immune thrombotic thrombocytopenia

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The COVID-19 pandemic has caused significant disruption in the lives of people, affecting clinical services. For older people, there is a high risk of physical and psychological complications such as delirium, pressure injuries and risk of death.[1] In response to the pandemic, vaccines have been developed over compressed timelines including new platforms, such as mRNA vaccines, with international mass vaccination programs currently underway to achieve herd immunity and curb this pandemic.

For clinicians and policy makers, there is a need to critically appraise a large amount of information for benefit-risk analysis for these vaccines. In terms of safety considerations, animal studies and human trials have been performed before vaccines are used for public health measures. However, post-marketing surveillance for emerging reactogenicity data is necessary, as adverse events following immunization (AEFI) may only be noticeable after the studies, particularly rare complications.[2] Older people, particularly those with multiple comorbidities also tend to be under-represented in large Phase III clinical trials. Therefore, separate benefit-risk analyses may be appropriate for this group.[2,3]

In addition, there have been emerging concerns regarding new AEFI with COVID-19 vaccines, particularly vaccine-induced immune thrombotic thrombocytopenia (VITT) with the viral vector COVID-19 vaccines and myocarditis with mRNA COVID-19 vaccines. In this review, an overview of safety surveillance approaches for cardiovascular complications are outlined, followed by a current review of VITT and a brief overview of diagnostic and management approaches.

SAFETY SURVEILLANCE FOR COVID-19 VACCINES

Vaccine safety monitoring is a process that involves effective reporting of AEFI, assessment and investigation of reported cases, which may require timely actions by regulatory authorities. Clinicians have a responsibility to report AEFI encountered by their patients to their respective national pharmacovigilance centers. Countries may also choose to undertake active surveillance, which includes proactive enquiry of vaccine recipients for AEFI and monitoring for adverse events of special interest.

AESI is defined as a 'pre-specified medically significant event that has the potential to be causally associated with a vaccine product that needs to be carefully monitored and confirmed by further special studies'. These are shortlisted based on associations with immunizations, vaccine platforms or adjuvants, or theoretical concerns based on immunology or pre-clinical studies. AESI conditions include anaphylaxis, generalized convulsions, Guillain-Barre syndrome, meningoencephalitis, acute cardiovascular injury such as myocarditis, coagulation disorders, thrombocytopenia, aseptic arthritis and cutaneous vasculitis.[4]

COVID-19 infections may cause cardiac complications such as cardiomegaly, right ventricular dilation, lymphocytic myocarditis, focal pericarditis, endocardial thrombosis and small vessel thrombosis, which has been confirmed on cardiac autopsies. While some patients have SARS-CoV-2 virus detected in cardiac myocytes, indirect cardiovascular injury such as hypoxia-induced by respiratory failure, small vessel ischemia due to microvascular injury or

thrombosis and right ventricular failure due to pulmonary thrombosis or embolism have been reported. More relevant to AESI is a dysregulated inflammatory or immune response with exposure to SARS-COV-2 antigen, causing endothelial injury, platelet activation and vascular thrombosis, acute coronary artery vasoconstriction from increased sympathetic activity, or an autoimmune phenomenon causing thrombotic arterial or venous occlusions and end-organ damage.[5,6] While the Phase 1 and 2 trials of COVID-19 vaccines review participants to ensure an appropriate T-cell response (less likely to induce an autoimmune response) before progressing to phase 3 trials, post-marketing surveillance for cardiovascular sequalae of COVID-19 vaccines are warranted.[2]

Some AEFI are not easily attributable to vaccinations and may initially appear as possibly unrelated conditions. Thus, AESI constitutes lists of conditions that clinicians should consider as potential red flags for reporting. For example, in 1991, a signal was detected and eventually it was confirmed that there was a potential association of aseptic arthritis with the rubella vaccine.[7] The smallpox vaccine was associated with a 200-fold increase in incidence of myocarditis and pericarditis compared to baseline incidence rates during the smallpox immunization program in the United States.[8]

The background rates of AESI is important and serves as a comparison for the incidence after a mass immunization program so that regulatory authorities can decide whether there is a potential safety concern or not, regardless of clinician reporting. It should be noted that baseline rates vary over time, by geography, gender, socioeconomic status and age group.[9,10] For example, a multinational network cohort study using thirteen databases from eight countries reported population-based, age and gender specific background incidence rates, and found that some AESI such as myocardial infarction and Guillain-Barre syndrome increased with age, while anaphylaxis and appendicitis were more common in younger people.[11]

When there is an increased incidence of an AESI, it is also important to ensure that cases meet the criteria for diagnoses. The Brighton Collaboration publishes definitions for AESI and criteria for diagnostic level of certainty to ensure the potential signal is truly there, rather than an inaccurate over-diagnosis of the condition.[10] Thus, in terms of AESI monitoring, clinicians need to detect and proactively report these cases for pharmacovigilance, which will require confirmation of diagnostic criteria and comparison with baseline rates to consider an increased cardiovascular safety signal.

VACCINE-INDUCED IMMUNE THROMBOTIC THROMBOCYTOPENIA (VITT)

Acute immune thrombocytopenia (ITP) have been reported post-vaccination, particularly with the measles-mumps-rubella (MMR) vaccine, with an incidence of one case for every 40,000 vaccines administered.[12] Case reports are also available for ITP after hepatitis A, varicella, and tetanus-diphtheria-acellular pertussis vaccines, mainly in older children. As the numbers are small and potential confounding factors exist, this association still requires further investigation.[13] This may also occur in older adults, as was observed in an ITP report post-Shingrix recombinant zoster vaccine.[14] However, a national case control study showed that in adults, exposure to common vaccines was not associated with the risk of developing ITP.[15]

Vaccine-associated autoimmune phenomena such as ITP may occur from antigen-mediated responses, but may also stem from other vaccine constituents, such as adjuvants, preservatives or diluents. However, the most likely mechanism is viral-induced molecular mimicry, where autoantibodies bind to platelets and megakaryocytes, or rarely T-cell immune mediated mechanisms and increased production of pro-inflammatory cytokines.[16]

In the United States, concerns regarding thrombocytopenia from COVID-19 vaccines initially emerged with the death of a patient from an intracranial hemorrhage after receiving the Pfizer (BNT162b2) vaccine. A case series of low thrombocytopenia occurring within two weeks of vaccination with the mRNA vaccines mRNA-1 273 (Moderna) and BNT 162b2 due to development of secondary immune thrombocytopenia (ITP) has also been reported. The 20 patients of median age 41 years were admitted to hospital with petechiae, bruising or mucosal bleeding with a median time of 5 days post-vaccination before onset of symptoms. A majority had

platelets below 10×10^9/L. Of these, 4 (20%) had previous platelet abnormalities, and three had autoimmune conditions.[17]

The United States Vaccine Adverse Events Reporting System (VAERS) data also supported this potential safety signal. In early February 2021, there were five additional patients with ITP and 14 patients with bruising or bleeding. There were also 51 patients with bleeding or hemorrhage, ranging from vaginal, conjunctival, cerebral, and gastrointestinal, epistaxis. However, limited information was available regarding platelet counts or the possibility of other existing pathology. In addition, the incidence rate of 39,000 to 78,000 cases annually was similar to baseline rates.[18]

A retrospective cohort study estimated the absolute risk of cerebral venous sinus thrombosis (CVST) and portal vein thrombosis (PVT) two weeks after a diagnosis of COVID-19 infection and compared the relative risk with administration of the mRNA vaccines (BNT162b2 and mRNA-1 273). The relative risk of CVST and PVT with COVID-19 infection versus mRNA vaccines were 6.67 and 7.4, respectively. This provides some context to the risk versus benefit of COVID-19 vaccination, which should not deter recipients of mRNA vaccines due to the potential risk of thrombosis.[19]

Since then, concerns emerged regarding the possible risk of thrombosis in recipients of AZD1222 (ChAdOx nCoV-19 by Oxford-AstraZeneca), leading to temporary suspension of its use in several countries. Three independent reports were published of 39 people with a syndrome of thrombosis and thrombocytopenia developing 5 to 24 days after.[20–22] These reports of vaccine-induced immune thrombotic thrombocytopenia (VITT) occurred mostly in women younger than 50 years, with some receiving estrogen replacement therapy or oral contraceptives. There was a high rate of thromboses at unusual sites including cerebral venous sinus thrombosis or thrombosis in the portal, splanchnic or hepatic veins. Others presented with deep venous thrombi, pulmonary emboli or acute arterial thromboses. The patients also had a high D-dimer with low fibrinogen, indicating systemic activation of coagulation. In this case series, patients had approximately 40% mortality from ischemic brain injury, superimposed hemorrhage or both, usually after anticoagulation. These patients also had high levels of antibodies to platelet factor 4 (PF4)-polyanion complexes identified by enzyme-linked immunosorbent assay (ELISA), which is similar to heparin-induced thrombocytopenia (HIT). However, the patients were not exposed to heparin. [23]

Another two case reports of VITT occurred in women in their 50 s; one sustained a large central pulmonary embolus,[24] while another had bilateral superior ophthalmic vein thrombosis and an ischemic stroke.[25] All these cases responded to corticosteroids and intravenous immunoglobulin (IVIG) but derived little benefit from platelet transfusions.

The Danish National Patient Registry was used to estimate the incidence rate for venous thromboembolism (VTE) among the population. This found that the reported VTE rate for recipients of AZD1222 was not increased compared to the expected baseline rates before the roll-out of the vaccines.[26] However, a population-based cohort study using registry data from Denmark and Norway found an increased risk of VTE in the vaccinated cohort compared to the general population with a standardized morbidity ratio of 1.97 and 11 excess events per 100,000 vaccinations. For CVST, the standardized morbidity ratio of 20.25, with an excess of 2.5 events per 100,000 vaccinations. This confirms an association of VTE, especially CVST with AZD1222, albeit a small absolute risk of these complications.[27]

The World Health Organization (WHO) Global Database for Individual Case Safety Reports (VigiBase) was utilized to assess the reporting rate for thrombosis complications following immunization with BNT162b2, mRNA-1 273 and AZD1222. This found that there was an imbalance between venous and arterial thromboses with mRNA vaccines; 31.8% versus 67.9% for BNT162b2, and 24.6% versus 77.6% for mRNA-1273. The reported arterial and venous thromboses rates were evenly shared for AZD1222. For CVST, there was a relatively high reporting rate for such a rare event; 0.4%, 0.9% and 1.1% for BNT162b2, mRNA-1 273 and AZD1222 respectively. This suggests that VITT may occur with any of these COVID-19 vaccines.[28]

This has also subsequently been reported for the Ad26.COV2.S vaccine by Janssen. A case report was published of a 48-year-old woman who sustained extensive thrombosis, thrombocytopenia and dis-

seminated intravascular coagulation resembling autoimmune HIT. [29] A case series of 12 patients, all women between 18 to 60 years of age, developed CVST and thrombocytopenia 6 to 15 days following Ad26.COV2.S vaccination.[30]

Overall, while VITT has been publicized mainly against AZD1222, this has been reported to occur with the other vaccines by Pfizer-BioNTech, Moderna and Janssen. The benefits of vaccination against COVID-19 appears to outweigh the small absolute risk of VITT. For clinicians, it is crucial to recognize this AEFI, report to the national pharmacovigilance centers, and manage these complications.

APPROACH TO DIAGNOSIS AND MANAGEMENT FOR VITT

This section briefly covers a suggested approach for diagnosis and management for VITT. As this entity is likely due to the development of vaccine induced antibodies, the recommended management approach is similar to and adapted from the clinical experience of managing HIT.[31] A case report of a patient with VITT post-AZD1222 showed that treatment with non-heparin anticoagulation, high-dose IVIG and Prednisone resulted in significant improvement in laboratory and clinical parameters.[32]

The Scientific and Standardization Committee (SSC) of the International Society on Thrombosis and Hemostasis (ISTH) have issued guidelines based on expert recommendations for diagnosis and management of VITT. Essentially, for patients with suspected VITT who received a COVID-19 vaccine within 20 days, platelet count, activated partial prothrombin time, partial thromboplastin time, fibrinogen and D-dimer levels should be obtained. For patients with low platelet count and abnormal coagulation, specific VITT-testing with the antigen-binding assay (ELISA) for PF4/heparin antibodies. If positive, functional platelet activation testing should be performed to confirm the diagnosis.[33]

This diagnostic approach should be undertaken for patients who present with symptoms suggestive of CVST and recently received a COVID-19 vaccine. The American Heart Association and American Stroke Association have guidelines available to assist clinicians in the diagnosis and management of CVST.[34] Symptoms of CVST are due to its effects on venous drainage, resulting in increased intracranial pressure and focal brain injury with infarction or hemorrhage. This can present as a headache and focal neurological deficits (with the specific clinical manifestation depending on which part of the brain is affected by the thrombosis). Diagnostic imaging is warranted; with contrast-enhanced computed tomography or magnetic resonance imaging, which is more sensitive.[34]

Once VITT is confirmed, it is recommended that patients be treated with high dose IVIG (1mg/kg) for two consecutive days. Treatment of thrombosis should preferably be with non-heparin anticoagulation. Additional antiplatelet therapy for autoimmune thrombosis due to COVID-19 vaccines is not indicated.[35]

CONCLUSION

It is important for clinicians to contribute to COVID-19 vaccine safety surveillance for ongoing evaluation of the benefit-risk of immunization. Regular updates regarding emerging concerns of associated adverse events such as VITT is required so that clinicians are vigilant for these AEFI, in addition to understanding the diagnostic and management approaches should AEFI occur.

CONFLICT OF INTEREST

The author has no conflicts of interests to declare.

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