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Immune thrombocytopenia: vaccination does not equal causation

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Vaccination is the most important tool available for decreasing the incidence of severe disease and death due to SARS-CoV-2.[1] Early case reports and media coverage of patients diagnosed with immune thrombocytopenia (ITP) after receipt of a SARS-CoV-2 vaccine raised concern among patients and providers.[2] In this issue of *Haematologica*, Choi et al. describe the clinical course of a series of patients with a diagnosis of immune thrombocytopenia (ITP) in the 6 weeks following SARS-CoV-2 vaccination as identified by a national survey of hematologists in Australia.[3] Patients with features of the more lethal and rare vaccine-related phenomenon, vaccine-induced immune thrombotic thrombocytopenia, were excluded.[3]

At the time of this writing, 4.48 billion patients worldwide have received at least one dose of a SARS-CoV-2 vaccine.[4] It is now increasingly apparent from large epidemiologic studies that *if* there is an association with vaccination and ITP, the overall incidence is low (Table 1).[5–7] In the current study, *Choi et al.* explicitly do not set out to describe the incidence of ITP following vaccination nor determine causality. However, it is reassuring that only 14 patients (10 *de novo* cases) were identified with ITP in this survey of hematologists across Australia. ITP is not a particularly uncommon diagnosis, with an estimated incidence rate of 3 cases of primary ITP diagnosed per 100,000 adults per year.[8] Given that 4.2 million adults in Australia had been vaccinated at the time of the study by Choi et al., we would expect about 126 of these individuals to be newly diagnosed with ITP during the ensuing 12 months by chance alone, regardless of vaccination status. Using this estimate, we would anticipate roughly 15 individuals to be newly diagnosed with ITP during any 6-week period, whether they received vaccination or not. This simplified analysis does not take into account seasonal variation in the incidence of ITP or differences in incidence based on age or gender.[8,9] Nonetheless, the number of new cases of ITP (n=10) identified by Choi et al. in the 6 weeks following SARS-CoV-2 vaccination is in line with this expected incidence, suggesting that some or all of the cases identified by the authors may have occurred in proximity to vaccination purely by chance.

While we cannot conclude causality from the study, it is certainly plausible that vaccination could trigger an ITP episode. Any stimulus to the immune system may theoretically induce production of platelet auto-antibodies, as has been observed with certain pathogens and with live vaccines, including the measles vaccine.[10]

Choi et al.'s study provides important details regarding the clinical course of ITP following SARS-CoV-2 vaccination. Most cases responded rapidly to standard first-line therapies (corticosteroids, intravenous immunoglobulin), as would be expected in adults with garden-variety primary ITP. This experience suggests that patients who are diagnosed with ITP in proximity to SARS-CoV-2 vaccination may generally be treated with standard ITP therapy.

With the rampant increase in the delta variant of SARS-CoV-2, it is all the more important to instill confidence in the vaccines' safety, while also being careful to not be dismissive of safety concerns. *Choi et al*.'s study adds to literature reinforcing the safety of the SARS-CoV-2 vaccines by demonstrating that occurrence of ITP following vaccination is uncommon, perhaps no greater than what would be expected to occur purely by chance, and that most cases are treatable with standard first-line therapies. Patients with known ITP should be counseled to monitor for signs/symptoms of recurrence (i.e, petechiae, mucosal bleeding) after vaccination. Clinicians may consider obtaining platelet counts, particularly in patients without stable counts, before and after vaccination. Overall, the benefits of vaccination against COVID-19 continue to vastly outweigh the risks in patients with ITP and in the population at large.

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Table 1. Incidence of immune ihrombocytopenia following SARS-CoV-2 vaccination from selected epidemiologic studies.

Study	Vaccine	Definition of ITP	Population	Incidence	Relative Risk
Simpson et al.[5]	ChAdOx1	Diagnosis code (read code)	Age ≥18, Scotland	1.13 (95% CI 0.62-1.63) cases per 100,000 vaccinations	aRR 5.77 (95% CI 2.41-13.83)*
Simpson et al.[5]	BNT162b2	Diagnosis code (read code)	Age ≥18, Scotland	NR	aRR 0.54 (95% CI 0.1-3.02)*
Pottegard et al.[6]	ChAdOx1	Diagnosis code (ICD-10)	Age 18-65 years, Denmark and Norway	<5 cases out of 281,264 first doses	NR
Welsh et al.[7]	BNT162b2 or mRNA-1273	VAERS report of thrombocytopenia (did not specify ITP)	Adults, United States	0.8 cases per million doses	NR

aRR, adjusted relative risk; CI, confidence interval; NR, not reported

*Adjusted relative risk of ITP occurring 0-27 days after vaccination