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Research Article

Epidemiology of VITT

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ABSTRACT

Vaccine-induced immune thrombotic thrombocytopenia (VITT) is a life-threatening syndrome of aggressive thrombosis, often profound thrombocytopenia, and frequently overt disseminated intravascular coagulation. It has been associated with 2 adenovirus vector COVID-19 vaccines: ChAdOx1 nCoV-19 (AstraZeneca) and Ad26.COV2.S (Janssen). Unlike the myriad of other conditions that cause thrombosis and thrombocytopenia, VITT has an important distinguishing feature: affected individuals have platelet activating anti-PF4 antibodies that appear in a predictable time frame following vaccination. The reported incidence of VITT differs between jurisdictions; it is dependent on accurate ascertainment of cases and accurate estimates of the size of the vaccinated population. The incidence ranges from 1 case per 26,500 to 127,3000 first doses of ChAdOx1 nCoV-19 administered. It is estimated at 1 case per 518,181 second doses of ChAdOx1 nCoV-19 administered, and 1 case per 263,000 Ad26.COV2.S doses administered. There are no clear risk factors for VITT, including sex, age, or comorbidities. VITT is a rare event, but its considerable morbidity and mortality merit ongoing pharmacovigilance, and accurate case ascertainment.

In February 2021, early reports of cases of thrombosis and thrombocytopenia began emerging from a number of European countries using the ChAdOx1 nCoV-19 (AstraZeneca, University of Oxford, and Serum Institute of India) COVID-19 vaccine. Similar cases were soon reported in Canada and Australia, and then from the United States in patients receiving the Ad26.COV2.S (Janssen) vaccine. Several terms were initially used to describe this life-threatening syndrome of aggressive thrombosis, often profound thrombocytopenia, and frequently overt disseminated intravascular coagulation; however, the term that has become most widely accepted is vaccine-induced immune thrombotic thrombocytopenia (VITT) [1]. Since early 2021, there have been significant advances in developing an appropriate case definition of VITT. We also have a better understanding of the risk of this syndrome, in terms of its incidence and potential risk factors.

Implicated vaccines

Two adenovirus vector vaccines have been associated with VITT: ChAdOx1 nCoV-19 (Oxford/AstraZeneca) and Ad26.COV2.S (Janssen/Johnson & Johson)

To date, no other adenoviral COVID-19 vaccines - Ad5-based COVID-19 vaccine (CanSino Biologics) and Gam-COVID-Vac/Sputnik V (Gamaleya Institute) – have been associated with reported cases of VITT. It remains unclear if these vaccines are truly not capable of causing VITT. A study by Michalik and colleagues has shown substantial compositional differences between the ChAdOx1 nCoV-19 and Ad26.COV2.S vaccines, which potentially influence differences in the risk of triggering VITT [2]. Compositional differences between these 2 known VITT-inducing vaccines and the other adenoviral vector vaccines could thus be relevant.

There has been 1 published case of thrombosis and thrombocytopenia related to the second dose of mRNA-1273 (Moderna), and an additional TTS case reported to the United State Vaccine Adverse Event Reporting System (VAERS) also following the second dose of mRNA-1273 [3,4]. It is unclear if these cases reported following mRNA-1273 (Moderna) vaccination represent true cases of VITT. See et al. posited that these cases – which had a low reporting rate in the VAERS database and in thorough pharmacovigilance studies – may represent background cases of spontaneous HIT syndrome (another rare, likely environmentally-triggered anti-PF4 syndrome that has striking similarities to VITT, but which is unrelated to preceding vaccination [5]. There have been no cases of VITT related to the mRNA-based vaccine BNT162b2 (Pfizer-BioNTech) or the protein-based vaccine NVX-CoV2373 (Novovax). Interestingly, a case strongly resembling VITT – with thrombocytopenia, venous thrombosis, hypercoagulability, and anti-PF4 antibodies - was reported in a 25-year-old woman who had received Gardasil vaccination for human papillomavirus 10 days prior [6].

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Case definition

The Brighton Collaboration is an international voluntary collaboration of scientific experts that releases standardized case definitions for vaccine adverse events, as well as reporting templates for benefit–risk assessment of vaccines. Use of the Brighton Collaboration's standardized definitions and tools allows for a structured approach to evaluating vaccine safety, across jurisdictions. The Brighton Collaboration has proposed the term "thrombosis and thrombocytopenia syndrome" (TTS) in their Case Definition, instead of VITT [7]. This was an intentional choice, as TTS does not imply causality or a relationship to anti-PF4 antibodies or vaccines. It is an overarching term, and includes patients with VITT as well as patients who have thrombosis and thrombocytopenia for other reasons, such as (non-VITT) disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, or cancer. It also encompasses patients with non-immune thrombosis who have mild preexisting thrombocytopenia for various reasons (eg, ITP, hypersplenism, hereditary causes).

The advantage of a broad term like TTS is that it allows for straightforward comparative data to be collected by regulatory authorities. However, these data then need to be examined to determine what proportion represent true cases of VITT – a condition that, by definition, is induced by vaccines, and for which a definitive laboratory marker (platelet-activating anti-PF4 antibodies) has been identified.

The November 11, 2021 update of the Brighton Collaboration Case Definition for Thrombosis with TTS encompasses 5 criteria: (1) evidence of new thrombocytopenia with no recent exposure to heparin; (2) presence of thrombosis or thromboembolism confirmed by imaging, surgical procedure, or pathologic examination OR severe and persistent headache with elevated D-dimer (suggesting cerebral vein sinus thrombosis [CVST]); (3) clinical symptoms of thrombosis; (4) imaging or laboratory findings supporting the diagnosis of thrombosis or thromboembolism; (5) laboratory findings supporting the diagnosis of platelet-activating antibody-mediated thrombosis, that is, elevated D-dimer, positive specific anti-PF4 enzyme-immunoassay (EIA), positive functional (platelet activation) test with addition of PF4 [7]. Cases that fulfill more, or more highly weighted, criteria can be determined to represent TTS with greater certainty.

The Brighton Collaboration's case definition is useful in standardizing case ascertainment and reporting of VITT; this is essential for pharmacovigilance activities, research around diagnosis and treatment, and issuing of clinical guidance to ensure individuals with VITT get appropriate and timely care. The case definition also has value because it does not require a positive anti-platelet factor 4 assay to confirm TTS; these assays can be difficult, if not impossible, to access in low resource settings.

The Brighton Collaboration's case definition is challenged by the emphasis it puts on its first criterion: evidence of new thrombocytopenia with no recent exposure to heparin. This criterion is heavily weighted determining the level of certainty of a case of TTS. However there have been published report of patients who presented with thrombosis but had either normal platelet counts or very mild thrombocytopenia [8,9]. There is also an emphasis on thrombosis as a presenting symptom – either objectively confirmed or strongly suggested by clinical presentation. Thaler et al. were the first to report a case of a VITT in a 62-year-old woman who received the ChAdOx1 nCoV-19 vaccine, and presented with thrombocytopenia, elevated D-dimer, and a positive platelet factor 4 ELISA [10]. However, signs and symptoms of thrombosis were absent. She was immediately treated with non-heparin anticoagulation, corticosteroids, and intravenous immune globulin, and steadily responded before developing thrombosis. Similar reports followed, including a case reported by Kennedy et al., of a young man who presented 13 days after Ad26.COV2.S vaccination [11]. He also presented with thrombocytopenia, elevated D-dimers, and a positive platelet factor 4 EIA. This patient had a 5-day history of progressive leg pain, but had no radiographically demonstrable thrombosis. He received immediate treatment for VITT, then improved. Patients who present in this fashion are considered to have VITT and should be treated accordingly. Some experts have suggested the term "pre-VITT" – suggesting that subsequent development of thrombosis can happen without appropriate treatment to extinguish the highly prothrombotic state caused by platelet activation fueled by anti-PF4 antibodies [12]. This concept was explored in a recent publication from Salih et al., which described how failure to initiate treatment with anticoagulation and intravenous immune globulin in a patient with pre-VITT led to subsequent development of cerebral vein sinus thrombosis [13].

By way of analogy, it is well-recognized that in heparin-induced thrombocytopenia (HIT) a significant proportion of patients (approximately 25%-50%) do not develop thrombosis; however the frequency of thrombosis in atypical presentations of HIT, such as "autoimmune HIT" that features strong heparin-independent platelet-activating properties, appears to be >95%, [14] Nevertheless, thrombosis is not a necessary criterion to diagnose HIT; patients whose platelet count fall bears a temporal relationship to preceding heparin treatment, and whose blood contains platelet-activating anti-PF4 antibodies, are widely accepted as having "HIT" even if a thrombotic event is never detected. It seems plausible therefore that patients who develop thrombocytopenia in the setting of platelet-activating anti-PF4 antibodies following vaccination could also be deemed to have VITT even if thrombosis is not clinically evident, and even if this may be a relatively uncommon presentation

Nomenclature: VITT vs TTS

Differentiating VITT and TTS is not a purely academic exercise. TTS is a useful label to describe patients with thrombosis and thrombocytopenia after vaccination, who represent a myriad of aetiologies. VITT represents a more narrow group of patients, who have a high mortality, and require urgent, early, and specific diagnosis and treatment. The term VITT implies both causality (ie, a vaccine) and a mechanism (ie, immune-mediation). A recent publication by Thiele and colleagues retrospectively reviewed 106 suspected TTS cases reported to the Paul-Ehrlich Institute in Germany, between February 21 and May 21, 2021 [15]. Of these cases, 52 fulfilled the Brighton Case Definition for TTS – and all 52 had positive anti-PF4 testing done using an IgG. An additional 17 cases did not fulfill the Brighton Case Definition for TTS. Nine of the 17 cases that did not fulfill the definition for TTS had thromboses without thrombocytopenia, and none tested positive for PF4-dependent platelet activating antibodies. Eight of the 17 cases that did not fulfill the definition for TTS had isolated thrombocytopenia, and 4 of them tested positive for PF4-dependent platelet activating antibodies. The authors concluded that combined anti-PF4/heparin IgG EIA and PF4-dependent platelet activation testing was 96% sensitive (95% confidence interval 87%-100%) and 77% specific (50%-93%) for TTS. The lower specificity could be explained by the 4 patients with thrombocytopenia but without thrombosis, who had anti-PF4 antibodies; it was noted that these cases all had additional cerebral symptoms, suggesting subclinical CVST. This paper suggests that overreliance on the presence of thrombosis to make the diagnosis of VITT would result in missed cases. An intriguing concept posited by this study is that a patient with relevant symptoms (eg, headache) who has a strong clinical picture of VITT (clear thrombocytopenia beginning 5 to 45 days postvaccination, platelet-activating anti-PF4 antibodies) may have subclinical thrombosis even if imaging studies are negative.

Reports of VITT without thrombocytopenia, or without thrombosis – which otherwise fulfill the criteria of the syndrome, including laboratory criteria - may represent early presentations of disease that can be effectively managed with early treatment. They also underscore that the diagnosis of VITT can reliably be made through detection of platelet-activating anti-PF4 antibodies. As the definition of VITT evolves, clinicians should keep an open mind when faced with a possible case. They should also appreciate that detection of platelet activating anti-PF4 IgG has high sensitivity for TTS, and can pick up cases that may fall outside of the Brighton Collaboration Case Definition [15].

Incidence

Like many aspects of the COVID-19 pandemic, literature on the epidemiology of VITT is constantly evolving. It can be challenging to understand the true incidence of VITT, as information from different jurisdictions can be found in reports from regulatory authorities, press releases, scientific journals, and media stories.

Published estimates of the risk of VITT range from 1 case per 26,500 first doses of ChAdOx1 nCoV-19 administered (reported in Norway) to 1 case per 127,300 first doses of ChAdOx1 nCoV-19 administered (reported in Australia) [16,17]. Data from the United Kingdom suggest that the risk of VITT after second doses of AstraZeneca/COVISHIELD vaccines is likely lower than after first doses [18]. This risk is currently estimated at 1 case per 518,181 second doses of ChAdOx1 nCoV-19 administered [18]. A December 2021 report from the United States Advisory Committee on Immunization Practices (ACIP) calculated the incidence of VITT after Ad26.COV2.S as 1 case per 263,000 doses administered [19].

The risk of VITT varies between jurisdictions for 2 key reasons: the accuracy of case ascertainment (the number of reported VITT cases used as numerator), and the accuracy of the estimated size of the vaccinated population (the number of people at risk by virtue of receiving a dose of vaccine 5-30 days prior) [20]. The numerator can be unreliable if VITT is underdiagnosed, which can occur if cases are missed, or if they are unconfirmed (eg, due to inaccessibility of anti-PF4 antibody testing). The numerator becomes more reliable if centralized systems are used to record cases, if active prospective pharmacovigilance is used (as opposed to retrospective review), and if experts review cases to confirm the diagnosis of VITT. The denominator can be unreliable if vaccination is ongoing, which can overestimate the size of the population. The denominator becomes more reliable if vaccination with the vaccine of concern is paused, allowing for an accurate estimation of who has received it. Countries with higher data quality tend to show higher estimates of the risk of VITT.

Risk factors

Initial reports emphasized female sex and younger age as risk factors for VITT; this led several jurisdictions to restrict the use of adenoviral vector vaccines. However, many of these initial observations were likely artefactual; in many countries, health care professionals (whose demographics skew towards younger females) were prioritized in the initial rollout of the ChAdOx1 nCoV-19 vaccine, which led to a predominance of certain demographic factors in early reports of VITT [21].

Sex

Initial reports from Norway and Germany suggested female sex was a risk factor; 13 of the 16 patients in these reports were female [17,22]. A female predominance seemed logical; heparin-induced thrombocytopenia, a related condition, tends to affect females, and immune disorders in general are more common in females [23]. However, it soon became clear, as other countries began reporting cases, that the apparent female predominance simply reflected the demographics of the initial rollout of the vaccine. Canada restricted the ChAdOx1 nCoV-19 to older individuals, and preferentially gave mRNA vaccines to health care professionals; in 3 of the first cases from Canada, 2 were males, and all were over age 60 [24]. In a series of 220 definite and probable VITT cases associated with the ChAdOx1 nCoV-19 vaccine from the United Kingdom, there was no female sex preponderance [25]. In ACIP's December 2021 report on VITT cases associated with the Ad26.COV2.S vaccine, rates were similar between males and females in all age brackets, except in ages 30 to 49 years, where females were more likely to be affected. (ACIP reported an overall rate of 3.83 cases per million doses, but females 30-39 years of age had a rate of 10.6 per million doses and females 40-49 years of age had a rate of 9.0 per million doses) [19].

Age

There does appear to be an association between the risk of VITT and younger age. The United Kingdom reports the risk of VITT after the first dose of ChAdOx1 nCoV-19 as 1 in 100,000 for people older than 50 years of age and 1 in 50,000 for those younger than 50 years of age [21]. In a UK VITT case series of 220 patients by Pavord et al., the mean age at diagnosis was 48 years and 85% of individuals were less than 60 years old [25].

Comorbidities

There have been no large studies comparing the comorbidities of individuals with VITT with those of the general population. However, in the descriptive case series by Pavord et al., 165 of 220 patients had information available on their medical history [25]. A total of 41% of these patients had no past medical history. A total of 8% had a history of an autoimmune disorder, 2% had a history of previous venous thrombosis, 1% had a known prothrombotic disorder (all myeloproliferative disease, and none with known thrombophilia), and 19% had 1 or more risk factors for arterial disease. A total of 5% had serological evidence of previous infection with SARS-CoV-2, and 2% had COVID-19 in the previous 3 months. No patients had active SARS-CoV-2 infection. It is clear from these observations that an underlying history of thrombosis or medical comorbidity is not required to explain occurrence of VITT or associated thrombosis. This supports the concept that VITT represents an independent, strongly prothrombotic hypercoagulability state.

An association between the formation of anti-SARS-CoV-2 antibodies and the formation of anti-PF4 antibodies does not appear to exist, as illustrated in a study by Uzun and colleagues, which compared antibody titres in healthy vaccinated controls and individuals with VITT [26]. These findings are also consistent with studies indicating that VITT antibodies do not cross-react with the SARS-CoV-2 spike protein, suggesting that the intended vaccine-induced immune response against SARS-CoV-2 spike protein is not the trigger of VITT [27].

Conclusion

VITT is a rare vaccine adverse event – however its mortality and morbidity, and the sheer numbers of individuals who have and will receive implicated vaccines make it a serious entity that merits pharmacovigilance, and concerted efforts to raise health care professional and public awareness. Case ascertainment should be guided by standardized definitions, and should also take into account early and seemingly atypical presentations.

Conflicts of interest

Dr. Pai has provided expert witness testimony relating to non-VITT thrombocytopenic and coagulopathic disorders.

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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