Editorial

COVID-19: SARS-CoV-2 Vaccine-Induced Immune Thrombotic Thrombocytopenia

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Vaccination against SARS-CoV-2 is considered the most promising strategy to combat and control the COVID-19 pandemic. Consequently, highly effective vaccines have been developed with unprecedented speed, using distinct technologies such as messenger RNA-based products (with a lipid nanoparticle vehicle) or DNA-based vaccines (utilizing recombinant adenoviral chimpanzee or human vectors) both of which are encoding the SARS-CoV-2 spike glycoprotein. On the basis of randomized, blinded, controlled trials, the European Medicines Agency gave approval to four vaccines, including mRNA-BNT162b2 (BioNTech/Pfizer), mRNA-1273 (Moderna), ChAdOx1 nCov-19 (AstraZeneca), and Ad26.COV2.S (Johnson & Johnson/Janssen). The available vaccines have proven highly safe and effective.[1] Specifically, until very recently, no major safety warnings, other than exceedingly rare cases of anaphylaxis, were reported in initial trials. Moreover, the risk of serious adverse effects was demonstrated to be remarkably low following the vaccination of more than 400 million people worldwide.[2]

A Syndrome of Unusual Thrombosis with Thrombocytopenia and Systemic Activation of Hemostasis

Beginning in late February 2021, sporadic cases of an unusual thrombotic syndrome associated with thrombocytopenia were observed in individuals who had received the ChAdOx1 nCov-19 vaccine ("Vaxzevria"). Subsequently, similar findings were reported in a very small number of recipients of Ad26.COV2.S ("COVID-19 Vaccine Janssen"), also an adenoviral-based product. Prior to vaccination, the affected patients had been healthy or in medically stable condition; only very few were known to have a prior history of thrombosis or a preexisting prothrombotic condition. Remarkably, the majority of the patients experiencing post-vaccination thrombosis and thrombocytopenia were women younger than 55 years (median age 46 years). Some of them were on oral contraceptives or receiving estrogen replacement therapy.

Another distinctive feature of the syndrome is the unusual location of the thromboses. Among the affected patients, cerebral venous sinus thrombosis or thrombosis in the splanchnic (portal, splenic, or mesenteric), or adrenal veins occurred. Several other patients had deep venous thrombosis and/or pulmonary embolism, or presented with arterial thromboses including ischemic stroke and/or peripheral arterial occlusion.[3–5]

At diagnosis, median platelet counts were as low as 20,000 to 30,000/µL (ranging from ~10,000 to 110,000/µL). High levels of D-dimers and low levels of fibrinogen were frequently found indicating systemic activation of coagulation. Among the initially studied subjects, 16 of 39 patients (41%) died, some from ischemic brain injury, superimposed intracranial hemorrhage, or both.[3–5]

Since the initial research communications by early April 2021, additional cases of thrombotic thrombocytopenia in recipients of the AstraZeneca ChAdOx1 nCoV-19 and the Johnson & Johnson/Janssen Ad26.COV2.S vaccines have been reported to the European Medicines Agency (EMA) and the Centers for Disease Control and Prevention (CDC). As of

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May 11 or 14, 2021, respectively, nearly 400 patients have been recorded in European countries, Canada, and Australia (►Table 1).[6,7] Out of more than eight million doses of the Johnson & Johnson vaccine that have been administered in the US, the CDC has reported 17 confirmed cases of post-vaccination thrombotic thrombocytopenia but none upon administration of the Pfizer/BioNTech and Moderna vaccines.[8]

The post-vaccination thrombosis with thrombocytopenia syndrome (TTS) has now been named vaccine-induced immune thrombotic thrombocytopenia (VITT) or referred to as vaccine-induced prothrombotic immune thrombocytopenia (VIPIT).

Table 1 Estimated risk of VITT following first doses of AstraZeneca ChAdOx1 nCoV-19 vaccine, with countries ordered by risk of VITT from highest to lowest. Modified version of the original table provided by Chan et al. (on May 11, 2021).[6] Update for Germany according to the hemovigilance report by the Paul Ehrlich Institute (on May 14, 2021)[7]

Country	Cases	Estimated Persons Receiving 1st Dose of Vaccine	Incidence	Data Quality	Peer Reviewed	Case Ascertainment and Estimation of Denominator Population
Norway	5	132,686	1:26,500	High	Yes	Centralized electronic health record system used to ascertain cases. Vaccination paused after cases discovered allowing accurate estimation of the denominator population at risk of VITT.
Netherlands	8	400,000	1:50,000	Uncertain	No	Unclear.
Canada	NA*	NA*	1:55,000	Uncertain	No	Retrospective ascertainment of cases since April 2021, frequency of cases may therefore be underestimated. Vaccination ongoing, size of the denominator population therefore overestimated.
Denmark	2	148,792	1:74,400	High	No	Centralized electronic health record system used to ascertain cases. Vaccination paused after cases discovered allowing accurate estimation of the denominator population at risk of VITT.
Germany	77	6,991,964**	1:90,800	Uncertain	No	Unclear.
UK	242	22,600,000	1:93,400	Moderate	No	Ambispective pharmacovigilance for thrombotic events after vaccination, frequency of cases may therefore be underestimated initially. Vaccination ongoing, size of the denominator population therefore overestimated.
France	23	2,725,089	1:118,500	Moderate	No	Ambispective pharmacovigilance for thrombotic events after vaccination, frequency of cases may therefore be underestimated initially. Vaccination ongoing and no distinction made between first and second doses, size of the denominator population therefore overestimated.
Australia	11	1,400,000	1:127,300	Moderate	No	Ambispective pharmacovigilance for thrombotic events after vaccination, frequency of cases may therefore be underestimated initially. Vaccination ongoing and no distinction made between first and second doses, size of the denominator population therefore overestimated.
Italy	11	1,630,000	1:148,200	Uncertain	No	Unclear.

Abbreviations: NA, not available; VITT, vaccine-induced thrombotic thrombocytopenia.
*The risk of VITT in Canada as of May 8, 2021 has been estimated to be ~1 per 55,000 doses, but several presumptive cases are still under investigation.
**Includes 202,796 subjects receiving 2nd dose of AstraZeneca ChAdOx1 nCoV-19 vaccine ("Vaxzevria").

Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT)

The striking clinical similarities of VITT to heparin-induced thrombocytopenia (HIT) and identification of antibodies against cationic platelet factor 4 (PF4) in the index patients prompted Greinacher et al.[3] and other investigators from Norway[4] and UK[5] to study VITT in detail. As demonstrated by a series of three very recent articles published in *The New England Journal of Medicine*, in almost every patient with clinical symptoms of VITT, high levels of platelet-activating antibodies directed against PF4-polyanion complexes were detected by ELISA and subsequently by uniformly positive platelet activation assays.[3–5] A common characteristic of these immunoglobulin G (IgG) antibodies is that they are capable of activating platelets via low-affinity platelet FcγIIa receptors (i.e., receptors on the platelet surface that bind the Fc portion of IgG). Ultimately, activation of platelets (and possibly activation of other cells such as neutrophils) results in marked stimulation of coagulation, consumption of platelets, and clinically overt thromboembolic events.

In VITT, however, generation and binding of anti-PF4 antibodies to platelets occurs in the absence of heparin. This serologic feature strongly resembles autoimmune HIT, an atypical form of HIT, displayed by a small portion of patients who have a mix of heparin-dependent and heparin-independent antibodies.[9] A subtype of autoimmune HIT is spontaneous HIT in which no preceding exposure to heparin (or any other polyanionic medication) is required to produce the clinical and laboratory picture.[3]

While a mechanistic explanation has been provided for VITT, its pathogenesis is unknown so far. Specifically, the molecular and cellular pathways by which an adenovirally vectored vaccine triggers the generation of pathogenic platelet-activating antibodies remain to be elucidated. Currently, two possible explanations are under consideration[3]: (*i*) Vaccination induces a strong inflammatory response that in turn leads to the generation of autoantibodies against PF4 or PF4-polyanion complexes, respectively. (*ii*) The vaccine causes formation of antibodies against the SARS-CoV-2 spike protein that may cross-react with PF4-heparin complexes. The latter option was very recently shown to be rather unlikely. Thus, as also demonstrated by Greinacher et al., antibodies to PF4 do not cross-react with the SARS-CoV-2 spike protein through molecular mimicry.[10] Other explanation attempts comprise the possibility that components of the vaccine, including viral proteins or free DNA (but also RNA) can bind to PF4, thereby forming multimolecular complexes and generating a neoantigen.[3]

In addition, Cines and Bussel raised several important questions with strong clinical implications.[2] For example, does the atypical distribution of thrombi relate to antigen localization or vascular response, and is thrombosis propagated along vascular and hematopoietic surfaces that release diverse anionic cofactors? Conclusive answers to those and other issues will be required to provide insight into the risk of VITT and underlying pathophysiological mechanisms.

SARS-CoV-2 Vaccination – GTH Activities

Based on Andreas Greinacher's outstanding expertise, his pioneering work, and the extensive activities of the Greifswald team analyzing the phenomenon of SARS-CoV-2 vaccination-associated thrombotic thrombocytopenia, as early as mid of March 2021, the Society of Thrombosis and Hemostasis Research (GTH - Gesellschaft für Thrombose- und Hämostaseforschung e.V.) issued a guidance statement and a management algorithm both of which were rapidly updated.[11] Thus, the GTH took a leading position in providing guidance in the diagnosis and therapy of VITT. Moreover, the GTH recommendations were communicated as full paper and made available by eFirst publication on April 1.

This issue of *Hämostaseologie – Progress in Haemostasis* now presents the printed version.[12] Soon after, a task force of the International Society on Thrombosis and Haemostasis (ISTH) and a group of experts of the American Society of Hematology (ASH) published similar recommendations.[8,13]

Vaccination in patients with hemophilia represents another hot topic, in particular in times of COVID-19. Based on a consensus statement, a GTH working group under the leadership of Christian Pfrepper, Katharina Holstein, Christoph Königs, and Andreas Tiede has made recommendations for intramuscular administration of SARS-CoV-2 vaccines in patients with rare bleeding disorders.[14]

The current issue continues the series of GTH 2021 reviews, highlighting the recent Lausanne Congress, this time with a focus on platelet biology and pathology – but outside of the COVID-19 pandemic and related complications. Franziska Zeeh and Sara Meyer didactically resume current concepts of the pathogenesis and treatment of myeloproliferative neoplasms.[15] Yavar Shiravand et al. detail the fine-tuning of platelet responses provided by serine/threonine protein kinases and phosphatases.[16] Alix Garcia et al. highlight platelet regulation by microRNAs.[17]

Conflict of Interest

The authors declare that they have no conflict of interest.

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