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COMMENTARY

The path of uncovering a prothrombotic thrombocytopenic syndrome after viral vector-based COVID-19 vaccination: Where there is much light, the shadow is deep

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"Where there is much light, the shadow is deep."[1] These famous words from a play by Johann Wolfgang von Goethe, a great poet and multitalented individual in the 18th century, are true beyond the obvious field of physics. Also, in modern medicine, light and shadow often coexist.

1 | LIGHT

In March 2021, only a few weeks after the first cases of unusual thromboses associated with ChAdOx1 nCov-19 vaccination were observed, Greinacher et al[2] published a preprint article that characterized this syndrome and suggested a treatment strategy, which later turned out to be highly effective. Pointedly, they referred to this as a prothrombotic syndrome that clinically resembles heparin-induced thrombocytopenia (HIT; but without exposure to heparin) and coined the term *vaccine-induced prothrombotic immune thrombocytopenia* (VIPIT). During the following weeks and months, further clinical and experimental data were published at an impressive pace, setting the ground for evidence-based effective treatment.[3-8]

In this journal, (*Research and Practice in Thrombosis and Haemostasis*) Noikongdee et al and Uapraset et al report in two independent studies on the prevalence of platelet factor 4 (PF4)/polyanionic antibodies in health care workers in Thailand who received the first coronavirus 2019 (COVID-19) vaccination with ChAdOx1 nCoV-19 (vector-based vaccine, both studies) and CoronaVac (inactivated virus vaccine, in the report of Noikongdee et al). In both well designed and methodologically sound studies, the IgG-specific Zymutest HIA ELISA from Hyphen Biomed (Neuville-sur-Oise, France), known to be sensitive in detection of the PF4/polyanion antibodies in VIPIT, was used for screening, and positive samples were tested for platelet-activating antibodies by in-house platelet aggregometry. In the study by Noikongdee et al., 221 participants received ChAdOx1 nCoV-19 and 232 received CoronaVac. The prevalence of anti-PF4/polyanion antibodies was 2.3% and 1.7%, respectively and none of the positive sera induced platelet aggregation. Uapraset et al included 521 participants who received the ChAdOx1 nCoV-19 vaccine and found PF4/polyanion antibody positivity rates that were similar between vaccinated and unvaccinated Thais (3.1% and 4.1%, respectively), and again none of the positive sera induced platelet aggregation. Further, none of the participants had a fall in platelet counts of >30%, and all reported symptoms after vaccination were mild and resolved within 72 hours. Noikongdee et al sharply note in their article that in Asians the incidence of this syndrome may be lower than in other ethnic groups because >1.7 million doses of ChAdOx1 nCoV-19 have been administered in Thailand and only two cases of VIPIT have been reported. However, these rates are very comparable to the findings reported in two studies performed in Germany and Norway.[9,10]

These findings are important because they add evidence to published guidance indicating that in asymptomatic individuals and those with only mild symptoms after vaccination and normal routine laboratory findings (particularly normal platelet count and negative D-dimer) VIPIT can be ruled out safely.

2 | SHADOW

Several years ago, HIT was defined as an immunological complication of heparin therapy caused by antibodies to complexes of PF4 and heparin.[11,12] It has been firmly established since then that, as soon as HIT is suspected (eg, via the clinical 4T score), heparins need to be stopped and nonheparin anticoagulation should be initiated even at low platelet counts, to prevent thrombosis. Importantly, thrombosis is the most dangerous complication of HIT, and must be prevented, if not already present. Obviously, the hypothetical idea that thrombosis (ie, the complication of HIT) needs to be present for diagnosing HIT seems quite distorted. However, exactly this has happened in the nomenclature and diagnostic work-up of ChAdOx1 nCoV-19 induced PF4/polyanion antibody-mediated thrombocytopenic prothrombotic complications.

When extended data from the aforementioned preprint article by Greinacher et al[13] was finally published in the *New England Journal of Medicine (NEJM)*, surprisingly, a novel term was introduced to describe the syndrome, namely, *vaccine-induced thrombotic thrombocytopenia* (VITT), and the term *VIPIT* was suddenly ignored. Also, in a second article published in the same issue of the *NEJM*, the term *VITT* was used.[3] In both studies, all included patients had developed thrombosis. Consistent with this novel nomenclature and data from these two studies, in which all included patients had developed thrombosis, guidance statements from the World Health Organization, ISTH, and Brighton Collaboration[14-16] made thrombosis a conditional part of this syndrome. For example, the still valid ISTH guidance recommends specific treatment (ie, nonheparin anticoagulation and high-dose intravenous immunoglobulins) only if thrombosis is present. Even in patients who present with all other clinical and laboratory signs of vaccine-induced prothrombotic thrombocytopenia but without thrombosis, guidance does not suggest treatment in these cases.

We published a case report indicating that thrombosis can be prevented in these patients upon rapid initiation of treatment, very much like the case in patients with HIT.[5] Recently, we also published a case series supporting our view that upon swift initiation of treatment, thrombosis can be prevented in these patients.[17] We reemphasized that the umbrella term *VIPIT* should be used, as it comprises both patients with and without thrombosis, who present with clinical and laboratory criteria of the syndrome (ie, previous administration of viral vector-based COVID-19 vaccine [approximately 1–2 weeks ago], elevated D-dimer, thrombocytopenia, hypofibrinogenemia [nonconditional], and presence of PF4/polyanion antibodies). Consistent with our findings, another recent case series published in the *NEJM* reported on patients without thrombosis but clinical and laboratory confirmation of the syndrome. Interestingly, here a new term, *pre-VITT*, was coined.[18] Why is this so problematic? First of all, the nomenclature of VITT and pre-VITT is very confusing because it (in addition to available guidance) suggests that rapid initiation of a lifesaving treatment may not be warranted in patients without thrombosis, as they only have a "pre"syndrome. This is obviously wrong and can be very easily misinterpreted by the majority of physicians who are not coagulation experts.

We maintain that patients with VIPIT without thrombosis should be treated similarly to those with thrombosis. The term *VIPIT* is more encompassing and may be preferred to other nomenclature. More research on intervention in the absence of thrombosis is needed to bring knowledge from the Shadow into the Light.

RELATIONSHIP DISCLOSURE

PK and JT declare no conflicts of interest. CA declares that he handled the manuscripts by Noikongdee et al and Uapraset et al as associate editor of *Research and Practice in Thrombosis and Haemostasis*.

AUTHOR CONTRIBUTIONS

JT, PK, and CA drafted, reviewed and edited the entire manuscript and approved the final version of the manuscript.

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