CORRESPONDENCE

Decline in Pathogenic Antibodies over Time in VITT

TO THE EDITOR: Vaccine-induced immune thrombotic thrombocytopenia (VITT) has been described after vaccination with the adenoviral vector vaccines ChAdOx1 nCoV-19 (Oxford–AstraZeneca) and Ad26.COV2.S (Johnson & Johnson–Janssen). VITT is caused by platelet-activating anti–platelet factor 4 (PF4) IgG antibodies,[1-3] the presence of which can be confirmed by anti–PF4–heparin IgG enzyme-linked immunosorbent assay (ELISA) in combination with PF4-enhanced washed-platelet–activation assays.[1] Clinical and in vitro characteristics of acute VITT closely resemble (autoimmune) heparin-induced thrombocytopenia.[4] A hallmark of heparin-induced thrombocytopenia is the transience of anti-PF4 antibodies.[5] The persistence of pathogenic anti-PF4 antibodies in VITT is not well understood.

We conducted a study involving 35 patients with serologically confirmed VITT (27 women and 8 men; median age, 53 years [range, 18 to 77 years]). The patients' clinical symptoms started between days 5 and 18 after vaccination. All the patients presented with thrombocytopenia, and 30 presented with thrombosis. The median follow-up time after diagnosis of VITT was 11 weeks (range, 4 to 19) (a description of the methods is provided in the Supplementary Appendix, available with the full text of this letter at NEJM.org).

During follow-up, results of the PF4-dependent platelet-activation assay became negative in 23 of 35 patients (66%; 95% confidence interval [CI], 49 to 79). In 14 of the 15 patients with follow-up of more than 12 weeks (93%; 95% CI, 70 to 100), the platelet-activation assay became negative within a median of 12 weeks (95% CI, 10 to 13). In addition, the median optical density on anti–PF4–heparin IgG ELISA declined by 53% between the first and last available blood samples (median optical density, 2.98 vs. 1.39; P<0.001 by signed-rank test). However, full seroreversion to a negative ELISA result (i.e., an optical density of <0.5) was seen in only 3 patients (Fig. 1). In 1 patient, PF4-dependent platelet-activating antibodies and ELISA optical density values of greater than 3.0 persisted for more than 12 weeks in association with recurrent episodes of thrombocytopenia.

Five patients received the messenger RNA (mRNA) vaccine BNT162b2 (Pfizer–BioNTech) as a second vaccination 10 to 18 weeks after their first vaccination, while they were still receiving therapeutic-dose anticoagulation. All but one patient had a negative platelet-activation assay result before the second-dose vaccination. Clinically symptomatic new thrombotic complications or an increase in optical density by more than 0.5 on anti–PF4–heparin IgG ELISA did not occur in any of the patients.

Our study indicates that anti-PF4 antibodies are transient in most patients with VITT. In a subgroup of these patients, pathogenic platelet-activating anti-PF4 antibodies may persist for more than 12 weeks. Further studies are needed to clarify whether these patients should receive prolonged anticoagulation or additional treatment.

To achieve full protection against coronavirus disease 2019 (Covid-19), a second vaccination is needed after a first dose of ChAdOx1 nCoV-19. On the basis of our small series of patients, subsequent vaccination with an mRNA vaccine appears to be safe after results of platelet-activation assays for VITT antibodies have become negative. When no platelet-activation assay is available, a substantial decline in the optical density on anti–PF4–heparin IgG ELISA may be used as a decision criterion. However, further studies are warranted to define optical density cutoff values for different anti–PF4–heparin IgG ELISAs. In many parts of the world, anti-PF4 antibody tests are not available. In that situation, a pragmatic

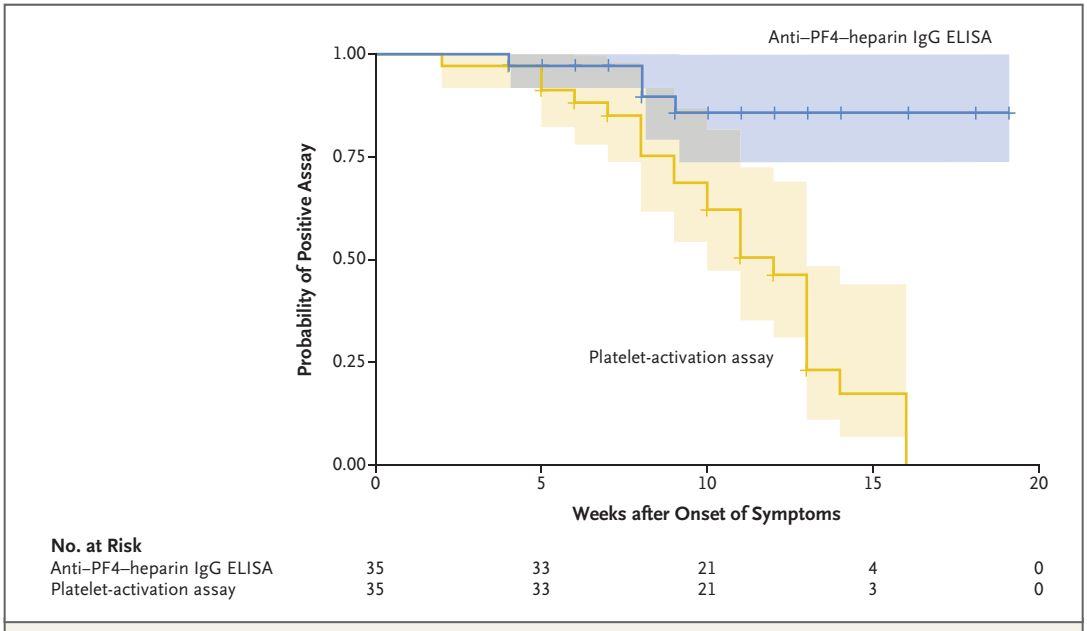

Figure 1. Kaplan–Meier Analysis of the Proportion of Patients with Positive Assay Results.

The time to an optical density of less than 0.5 on the anti–platelet factor 4 (PF4)–heparin IgG enzyme-linked immunosorbent assay (ELISA) and to a negative result on the platelet-activation assay is shown. Shaded areas indicate 95% confidence intervals. Most patients initially had very strongly positive reactivity on anti–PF4–heparin IgG ELISA, with optical densities of greater than 2.0 at the time of diagnosis of vaccine-induced immune thrombotic thrombocytopenia. Antibody levels decreased over time during follow-up but did not fall below the cutoff value. All the patients initially had positive results on an assay for PF4-dependent platelet-activating antibodies and repeatedly underwent testing (median follow-up, 11 weeks; range, 4 to 18). After 12 weeks, platelet-activating antibodies had disappeared in most patients.

approach is to wait for at least 12 weeks after an episode of VITT before the second vaccination is considered. Our study shows that in more than 90% of patients, pathologic, platelet-activating anti-PF4 antibodies have disappeared by then.

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