HEMOSTASIS AND THROMBOSIS

Brief report

Natural history of anti-PF4 antibodies in patients with vaccine-induced immune thrombocytopenia and thrombosis

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INTRODUCTION

The vaccination campaign against COVID-19, with over 13 billion doses administered worldwide represented the main game-changing strategy in the ongoing pandemic, determining a radical decrease in hospitalizations, severe cases and deaths[1]. Unfortunately, during the first half of 2021 very rare cases of thrombocytopenia combined with thrombosis (venous and/or arterial), have been reported following the vaccination with Adenovirus-based vaccines (namely Vaxzevria, Ad26.COV.2.S Johnson & Johnson/Janssen [New Brunswick, NJ, USA], Gam-COVID-Vac/Sputnik V [Gamaleya Research Institute of Epidemiology and Microbiology, Moscow, Russia] Ad5-nCoV [CanSino Biologics, Tientsin, China]). These vaccines were extensively evaluated before regulatory authorization for utilization and did not demonstrate any safety concerns. However, ongoing safety surveillance identified an association between adenovirus-based vaccines and the rare development of thrombocytopenia and thrombosis also in atypical sites, including cerebral venous sinuses and splanchnic veins, usually 5 to 30 days after vaccination[2-6]. These cases have been soon recognized as a new clinical syndrome termed VITT[7,8], which shares same of the pathogenetic mechanisms of autoimmune heparin-induced thrombocytopenia (aHIT)[9,10]. Specifically, both VITT and aHIT-patients develop a high serum titer of IgG antibodies directed against platelet-factor-4 (PF4) even in the absence of heparin exposure, which triggers an uncontrolled platelet activation leading to multiple venous and/or arterial thrombosis associated with consumptive thrombocytopenia and, sometimes, disseminated intravascular coagulation (DIC), with a high fatality rate[11,12].

Initial data on the natural history of PF4 antibodies in large VITT-patient cohorts have been recently published, suggesting a longer antiPF4 titer durability compared to what has been previously described in aHIT patients[13-16].

Here, we present the results of a study on a cohort of VITT patients followed with serial determinations up to 15 months by both immunological and functional assays.

MATERIALS AND METHODS

Study population

Among all patients with suspected VITT who were referred to the Thrombosis Center of Careggi University Hospital in Florence between March and June 2021, those with confirmed definite or possible VITT were enrolled in a prospective registry. Possible or definite diagnosis of VITT was defined according to the UK Expert Hematology Panel[5].

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For each patient clinical and anamnestic data including all the information about thrombotic events and vaccinations were recorded.

Laboratory examination

PF4-heparin antibodies were detected by a standard enzyme-linked immunoadsorbent assay (ELISA) (Lifecode PF4-IgG test, Immucor, Milan, Italy); by following manufacturer's instruction on citrated samples the cut-off for positivity for this ELISA assay was 0.4 OD (optical density). The analysis was also performed with another immunoenzymatic assay (Zymutest, Hyphen Biomed, Neuville-sur-Oise, France). Functional heparin-induced platelet activation test (HIPA), modified by the addition of PF4, was performed in order to detect the antibodies' functional ability to induce platelet activation. This assay tests the ability of patient's serum/plasma to aggregate washed control platelets in the presence of low (0.2 IU/mL) and high (100 IU/mL) heparin concentrations, in the absence of heparin (buffer control) and in the presence of exogenous PF4 (10 µg/mL) (Chromatec, Greifswald, Germany)[3,17]. The test was considered positive if platelet suspensions from 5 different donors aggregated within 45 minutes in the presence of only buffer control or PF4 (10 µg/mL). For patients with a negative HIPA and positive ELISA, the HIPA test was repeated after 1:4 dilution of the serum sample[3,18]. D-dimer was measured with the immunoturbidimetric (Werfen, Barcelona, Spain).

Follow-up and aim of the study

Follow-up was performed at 3, 6 and 12 months; for each patient clinical examination was performed and a serum sample was obtained and tested for immunological and functional assays.

The aim of the present analysis was to assess long term natural history of antiPF4 IgG antibodies and their correlation with clinical outcomes.

RESULTS

The cohort of patients of the present analysis consisted of ten patients (7 females, median age at the time of diagnosis 63.5 years, IQR 41-78), nine with a diagnosis of definite VITT and one with a diagnosis of possible VITT.

Clinical presentation

Eight patients were vaccinated with Vaxzevria and two patients received Ad26.COV.2.S Johnson & Johnson/Janssen. The median time span between vaccination and clinical onset was 8 days (IQR 6-23 days). All patients with definite VITT presented thrombotic manifestations, confirmed by imaging tests: seven patients developed venous thrombosis, usually in multiple sites and three of them showed an association with multiple arterial thrombotic events, too; the remaining two patients reported multiple arterial thrombotic events, affecting respectively the anterior cerebral circulation and the lower limbs circulation. Patient #10 was included as a case of possible VITT: he presented with diffuse skin bruising, thrombocytopenia and D-Dimer elevation, without developing any thrombotic manifestation. At the time of diagnosis, he had a negative quantitative ELISA test and a positive functional assay. Four patients (40%) presented also major hemorrhagic complications, always involving the intracranial district, leading to death in two cases, and to severe disability in the other cases.

The majority of patients did not present any major risk factor for venous thromboembolism (VTE); only one patient showed a previous VTE episode (pulmonary embolism after a hip fracture). Thrombophilia risk factors (FV Leiden, FII G20210A, AT, PS and PC deficiencies, elevated FVIII levels, hyperhomocysteinemia and antiphospholipid antibodies) were ruled out in all patients, whereas the most frequent cardiovascular risk factor was arterial hypertension (**Table I**). More detailed information regarding clinical characteristics of the cohort is included in **Table I**.

Laboratory examinations

All patients developed thrombocytopenia with a median platelet count at the nadir of 23,500/mmc (IQR 17,500-50,000/mmc). Median D-Dimer level at the presentation was 24583 ng/ml (IQR 5,141-58,881 ng/mL). At the time of diagnosis, the median antiPF4 antibodies quantitative titer resulted extremely high (2,192 ODs, IQR 1,260-3,084), and it was associated with a positive functional test in all definite VITT, **Figure 1** and **Figure 2**. The results of the ELISA assays were consistent in all cases except for patient #2 in whom the Hyphen assay was negative.

Treatment

In terms of treatment, all patients received systemic corticosteroids, anticoagulation (using in most cases fondaparinux as first-line medication) and intravenous immunoglobulins; none of them received

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Table I - *Clinical characteristics of the population*

	Sex	Age	Vaccine	Days from vaccination	PLT nadir (mm/c)	D-dimer baseline (ng/mL)	Anti-PF4 Ab-IgG titer (OD) at baseline (Immucor)	Anti-PF4 Ab-IgG titer (OD) at baseline (Hyphen)	Comorbidities	Antithrombotic therapy in the acute setting	Venous thrombosis	Arterial thrombosis	Bleeding	Clinical outcome
P1	F	57	Vaxzevria	6	10,000	7,690	2,472	1,940	None	Aspirin 100 mg Fondaparinux 7.5 mg → Dabigatran 150 mg b.i.d.	PE+PVT	Abdominal aorta, lienal artery		No disability
P2	F	73	Vaxzevria	23	95,000	5,151	1,912	238	Hypertension, dyslipidemia. Previous appendectomy and cholecystectomy	Fondaparinux 2.5 mg → 5 mg	CSVT, PE, RVT	Stroke, lower extremities		No disability
P3	M	66	Vaxzevria	10	53,000	28,383	1,260		Smoke habit, hypertension. Chronic kidney disease, abdominal aorta aneurysm	Argatroban	DVT, PE	NSTEMI, stroke, thoracic/ abdominal aorta	IPH, LEH	Deceased
P4	M	72	Vaxzevria	6	10,000	36,534	2,889	3,316	Previous hip fracture treated surgically and complicated by PE	Fondaparinux 7.5 mg → 5 mg	PE		SAH, IVH, IPH	Severe Disability
P5	F	78	Janssen	10	24,000	87,037	3,339	3,763	Hypertension, dyslipidemia. Peripheral artery disease	Fondaparinux 2.5 mg → 7.5 mg	DVT			No disability
P6	F	42	Vaxzevria	9	49,000	5,110	1,473	3,631	None	Alteplase Fondaparinux 2.5 mg → 7.5 mg		Stroke	IPH	Severe Disability
P7	F	75	Vaxzevria	7	23,000	53,800	1,260	2,256	Osteroporosis, Polymyalgia rheumatica	Fondaparinux 7.5 mg	PVT, CSVT		SDH, IVH, IPH	Deceased
P8	M	61	Vaxzevria	8	20,000	74,124	3,257	3,691	None	Fondaparinux 5 mg → 7.5 mg		Lower extremities		No disability
P9	F	60	Vaxzevria	10	24,000	20,782	3,026	2,543	None	Fondaparinux 2.5 mg → 7.5 mg	DVT, CSVT, SVT, PE			No disability
P10	F	61	Janssen	20	23,000	1,669	125	109	Hypothyroidism	Fondaparinux 7.5 mg			Skin bruising	No disability

CSVT: cerebral sinovenous thrombosis, DVT: deep vein thrombosis, F: female, IPH: intraparenchymal (cerebral) hemorrhage, IVH: intraventricular (cerebral) hemorrhage, LEH: lower extremities (intramuscular) hematoma, M: male, NSTEMI: non ST-segment elevation myocardial infarction, PE: pulmonary embolism, SAH: subarachnoid hematoma, SDH: subdural hematoma, SVT: splanchnic vein thrombosis.

plasma-exchange (PEX). After platelet count recovery, all patients received oral anticoagulation therapy, which was maintained for 6 months.

Follow-up

The overall mortality rate in this cohort was 20% (2/10), whereas another 20% (2/10) of patients survived with residual severe disability. The follow-up was conducted in the survivor's cohort (8 patients) over a median period of 10.5 months (IQR 2-15 months), **Figure 1** and **2**. At 6-9 months 4/7 patients (57.1%) presented a positive anti-PF4 IgG titer (#4, #5, #6 and #8), of whom 3 showed also a positive HIPA test (#4, #5 and #6). At 12-15 months

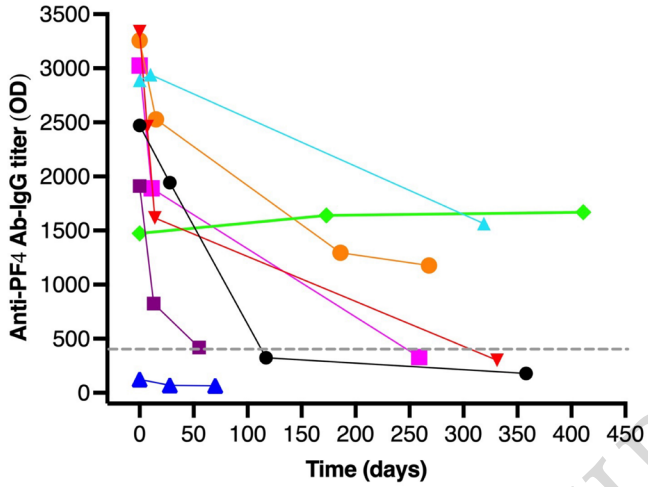

Figure 1 - Anti-PF4 Ab-IgG titer durability
The dotted line represents the threshold for a positive assay (400 OD).

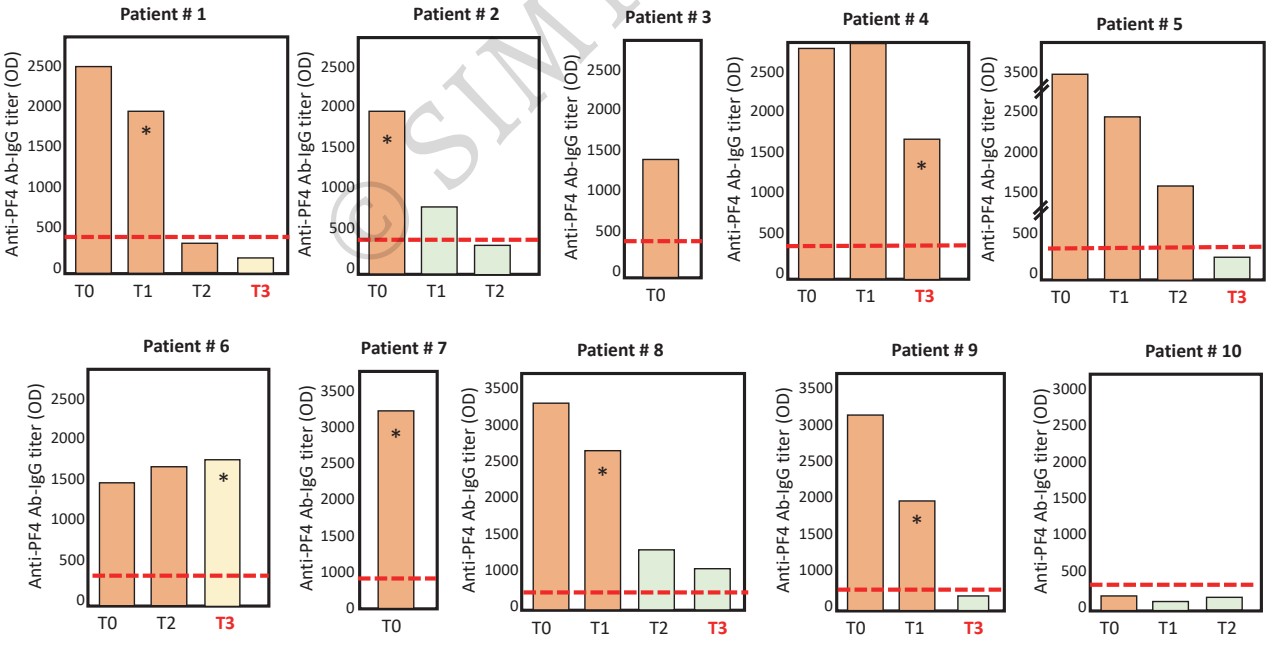

Figure 2 - Representation of the immunological and functional assay for each patient of the cohort
The dotted line represents the threshold for a positive ELISA assay (400 OD). T0: VITT Diagnosis; T1: 1-3 months; T2: 6-9 months; T3: 12-15 months. The results of the functional test are depicted with colored bars: orange, positive test (HIPA≥2/5); yellow, weakly positive test (HIPA 1/5); green, negative test (HIPA 0/5). * HIPA assay was negative before 1:4 dilution of serum samples.

follow-up was performed in 6 subjects. A positive antiPF4 quantitative titer was still detectable in 3 of them (50%, patient #4, #6 and #8), with an average OD value of 1414±355. Patient #8 showed the longer durability (15 months) of a positive quantitative assay inside the cohort, while the functional assay turned negative 6 months after diagnosis. This patient developed a severe peripheral arterial disease of both lower extremities, even in the absence of significant functional impairment. Patient #4 showed instead the maximum durability of a positive functional assay (almost 12 months). Together with patient #6, in whom the HIPA test performed at 12 months was slightly positive, he reported the worst outcome with severe disability and functional impairment. In one case (patient #1) we found a still detectable slightly positive functional assay after almost 1 year from diagnosis, despite seroconversion to negative quantitative test already occurred after 4 months. For what concerns the patient with possible VITT (case # 10), both quantitative and functional tests were negative at 3-months follow-up.

Regardless of these data, none of the surviving patients included in this study showed clinical manifestations of relapse. Only two patients underwent additional COVID vaccination with mRNA vaccines (patient #4 and #9); no manifestation of VITT clinical relapse was reported. Patient #1 contracted SARS-CoV-2 infection after 14 months since VITT diagnosis, developing a paucisymptomatic infection of upper airways (no signs of pneumonia were detected at chest CT scan). The patient was treated with anti-SARS-CoV-2 monoclonal antibodies, without any complications or any clinical sign of VITT relapse.

DISCUSSION

In the present study we documented the natural history of anti-PFA IgG antibodies by both immunological and functional assays in a real-word cohort of unselected VITT patients. As already reported, VITT seems to share the same pathogenetic mechanisms of aHIT, but few data on the durability of these antibodies were reported so far. A previous work from Warkentin TE *et al.* described a maximum antiPF4 heparin-induced antibodies titer durability from 50 to 85 days (depending on the assay performed) in an aHIT-patients cohort[19], whereas Craven B and coworkers outline that 72% of a quite large (148) VITT-patients cohort shows persistence of anti PF4 antibodies after 105 days[14]. In 65 VITT-patients followed for a median duration of 175 days, the authors demonstrated a sero-reversion to a negative anti-PF4 result only in 21.5% patients[13]. The same authors, in a recent publication, observed that only 32 of 71 patients (45.1%) reached an ELISA result below the cut-off within the study period (median time weeks; range, 8-94 week), confirming the long antibody response of VITT[20]. In the present study we found a high immunological titer in 50% of patients who were tested after a median follow-up duration of 12.5 months (IQR 12-13.5), with an average OD value of 1,414±355. Therefore, our data are in line with the previous ones, suggesting a longer persistence of anti PF4 antibodies in VITT as compared to aHIT. The cause underlying this durability is still debated, with some authors suggesting a role of the primarily oligoclonal nature of the VITT antibody response in comparison to a polyclonal immune response in HIT[21,22]. It should also be noticed that VITT seems also to be characterized by an extremely high quantitative titer of anti-PF4 antibodies at the time of diagnosis, which can affects antibody dynamic of seroreversion over time[3,12,15,23].

As already reported previously in other VITT and aHITT cohorts[15,19,20], first, the functional test became negative, and later the anti-PF4/heparin IgG assay. In our cohort, the functional test persisted positive at 12-15 months in 1 out of 6 patients and it resulted slightly positive in other 2 subjects.

It is worth considering that the HIPA test performed in patient #4 at 12 months resulted positive only after 1:4 dilution of the serum samples. This procedure optimizes the stoichiometric ratio between PF4 and anti-PF4 antibodies, therefore enhancing their binding, as already described for VITT[18]. The same was observed also at T0 for patients #2 and #7 who showed a high anti-PF4 IgG titer but a negative or weakly positive HIPA when we used undiluted samples serum. In this setting the diluting process may also counteract the effect of high levels of IgG after IVIG treatment, that can inhibit platelet activation[24,25].

The patient with possible VITT (# 10) showed a positive functional assay with negative anti-PF4/heparin IgG ELISA. In this case, the presence of platelet activation could be due to antibodies against other antigens such as interleukin (IL)-8 or neutrophil-activating peptide (NAP)

2, which have been described to be involved in HIT[26]. Interestingly, a recent report from Taiwan documented that AZD1222/ChAdOx1 vaccination was associated with mild thrombocytopenia with platelet activation and elevation of IL-8[27]. It could be therefore speculated that the inflammation related to vaccine immune response may play a role in the pathogenesis of VITT. In our case, the patient did not develop any thrombotic manifestation, questioning the role of any eventual other platelet-activating antibodies. However, the presence and pathogenic role of antibodies against other antigens in VITT require further confirmation.

Whether antibody titer or persistence is associated with different clinical outcomes has not been demonstrated. In the present study, we confirmed that VITT patients reported a particularly severe outcome, with a mortality rate of 20% and a high proportion of patients surviving with severe disability, especially if complicated by hemorrhagic events[5]. Interestingly, among survivors, patients with the worst functional outcome were also those who had the highest immunological titer at 12-15 months and a longer persistence of platelet-activating antibodies (patients #4 and #6). It could be hypothesized that a sustained immune response may be a reflection of a more aggressive disease in the acute phase. Despite this, no patients in our cohort showed recurrent thrombotic complications, even after the discontinuation of anticoagulant therapy after 6 months. A similar finding was also documented by Schönborn L. *et al.*, who observed recurrent episodes of thrombosis and thrombocytopenia only in one patient (1.4%)[20]. This datum suggests that discontinuation of therapy may be considered after 3-6 months regardless of antibody persistence.

Finally, despite the paucity of our data, we confirmed the safety of post-VITT COVID-19 mRNA vaccinations, as recently described by other research groups[28,29].

The present study has inherent limitations due to the observational nature of a small cohort of patients, that did not allow the performance of any statistical analysis. However, these results may still be considered significant in the light of the rarity of VITT. Besides, patients were referred from different hospitals and treatment was not standardized. Therefore, the correlation between immunological titer and outcome could only be hypothesized.

CONCLUSIONS

In conclusion, the data of the present analysis demonstrated a positive PF4 IgG titer and persistence of platelet-activating antibodies in a significative proportion of patients at 12-15 months, suggesting a longer antibody response than that described for aHIT. Whether this longer persistence is associated with a worst clinical outcome, requires confirmation in larger prospective studies.

ETHICAL CONSIDERATION

The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki.

AUTHORSHIP CONTRIBUTIONS

AMG, FC, AR, AB and DP performed the laboratory analysis and collected data; EL, FV and MB wrote the paper. BG and RM supervised the project. All Authors discussed the results and contributed to the final manuscript.

CONFLICTS OF INTEREST

RM: lecture fees from Sanofi, AMGEN, Bayer, Viatris, Werfen, Pfizer, Daichi- Sankyo. The other Authors have no conflicts of interest to declare.

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