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## TO THE EDITOR:

## Immune-mediated thrombotic thrombocytopenic purpura following COVID-19 vaccination

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Immune-mediated thrombotic thrombocytopenic purpura (iTTP) is a life-threatening form of thrombotic microangiopathy, which manifests by hemolytic anemia, consumptive thrombocytopenia, and diffuse microthrombi formation with organ damage resulting from a severe immune-mediated ADAMTS13 deficiency (activity below 10%).<sup>1</sup> Recently, several cases of iTTP have been described after coronavirus disease 2019 (COVID-19) vaccination.<sup>2,3</sup> These temporally associated events raise concerns about a potential causal link between vaccination and the development of the disease. Consequently, uncertainties persist regarding the best way to manage these cases as well as the approach to adopt in patients with known iTTP regarding vaccination. Finally, certain similarities with vaccine-induced thrombotic thrombocytopenia (VITT), a well-established complication of adenoviral vector-based vaccination,<sup>4</sup> raise the question of the differential diagnosis between these 2 entities.

The French Reference Center for Thrombotic Microangiopathies is a national network of French and French-speaking physicians involved in the diagnosis and care of patients with thrombotic microangiopathies. To investigate a possible link between COVID-19 vaccination and the occurrence of iTTP, all constitutive centers were asked to report cases of iTTP occurring in the 30 days following vaccination. We considered all episodes (new onset or relapse) of iTTP following the first or subsequent doses of 1 of the 4 COVID-19 vaccines licensed for use in France (BNT162b2, Pfizer-BioNTech; mRNA1273, Moderna; ChAdOx1 nCoV-19, AstraZeneca; Ad26.COV2.S, Janssen) occurring between December 2020 and November 2021. As an

exploratory analysis, the number of cases identified was compared with the expected number of cases, estimated by considering the theoretical incidence of iTTP in France as well as the duration of postvaccination follow-up truncated at 30 days for all vaccinations carried out. Because precise epidemiological data only exists for new-onset episodes in France, the statistical analysis was restricted to such episodes.<sup>5</sup> Importantly, such analysis is based on the assumption that the probability of new-onset iTTP is uniformly distributed and does not take into account ethnicity, gender, age, or seasonal variation in iTTP incidence.

Ten iTTP episodes occurring within 30 days after COVID-19 vaccination were reported, including 7 new-onset iTTP episodes and 3 relapses. Clinical and biological characteristics of patients are presented in Table 1. Overall, these cases appear to be very similar to iTTP episodes occurring outside the specific context of vaccination<sup>1</sup>: median age was 57 years, and presenting symptoms were mostly neurologic (n = 7; 70%). Cardiac involvement defined by troponin elevation was seen in 7 patients (70%). Three patients (30%) had a history of systemic autoimmune disease.<sup>6</sup> The clinical probability of severe ADAMTS13 deficiency was high in most patients according to the French score, with severe thrombocytopenia (platelets <30 × 10<sup>9</sup>/L in n = 8, 80%) and no/mild renal impairment (creatinine <2.25 mg/dL in all, 100%).<sup>6</sup> TTP diagnosis was confirmed by measuring ADAMTS13 activity in all patients. The immune-mediated mechanism was confirmed by the demonstration of anti-ADAMTS13 autoantibodies in 8 patients (80%) and the normalization of ADAMTS13 activity after the episode in all. Importantly, the 2

**Table 1. Clinical characteristics of iTTP episodes following COVID-19 vaccination**

	Patient #1	Patient #2	Patient #3	Patient #4	Patient #5	Patient #6	Patient #7	Patient #8	Patient #9	Patient #10
Age	36	54	60	60	38	68	66	70	22	20
Sex	Woman	Man	Woman	Woman	Man	Man	Man	Woman	Man	Woman
Previous medical history	SLE	iTTP	iTTP			MCTD iTTP		Ischemic strokes, hypertension		SLE
Vaccine	BNT162b2	mRNA1273	BNT162b2	BNT162b2	BNT162b2	BNT162b2	ChAdOx1 nCoV-19	ChAdOx1	BNT162b2	BNT162b2
Dose	First	First	First	First	Second	First	First	First	Second	First
Days since last dose	6	23	10	12	30	17	8	10	18	25
Type of episode	First	Relapse	Relapse	First	First	Relapse	First	First	First	First
Years since last episode*		19	27			6				
Clinical presentation	Bruising, headache	Bruising, diffuse mucocutaneous bleeding, headache, amnesia	Cerebellar syndrome	Cerebellar syndrome, aphasia, confusion, chest pain	Fever, headache, hemiparesis, bruising	Dizziness	Facial paralysis	Coma hemiparesis	Coma, seizures, purpura, fever	SLE Flare: polyarthritits, erythema
<b>Biology at diagnosis</b>										
Hemoglobin, g/dL	10.0	11.5	10.8	6.5	6.6	10.9	7.9	8.0	6.8	5.3
Platelets, ×10 <sup>9</sup> /L	10	17	27	20	9	39	11	6	10	51
Schistocytes, %	3	2	2	6	5	1	4	2	+	3
Creatinine, mg/dL	0.98	1.70	0.76	0.92	1.01	0.79	0.93	0.90	1.15	1.00

Abs, antibodies; BU, Bethesda units; FEU, fibrinogen equivalent units; IVIg, intravenous immunoglobulins; MCTD, mixed connective tissue disease; NA, not available; PF4, platelet factor 4; SLE, systemic lupus erythematosus; TPE, therapeutic plasma exchange; +, yes; -, no.

\*Due to the long delay since the last episode, these patients no longer had regular follow-up; consequently, no recent ADAMTS13 activity before vaccination is available.

†Defined as above the upper limit of normal value.

‡ADAMTS13 activity measurement was performed after initiation of immunosuppressive therapy.

§The presence of anti-ADAMTS13 antibodies was assessed either as the titer of total autoantibodies (inhibitory and noninhibitory) using an enzyme-linked immunosorbent assay expressed in arbitrary units (U/mL; the value of at least 25 U/mL was considered positive) or as the titer of inhibitory antibodies using a Bethesda assay expressed in Bethesda units (BU/mL), with 1 BU corresponding to the amount of inhibitor in 1 mL of plasma neutralizing 50% of ADAMTS13 activity of control levels (the value of at least 1.0 BU/mL was assumed to be positive).

||In these 2 patients, TPE was omitted. Patient #8 was very comorbid and TPE was deemed too invasive. Hence, ADAMTS13 replacement was performed with plasma infusion only. In patient #10, initial presentation was a lupus flare with mild features of thrombotic microangiopathy. Initial treatment only included high-dose corticosteroids, leading to a rapid improvement of both lupus symptoms and thrombocytopenia. Later, ADAMTS13 activity confirmed the diagnosis of iTTP, and only plasma infusion was added to corticosteroids until complete remission.

**Table 1. (continued)**

	All Median (range) or n (%)	Patient #1	Patient #2	Patient #3	Patient #4	Patient #5	Patient #6	Patient #7	Patient #8	Patient #9	Patient #10
Troponin elevated†	7 (70)	+	+	+	+	+	+	—	+	—	—
Fibrinogen, g/L	3 (2.4-6.7)	2.8	2.4	3.0	3.6	2.9	3.0	6.7	NA	NA	3.7
D-dimers, FEU	1571 (726-3768)	726	NA	NA	NA	3768	NA	1200	1942	NA	NA
ADAMTS13 activity, %	<5	<5	<5	<10	5	<1	2	<5	11‡	6	<10
Anti-ADAMTS13 Abs§	0.5 BU/mL	0.5 BU/mL	1.1 BU/mL	+	52 U/mL	+	—	—	140 U/mL	+	50 U/mL
Anti-PF4 Abs	—	—	NA	—	NA	—	NA	—	—	—	NA
French score	2	2	2	2	2	2	1	2	2	2	1
<b>Treatment</b>											
TPE (number)	4 (0-38)	8	3	3	3	38	4	5	0	17	0
Corticosteroids	10 (100)	+	+	+	+	+	+	+	+	+	+
Rituximab	8 (80)	+	+	+	—	+	+	+	+	+	—
Caplacizumab	6 (60)	—	+	—	+	+	+	+	+	—	—
Others	2 (20)	—	—	—	—	—	—	—	IVIg, plasma infusion	—	Plasma infusion
<b>Outcome</b>											
Outcome		Clinical remission	Clinical remission	Clinical remission	Clinical remission	Exacerbation under TPE, clinical remission	Clinical remission	Clinical remission	Death 2 mo after presentation	Clinical remission	Clinical remission
Rechallenge	1 (10)	0	0	0	0	0	0	+	0	0	0
Vaccine								BNT162b2			

Abs, antibodies; BU, Bethesda units; FEU, fibrinogen equivalent units; IVIg, intravenous immunoglobulins; MCTD, mixed connective tissue disease; NA, not available; PF4, platelet factor 4; SLE, systemic lupus erythematosus; TPE, therapeutic plasma exchange; +, yes; —, no.

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**Table 2. Differential diagnosis between iTTP and VITT**

Disease	iTTP	VITT
Presenting symptoms	Variable with frequent neurological presentation*	
Platelets	Severe thrombocytopenia (frequently $<30 \times 10^9/L$ )	
Microangiopathic hemolytic anemia	Present: low hemoglobin, LDH elevation, undetectable haptoglobin, schistocytes on blood smear	Usually absent†
Anatomical distribution of thrombosis	Microvascular	Macrovascular
D-dimers	Usually $<4000$ FEU	Usually $>4000$ FEU
Fibrinogen	Within normal range or slightly increased	Usually decreased
Specific diagnostic tests	ADAMTS13 $<10\%$	Anti-PF4 antibodies
	Anti-ADAMTS13 antibodies	
Type of vaccine‡	No increased incidence observed with any COVID-19 vaccines	Adenoviral vector-based

FEU, fibrinogen equivalent units; PF4, platelet factor 4.

\*As cerebral venous thrombosis represents the most common location of macrovascular thrombosis during VITT.

†Overt signs of microangiopathic hemolytic anemia should argue in favor of iTTP over VITT. However, these biological variables are rarely mentioned in VITT reports; therefore, their true prevalence is unknown in such condition.

‡As triggering factors for iTTP vs etiological agent for VITT.

patients who received an adenoviral vector-based vaccine tested negative for anti-PF4 antibodies, excluding VITT.<sup>4,7</sup>

Treatment included therapeutic plasma exchange (n = 8, 80%), anti-von Willebrand factor therapy with caplacizumab (n = 6, 60%), and immunosuppression combining corticosteroids (n = 10, 100%) and frontline rituximab (n = 8, 80%) according to the current standard of care.<sup>8</sup> One patient experienced exacerbation on-therapy but finally achieved clinical remission after intensification with twice-daily therapeutic plasma exchange. Only 1, heavily comorbid 70-year-old patient died 2 months after iTTP diagnosis from iTTP-related refractory status epilepticus sequelae. At the time of death, there was no feature of thrombotic microangiopathy, and the last available ADAMTS13 activity was 74%.

By 1 November, more than 51 million people out of 67 million inhabitants have received at least 1 dose of COVID-19 vaccine in France, with a total of 99 million doses administered, divided as follows: 80% BNT162b2, 11% mRNA1273, 8% ChAdOx1 nCoV-19, and 1% Ad26.COVS.2.S.<sup>9</sup> After excluding 1 case from Geneva, the observed incidence of new-onset episodes of iTTP occurring within 30 days of vaccination was compared with the theoretical incidence in France, estimated to be consistently of 1 case per million per year during these last years.<sup>5</sup> Thus, our 6 observations of new-onset iTTP following COVID-19 vaccination are below the expected incidence in the vaccinated population, making the causal link unlikely (6 observed vs 8 expected cases,  $\chi^2 = 0.5$ , not significant). Additionally, the observed proportion of each vaccine in our patients mirrors the repartition in the general population.

Notably, 1 patient subsequently received another dose of COVID-19 vaccine (patient #7). This rechallenge occurred 2 months after the episode of iTTP while ADAMTS13 remission

was achieved (ADAMTS13 activity 50%) and was uneventful, with no subsequent signs of iTTP recurrence.

We report 10 cases of iTTP occurring within 30 days after vaccination with both mRNA- and adenoviral vector-based vaccines. Although a risk of under-declaration cannot be excluded, the long-established structuring of the French Reference Center for TMA network definitely tends to minimize this risk. The lack of clinical distinction regarding presentation and response to therapy, the occurrence after any type of vaccine, the absence of increased epidemiological risk, as well as the absence of recurrence after rechallenge makes a direct causal link between COVID-19 vaccination and the development of anti-ADAMTS13 autoimmunity unlikely. Nonetheless, the experience from patients with congenital TTP as well as *adamts13* knock-out models in mice provided evidence that severe ADAMTS13 deficiency is not sufficient to cause a clinically perceptible disease that most often develops following endothelial aggression. Thus, it seems plausible that the vaccine could represent a nonspecific trigger of endothelial aggression in hitherto asymptomatic patients with severe ADAMTS13 deficiency, thereby precipitating the onset of clinical signs of overt disease. In line with this statement, COVID-19 vaccination has been reported as a potential trigger of TTP flare in a patient with congenital ADAMTS13 deficiency.<sup>10</sup>

Thus, cases of iTTP occurring after COVID-19 vaccination should be managed according to the current standards.<sup>8</sup> Importantly, iTTP shares similarities with VITT, especially neurologic presentation and severe thrombocytopenia. Nevertheless, these 2 entities can be distinguished in many points, including the anatomical distribution of thrombotic manifestations as well as concentrations of D-dimers and fibrinogen.<sup>7,11,12</sup> As management of these 2 conditions differs substantially, rapid distinction is of utmost importance (Table 2).

At a time when the world is facing a new surge of COVID-19, and because a booster injection is broadly recommended, an important question is how to proceed with SARS-CoV-2 vaccination in patients with a known history of iTTP. Given the paucity of data so far and based on our experience, we recommend monitoring ADAMTS13 activity.<sup>13</sup> If the activity is <20%, we recommend postponing the vaccination, which could trigger a clinical relapse; preemptive rituximab treatment in case ADAMTS13 activity is <20% may still be recommended.<sup>14</sup> If the activity is ≥20%, vaccination is probably safe. However, in patients who have received B-cell-depleting therapies such as rituximab, the vaccine response is likely to be poor.<sup>15</sup> In such patients, monitoring the vaccine response and/or providing additional doses could be useful. In persistent nonresponders, pre/postexposure prophylaxis with therapeutic anti-SARS-Cov-2 antibodies can be considered.

To conclude, there is no argument to date for a causal role of vaccination in the development of autoantibodies targeting ADAMTS13 and leading to iTTP. Nonetheless, vaccination could likely represent the trigger of endothelial aggression, leading to a clinical episode of iTTP in predisposed patients with a severe, so far undiagnosed, ADAMTS13 deficiency.

## Authorship

Contribution: A.P. and P.C. designed the study and drafted the first version of the manuscript; and J.-M.R., A.D., B.C., D.R., C.V.-M., C.S., M.B., A.W., P.P., E.P., L.R., J.-E.K., R.B., Y.B., B.J., A.V., and P.C. contributed to data acquisition, critically reviewed the manuscript, and approved the final version.

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## Footnotes

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Requests for original data may be sent via e-mail to the corresponding author.

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