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Letters to Blood

TO THE EDITOR:

De novo and relapsed immune thrombocytopenia after COVID-19 vaccines: results of French safety monitoring

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The development of new vaccines against SARS-CoV-2, along with the observation of immune thrombocytopenia (ITP) following COVID-19,[1] raised the concern about ITP triggered by COVID-19 vaccines. As soon as January 2021, a fatal case of ITP after administration of BNT162b2 (Pfizer-BioNTech) vaccine was reported in the United States.[2] Recently, a study conducted in the Vaccine Adverse Events Reporting System (VAERS) on 19 March 2021, described 77 de novo ITPs: 40 with BNT162b2 and 37 with mRNA-1273 (Moderna).[3] However, data about ITP after adenovirus vaccines (ChadOx1-S [AstraZeneca] and Ad26COV2 [Janssen]) are scarcer.[4-6] In France, these 4 vaccines have been marketed for adults. We describe here the cases of de novo ITP and ITP relapses reported to the national French COVID-19 vaccine safety program up to 15 August 2021.

The French National Agency for the Safety of Medicine and Health Products set up an active monitoring for COVID-19 vaccine adverse drug reactions (ADRs), relying on the French Pharmacovigilance network.[7] All ADRs are reported by health practitioners or patients on a secure platform and then analyzed by pharmacologists. They assess drug causality and record ADRs into a national database, encoded using the Medical Dictionary for Regulatory Activities classification.[7,8] All cases reported up to 15 August 2021, with the terms "thrombocytopenia," "immune thrombocytopenia," "purpura," "thrombocytopenic purpura," or "thrombotic thrombocytopenia" (to detect ITP cases miscoded as vaccine-induced immune thrombotic thrombocytopenia) were first reviewed by senior pharmacologists in the regional pharmacovigilance centers in charge of COVID-19 vaccine safety monitoring to detect potential cases of ITP. Medical charts were reviewed to provide more information about diagnosis and evolution if needed. Each deidentified selected case (n = 201) has been subsequently analyzed by 2 experts on ITP (G.M. and E.C./M. Mahévas). Eventually, 123 cases that occurred within the 6 weeks after vaccination were included (supplemental Material, supplemental Figure 1, available on the *Blood* Web site). De novo ITPs were subsequently classified as certain ITP when all other causes of thrombocytopenia were excluded, and probable ITP when the presentation and evolution were highly evocative of ITP but with missing data to formerly exclude other diagnoses. Descriptive analyses were conducted overall and by vaccines, and, as sensitivity analysis, by certain vs probable de novo ITP. We also calculated the frequency of de novo or relapsed ITP reports by number of vaccine doses dispensed up to 31 July 2021, in France. The 2-week period between dispensing data and the assessment of ADRs in the database was driven from the median time of vaccine-induced ITP.

De novo ITPs (n = 106) are described in Table 1. They were mostly reported with BNT162b2 (n = 58) and ChadOx1-S (n = 45). Only 2 cases were reported with mRNA-1273 and 1 with Ad26COV2. Cases occurred after a first dose in 74 (71.8%) patients and after a second dose in 29 (28.1%). Median age was 67 years (minimum-maximum: 16-98) and 54.7% of patients were women; 19 patients (17.9%) had a history of autoimmune disease. Additionally, 3 had hematological malignancies favoring ITP (2 with chronic lymphocytic leukemia and 1 with indolent lymphoma). The median time from vaccination to ITP onset was 11 days (minimum-maximum: 1-40). The median lowest platelet count was 7×10^9/L (minimum-maximum: 0-87); 81.4% of patients had bleeding. Treatment and outcome were available for 85 patients: 11 (12.9%) recovered without treatment, 55 (64.7%) with corticosteroids ± intravenous immunoglobulin, whereas 18 (21.2%) were active after corticosteroids; among them, 9 achieved complete response with thrombopoietin receptor agonists and 3 with rituximab (Table 1). Two intracranial hemorrhages were described (supplemental Material, supplemental Table 1). Seven patients were exposed to another dose of vaccine: 3 relapsed with ITP (with BNT162b2), whereas 4 did not (1 with BNT162b2 and 3 with ChadOx1-S).

The characteristics of de novo ITP cases were similar between BNT162b2 and ChadOx1-S vaccines, except with BNT162b2 a higher proportion of cases that occurred after the second dose (40.3% vs 11.4%, respectively) a slightly shorter median time to onset (9 vs 12 days) and a higher proportion of spontaneous recovery (17.6% vs 12.9%) or after receiving corticosteroids ± intravenous immunoglobulin (70.6% vs 45.2%).

Table 1. Characteristics of cases of de novo immune thrombocytopenia following COVID-19 vaccination

Characteristics	All cases (n = 106)	BNT162b2 (Pfizer-BioNTech, n = 58)	ChadOx1-S (AstraZeneca, n = 45)	mRNA-1273 (Moderna, n = 2)	Ad26COV2 (Janssen, n =1)
Median age, y (minimum-maximum)	67 (16-98)	68 (16-98)	69 (22-84)	51 (26-76)	97
Women, n (%)	58 (54.7)	34 (58.6)	21 (46.7)	2 (100)	1
History of autoimmune disease, n (%)	19 (17.9)*	12 (20.7)	7 (15.6)	1 (50.0)	No
Dose†					
1, n (%)	74 (71.8)	34 (59.6)	39 (88.6)	1 (50.0)	0
2, n (%)	29 (28.1)	23 (40.3)	5 (11.4)	1 (50.0)	0
Median time to ITP onset, days (minimum-maximum)	11 (1-40)	9 (1-35)	12 (2-40)	17 (10-24)	28
Median lowest platelet count, $\times 10^9$/L (minimum-maximum)‡	7 (0-87)	6 (1-87)	9 (1-68)	6.5 (6-7)	0
Bleeding§					
No bleeding, n (%)	19 (18.6)	10 (18.2)	9 (20.5)	0	0
All bleeding, n (%)	83 (81.4)	45 (81.8)	35 (79.5)	2 (100)	1
Mouth bullae, n (%)	23 (22.5)	17 (30.9)	6 (13.6)	0	0
Epistaxis, n (%)	6 (5.9)	4 (7.3)	2 (4.5)	0	0
Hemoptysis, n (%)	1 (1.0)	0	2 (4.5)	0	0
Intracranial, n (%)	2 (2.0)	2 (3.6)	0	0	0
Evolution and treatment‖					
Spontaneous recovery, n (%)	11 (12.9)	9 (17.6)	4 (12.9)	0	0
Recovery after corticosteroids ± IVIG only, n (%)	55 (64.7)	36 (70.6)	14 (45.2)	2 (100)	1
Recovery after need of TPORAs as second-line treatment, n (%)	9 (10.6)	3 (5.9)	6 (19.3)	0	0
Recovery after need of rituximab as second-line treatment, n (%)	3 (3.5)	0	3 (9.7)	0	0
Recovery after need of dapsone as second-line treatment, n (%)	1 (1.2)	0	1 (3.3)	0	0
Recovery after TPORAs as first-line treatment, n (%)	1 (1.2)	1 (2.0)	0	0	0
Active disease after corticosteroids without further follow-up, n (%)	5 (5.9)	2 (3.9)	3 (9.7)	0	0
Exposure to another dose of vaccine					
Relapse of ITP, n	3	3	0	0	0
No relapse of ITP, n	4	1	3	0	0
Absence of subsequent exposure to the vaccine, n	61	28	29	1	1
Unknown, n	38	26	13	1	0

Abbreviations: ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin; TPORA, thrombopoietin receptor agonist.

*5 patients with thyroiditis (including 2 Graves' disease), 2 with thyroiditis + psoriasis, 1 with thyroiditis + rheumatoid arthritis, 1 with systemic lupus erythematosus, 1 with sarcoidosis, 1 with granulomatosis with polyangiitis, 1 with autoimmune hemolytic anemia, 1 with rheumatoid arthritis, 1 with polymyalgia rheumatica, 1 with primary biliary cirrhosis + Biermer anemia, 1 with Behçet disease, 1 with multiple sclerosis, 1 with type 1 diabetes mellitus, and 1 with extramembranous glomerulonephritis.

†3 missing values (BNT162b, ChadOx1-S, Ad26COV2, n = 1 each).

‡1 missing value (with BNT162b).

§4 missing values (3 with BNT162b and 1 with ChadOx1-S).

‖21 missing values (7 with BNT162b and 14 with ChadOx1-S).

Table 2. Characteristics of cases of relapses of immune thrombocytopenia following COVID-19 vaccination

Characteristics	All cases (n = 17)	BNT162b2 (Pfizer-BioNTech, n = 12)	ChadOx1-S (AstraZeneca, n = 2)	mRNA-1273 (Moderna, n = 3)
Median age, y (minimum-maximum)	61 (22-87)	65 (22-87)	44 (25-63)	56 (50-62)
Women, n (%)	11 (64.7)	7 (63.6)	2 (100)	2 (66.3)
History of other autoimmune disease, n (%)	3 (17.6)*	3 (25.0)	0	0
Splenectomized, n (%)	2 (11.8)	1 (8.3)	1 (50.0)	0
Dose				
1, n (%)	12 (70.6)	7 (58.3)	2 (100)	3 (100.0)
2, n (%)	5 (29.4)	5 (41.7)	0	0
Median time to ITP onset, d (minimum-maximum)†	5 (1-32)	6 (1-27)	12 (2-40)	2 (2-19)
Median lowest platelet count, $\times 10^9$/L (minimum-maximum)	6 (0-61)	8 (1-31)	33 (5-61)	13 (0-21)
Bleeding†				
No bleeding, n (%)	1 (5.9)	1 (8.3)	0	0
All bleeding, n (%)	15 (88.3)	10 (83.3)	2 (100)	3 (100)
Mouth bullae, n (%)	1 (5.9)	1 (8.3)	0	0
Epistaxis, n (%)	0	0	0	0
Hemoptysis, n (%)	0	0	0	0
Intracranial, n (%)	0	0	0	0
Evolution and treatment‡				
Spontaneous recovery, n (%)	3 (27.3)	2 (22.2)	1 (100)	0
Recovery after corticosteroids ± IVIG only, n (%)	6 (54.5)	6 (66.7)	0	0
Recovery after reintroduction of TPORA, n (%)	1 (9.1)	0	0	1 (100)
Recovery after need of vinblastine for refractory disease to corticosteroids, IVIG and TPORA, n (%)	1 (9.1)	1 (11.1)	0	0
Exposure to another dose of vaccine				
Relapse of ITP, n	1	0	0	1
No relapse of ITP, n	2	2	0	0
Absence of subsequent exposure to the vaccine, n	6	6	0	0
Unknown, n	8	4	5	2

Abbreviations: ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin; TPORA, thrombopoietin receptor agonist.

*2 patients with Graves' disease and 1 with autoimmune hemolytic anemia (Evans' syndrome).

†1 missing value (with BNT162b).

‡6 missing values (3 with BNT162b, 2 with ChadOx1-S, and 1 with mRNA-1273).

In sensitivity analysis, the characteristics of certain vs probable de novo ITP cases were similar, except there was a higher median platelet count (15 vs 4 $\times$ 10^9/L), a lower frequency of bleeding (65.2% vs 94.6), and a higher frequency of spontaneous recovery (30.3% vs 1.9%) in the group of probable ITPs (supplemental Material, supplemental Table 3).

Relapses of known ITP (n = 17) were also mostly described with BNT162b2 (n = 12; Table 2). The median time from vaccination (first dose: 70.6%) was 5 days. The median lowest platelet count was 6 $\times$ 10^9/L (minimum-maximum: 0-61 $\times$ 10^9/L), 88.3% of patients had bleeding and all recovered with (72.7%) or without (27.3%) treatment. Three patients were exposed to another dose of vaccine: 1 relapsed (mRNA-1273 vaccine) and 2 did not (BNT162b2).

The rate of de novo or relapsed ITP reports by millions of vaccine doses administered was 1.69 (95% confidence interval, 1.42-2.01). It was the highest with ChadOx1-S, particularly after dose 1 (supplemental Material, supplemental Table 3).

Overall, the characteristics of the 106 de novo ITPs following COVID-19 vaccine in this series are in line with the 77 reported cases in VAERS,[3] except there was a slightly longer median time after vaccine in our study (11 vs 8 days). Of note, all reported cases in VAERS were associated with mRNA vaccines, whereas

42.5% of our cases were due to ChadOx1-S, with a slightly longer median time between vaccination and ITP, as previously reported in Australian series of 12 and 17 cases.[4,5] Reported relapses of known ITP were rare. Previous series demonstrated that if a mild decrease of platelet count has been observed in up to 50% of patients, severe relapses needing rescue treatment were rare, accounting from <10% of patients from referral centers (ie, possibly a subpopulation of severe, refractory ITP).[3,9-11] Of note, relapses of ITP could occur after dose 1 or dose 2.

The rate of reported ITPs by number of dispensed doses of vaccines was the highest with ChadOx1-S. We cannot exclude a reporting bias favoring cases of thrombocytopenia after the media coverage of vaccine-induced immune thrombotic thrombocytopenia. An Australian study observed a rate of 8.0 per 1 million doses (95% confidence interval, 5.4-12.7).[5] Population-based studies identified an increased risk of hospital contact for thrombocytopenia within the 28 days after ChadOx1-S vaccination (albeit lower than after a positive SARS-CoV-2 test),[12,13] but not within the 42 days after BNT162b2.[14]

This study has other limitations. We identified very few cases reported after mRNA-1273 and Ad26COV2 vaccines. Consequently, our results regarding these vaccines should be interpreted with caution. We described spontaneous reports and cannot ensure the full collection of cases; reporting bias may have also favored more severe cases. The 6-week risk period between vaccination and ITP occurrence for case selection is often used for such studies but remains arbitrary. Last, the causal mechanism is not ascertained and it is possible that some cases occurred during the risk period by chance.

However, this series provides important clinical insights for knowledge and management of this very rare event, with a slightly longer time from vaccine to ITP onset with the ChadOx1-S vaccine, a good response to usual management of ITP including in rare severe cases, and an unpredictable effect of rechallenge. There may be a pharmacovigilance signal for a higher frequency of ITP with ChadOx1-S in comparison with BNT162b2.

Acknowledgment

The authors deeply thank the French Pharmacovigilance Network.

Authorship

Contribution: G.M., F.S., and B.G. designed the study; N.M., M.-B.V.-R., M.A., and H.B. contributed to first case selection and collection of new data from medical files; L.T. coordinated the collection of new data from medical files and participated to data analysis; G.M., E.C., and M. Mahévas made the final selection of cases, their classification and case analysis; G.M. conducted the statistical analyses and wrote the paper; all authors reviewed the manuscript and gave final approval and agree to be accountable for all aspects of the work; G.M. attests that all the listed authors meet the authorship criteria and that no others meeting the criteria have been omitted, and is the guarantor; and all collaborators participated in complementary data collection from medical charts.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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Footnotes

Submitted 10 January 2022; accepted 21 February 2022; prepublished online on *Blood* First Edition 11 March 2022.

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Data may be obtained from a third party and are not publicly available. The data of the French National Pharmacovigilance database are anonymous. They can be accessed by submitting a request to the National Agency for Drug Safety (pharmacovigilance@ansm.sante.fr). The data management and statistical analysis code is available on reasonable request from the corresponding author.

The online version of this article contains a data supplement.

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DOI 10.1182/blood.2022015470

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%).[1] Recently, several cases of iTTP have been described after coronavirus disease 2019 (COVID-19) vaccination.[2,3] 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,[4] 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.[5] 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[1]: 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.[6] The clinical probability of severe ADAMTS13 deficiency was high in most patients according to the French score, with severe thrombocytopenia (platelets $<30 \times 10^9$/L in n = 8, 80%) and no/mild renal impairment (creatinine <2.25 mg/dL in all, 100%).[6] 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