Covid-19 vaccination in patients with immune-mediated thrombotic thrombocytopenic purpura: a single-referral center experience

Cases of immune-mediated thrombotic thrombocytopenic purpura (iTTP) following the administration of vaccines have been described in the literature.[1-2] Recently, *de novo* and relapsed iTTP have been reported during SARS-Cov-2 infection[3-5] and after the vaccine, mainly with adenoviral and rarely with mRNA vaccines.[6-11] The French Reference Center for Thrombotic Microangiopathies conducted a large multicenter retrospective study to investigate the possible link between COVID-19 vaccine and the new onset or recurrence of iTTP. Results showed that vaccination does not trigger relapse in these patients, particularly if they are regularly monitored and do not have low ADAMTS13 enzyme activity.[12] Similar results were described by the Vaccine Adverse Event Reporting System (VAERS), the US passive surveillance system for adverse events after immunization.[13] COVID-19 vaccine did not increase the risk of *de novo* or relapsed iTTP, except in individuals in hematologic remission with extremely low ADAMTS13 activity (<20%).[12-13]

We report here our single-center experience in 33 patients with pre-existing iTTP, followed at our Institute, who received regular mRNA COVID-19 vaccination (Pfizer-BioNTech vaccine: 31 cases; Moderna: 2 cases).

All 33 patients had been followed in our Institute since the first acute iTTP episode and had a confirmed iTTP diagnosis based on documented ADAMTS13 activity <10 UI/dL during the acute episodes of thrombotic microangiopathies; the immune-mediated mechanism was confirmed by the demonstration of anti-ADAMTS13 autoantibodies. Between March 2021 and March 2022, all 33 patients received mRNA COVID-19 vaccines, as scheduled for our fragile patients. Thirty-two of the 33 patients received the full scheduled mRNA COVID-19 vaccination; the last patient, who had previously contracted SARS-Cov-2 infection, without sequelae, received only one dose of the vaccine. Twenty-seven patients received a booster dose and seven patients received a second booster of vaccine during active immunosuppressive treatment. At the time of vaccine injection all patients were in clinical remission; 19 (57%) patients were out of treatment while 14 (43%) were still receiving immunosuppressive therapy. Patients' characteristics and details about iTTP as well as available laboratory data, including ADAMTS13 activity before and after the vaccine, are reported in Table 1.

Eighteen patients had previously presented one acute iTTP episode, eight patients had previously presented two episodes, five patients three episodes and two patients four iTTP acute episodes. Median time between the most recent acute episode and the first vaccine dose was 88 months (range, 5-259). Median ADAMTS13 activity in the 3 months before vaccination was 75 UI/dL (range, 10-135). Twenty-three patients showed enzyme activity >50 UI/dL (median 99% UI/dl; range, 54-135), eight patients had an enzyme activity ranging between 20 UI/dL and 50 UI/dL (median 39% UI/dl; range, 23-48) and the last two patients a very low activity (<20 UI/dL). Thirteen (39%) patients had received rituximab (CD20-targeted B-cell-depleting antigen), as part of iTTP treatment. The median interval between anti-CD20 therapy and first vaccine dose was 17 months (range, 2-151); in four patients pre-emptive rituximab was still ongoing before vaccination. After vaccine, all patients were checked with a peripheral blood count every week, for a total of 1 month from the date of each injection. The platelet count remained in the normal range; no episodes of anemia, renal impairment, neurologic symptoms were observed. No iTTP clinical relapse within 4 weeks of vaccination (first, second and booster doses) were documented. ADAMTS13 activity was monitored 1-3 months after vaccine in 31 of 33 patients and five of them (16%) showed a reduction in activity below <20 UI/dL. In these last five patients, the median of ADAMTS13 activity before vaccination was 45 UI/dL (range, 23-109), while the median activity after vaccination was 9 UI/dL (range, <3-14). Due to the drop of ADAMTS13 activity four of the five patients in clinical remission received pre-emptive immunosuppressive treatment (rituximab 3; azathioprine 1) with increase in the ADAMTS13 activity >20 UI/dL after rituximab; the patient, who received azathioprine treatment, remained in clinical remission with enzyme activity >10 UI/dL. The last patient with decreased ADAMTS13 activity after vaccine, contracted SARS-Cov-2 infection 2 months after vaccination with a concomitant iTTP relapse. A total of eight patients developed mild COVID-19 after a median of 3.5 months (range, 2-10) from the last vaccine dose; seven did not require hospitalization and/or anti-viral therapy, one patient was hospitalized for the treatment of iTTP relapse. In all seven patients there no was reduction in ADAMTS13 activity following the infection episode. SARS-Cov-2 infection occurred in two of 14 (14%) patients still receiving immunosuppressive treatment compared with six of 19 (31%) patients out of therapy (>9 months from the last treatment). Five of the

Table 1. Demographic and clinical characteristics of the 33 patients with immune-mediated thrombotic thrombocytopenic purpura.

Characteristics	
Patients, N	33
Age in years at diagnosis, median (range)	44 (11-68)
Sex, male/female, N	6/27
iTTP* episodes, N 1 2 3 4	 18 8 5 2
Ongoing treatment prevaccine, N No therapy Prednisone Azathioprine Rituximab Cyclosporine	 19 1 8 4 1
Vaccine dose, N First dose Second doses Third doses Fourth doses	33 1 32 27 7
Time in months of last TTP episode to 1st vaccine dose, median (range)	88 (5-259)
Prior rituximab therapy, N	13
Time in months from most recent rituximab dose and vaccine Median Range >1 year <6 months	 17 2-151 9 4
ADAMTS13 activity pre-vaccine (UI/dL), median (range)	75 (10-135)
ADAMTS13 activity post-vaccine (UI/dL), median (range)	75 (<3-137)

*iTTP: immune-mediated thrombotic thrombocytopenic purpura.

eight patients who were SARS-Cov-2 infected had already received the vaccine booster dose and only one of them was still in immunosuppressive treatment. No patient performed the anti-COVID-19 immune assessment after vaccine and the value of SARS-CoV-2 spike antibodies is not available.

Vaccinations can rarely induce autoimmune reactions including iTTP. According to the case reports, iTTP occurs within 2 weeks after vaccination, mostly with influenza vaccination, followed by vaccines against pneumococcus, rabies and H1N1.[1-2] To date, COVID-19 vaccination-associated iTTP is present in the literature.[4-11] The literature review demonstrates only few cases of mRNA COVID-19 vaccine-related iTTP. Giuffrida *et al.* described five post-vaccine recurrences among 32 vaccinated patients.[14] The French study showed that COVID-19 vaccination has no causal relationship with iTTP[12] and more recently, the multicenter, retrospective VAERS study confirmed that COVID-19 vaccination does not increase the risk of *de novo* or relapsed iTTP, particularly if patients are monitored regularly and have normal ADAMTS13 enzyme activity.[13] In this study, the rare iTTP clinical relapses (4/79) occurred only in those patients with low (<20%) or unknown ADAMTS13 activity levels within 3 months prior to vaccination.[13] Our study confirms that mRNA COVID-19 vaccine can be safely administered to patients with a previous iTTP diagnosis if patients are carefully monitored after vaccination. In order to prevent relapse, peripheral blood count and ADAMTS13 activity should be monitored to promptly initiate immunosuppressive treatment. The preemptive treatment although necessary, may alter the vaccine response for at least 6 months. In our study, no vaccine-related iTTP clinical recurrences were documented, even in patients with very low ADAMTS13 activity. Despite mRNA vaccination, eight patients were infected with SARS-Cov-2. None of them presented a severe viral infection but one patient showed a concomitant iTTP recurrence and required treatment with plasma exchange, caplacizumab, immunosuppressive treatment with steroids and rituximab. COVID-19-associated iTTP has been described in the literature.[3-5] Even though a causal relationship remains to be elucidated, viral infections are a known trigger for secondary or immune TTP, with proposed mechanisms including both direct endothelial injury and development of ADAMTS13 autoantibodies.[4,15] Time to diagnosis of TTP was 10 days from the onset of SARS-Cov-2 infection.[4] Treating TTP relapses during SARS-Cov-2 infection is not easy. The patients need daily plasma exchange and intensive immunosuppressive treatment that may worsen the course of viral infection resulting in a poor outcome.

In summary, our data confirm that mRNA COVID-19 vaccines does not increase the risk of relapsed iTTP, if patients are carefully monitored. Checking patients with blood counts and ADAMTS13 activity after vaccination is recommended, in order to administer preemptive therapy in those cases with very low enzyme activity. The incidence of SARS-Cov-2 infections after vaccination for patients in immunosuppressive therapy is low (14%) and none of them developed severe disease. These data confirm the efficacy of mRNA vaccines. SARS-Cov-2 infection itself can trigger TTP, with many other severe and devastating consequences, hence the benefits of the vaccine outweighs the risks.

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IM received honoraria for participating as a speaker at educational meetings organized by Instrumentation Laboratory and Sanofi. AA received honoraria for participating as speakers at educational meetings organized by Sanofi. FP has received honoraria for participating as a speaker in educational meetings organized by Grifols and Roche, and she is member of scientific advisory boards of Biomarin, Roche, Sanofi, Sobi, Takeda. The other authors have no conflicts of interest to disclose.

Contributions

ST and AMT managed the patients, collected data, wrote the manuscript and reviewed the literature; VC managed the patients and critically reviewed the manuscript; MB helped in data analysis and in writing the manuscript; GG managed the vaccinations schedule and critically reviewed the manuscript; IM performed ADAMTS-13 testing and critically reviewed the manuscript; AA and FP critically reviewed the manuscript. All authors reviewed the final manuscript revised version and gave approval for submission.

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Data-sharing statement

The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

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