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Clinical relapse of immune-mediated thrombotic thrombocytopenic purpura following COVID-19 vaccination

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INTRODUCTION

Immune-mediated thrombotic thrombocytopenic purpura (iTTP) is a rare thrombotic microangiopathy characterized by microangiopathic hemolytic anemia, severe thrombocytopenia, and ischemic end-organ injury due to microvascular platelet-rich thrombi. iTTP is caused by a severe deficiency (<10%) of the specific von Willebrand factor (VWF)-cleaving protease, ADAMTS-13.1 Severely deficient ADAMTS-13 activity should be measured before COVID-19 vaccination to address relapse risk.
activity alone does not uniformly lead to the development of iTTP, but rather it is thought that a "second hit" in the form of an immune stressor such as infection, inflammation, or pregnancy is often required for the development of an acute iTTP episode. Indeed, de novo and relapsed iTTP have been precipitated by various vaccines, including those for severe acute respiratory syndrome coronavirus 2 (COVID-19).

With this hypothesis in mind, it is possible that patients with TTP in clinical remission, but who have not achieved complete ADAMTS-13 remission, might be at increased risk for relapse following COVID-19 or any other vaccination. Additionally, typical immunosuppression targeting ADAMTS-13 autoantibodies for iTTP, like rituximab or corticosteroids, may blunt the immune response to vaccination. Given these emerging issues, the safety of COVID-19 vaccination in survivors of iTTP has been questioned by patients and physicians. We report the case of the tozinameran (BNT162b2, Pfizer-BioNTech) COVID-19 vaccine initiating an iTTP relapse in a patient with serial monitoring of the ADAMTS-13 activity during longitudinal follow-up in clinical remission.

2 | CASE PRESENTATION

A 28-year-old Black woman with no significant prior medical history was initially diagnosed with iTTP in late 2019 after presenting with fatigue, chest pain, rash, ecchymosis, petechiae, scant vaginal bleeding, and mild headaches. At the time of her initial diagnosis, informed consent was obtained, and she was enrolled in the prospective Ohio State University thrombotic microangiopathy registry. She was found to be severely thrombocytopenic (platelets, 17 × 10⁹/L) with evidence of microangiopathic hemolytic anemia on the peripheral blood smear. A diagnosis of iTTP was confirmed when the ADAMTS-13 activity returned <2.5%, with a demonstrable ADAMTS-13 inhibitor. She was treated with plasma exchange (PEX) and corticosteroids and achieved a clinical remission of iTTP with a plan for four weekly doses of rituximab (375 mg/m²) after hospital discharge. She was being treated on a clinical trial and was ineligible to receive caplacizumab therapy initially. Five days after being discharged, however, she developed recurrent thrombocytopenia and suffered an exacerbation of iTTP. PEX was then restarted with the addition of caplacizumab (11 mg subcutaneously daily as authorized by the Food and Drug Administration in the United States, 10 mg subcutaneously daily in Europe based on European Medicines Agency approval) to prevent further exacerbations of iTTP. She achieved a clinical response, but her ADAMTS-13 activity did not improve after 4 weekly rituximab infusions. After 8 weeks of caplacizumab and no recovery of her ADAMTS-13 activity, the decision was made to stop caplacizumab with no additional immune suppressive therapy given that this was her first iTTP episode. She did well clinically for over a year but did not achieve an ADAMTS-13 activity remission, which remained severely deficient until 12 months later, when she improved to 47.8% during remission on one measurement.

She did not have any additional measurements of the ADAMTS-13 activity until she received her first dose of the tozinameran (BNT162b2, Pfizer-BioNTech) COVID-19 vaccine 5 months later without our knowledge. Six days after her vaccine, she noted bruising on her arms, and subsequent laboratory studies revealed a mild thrombocytopenia (84 × 10⁹/L), a lactate dehydrogenase (LDH) of 205 U/L (range <190), and undetectable ADAMTS-13 activity (<2.5%). She reported that she had independently taken her two remaining caplacizumab injections in the prior 2 days given her concern for relapse of TTP. The following day her platelet count had normalized to 159 × 10⁹/L and her LDH normalized. She was instructed to repeat her labs in the next 2 to 3 days but did not have the recommended lab work performed.

One week later, she reported symptoms of ataxia and was directed to the hospital for further evaluation. This time, however, she was found to have a more significant thrombocytopenia (57 × 10⁹/L), an LDH of 216 U/L, and an undetectable haptoglobin. Schistocytes were seen in the peripheral blood smear, and she was admitted for treatment of an acute iTTP relapse. The ADAMTS-13 activity was again undetectable at the time of admission. Given that she was early in her relapse and our experience with the use of caplacizumab without PEX to treat iTTP, she was started on caplacizumab...
11 mg daily subcutaneously in addition to prednisone at a dose of 1 mg/kg daily. In the next 24 hours, her platelet count was normal, with normalization of her LDH on day 3. Given her laboratory and symptomatic improvement, she was discharged on the third day for outpatient follow-up. For more durable suppression of the ADAMTS-13 autoantibody she again received four weekly doses of rituximab (375 mg/m²), which was initiated after hospital discharge (Figure 1). She tapered the prednisone over the next 4 weeks, and 34 days after discharge she was found to have measurable and stable ADAMTS-13 activity (38%), and the caplacizumab was stopped. Her ADAMTS-13 activity (60%) eventually normalized 9 weeks after her first dose of rituximab, and she subsequently received her second dose of tozinameran without any difficulties or change her in platelet count or LDH. She has continued her recovery and has now achieved a sustained clinical and ADAMTS-13 remission.

3 | MANAGEMENT AND DISCUSSION

We present a well-documented case of the tozinameran (BNT162b2, Pfizer-BioNTech) COVID-19 vaccine triggering a relapse of iTTP, which uniquely occurred in a patient with serial longitudinal monitoring of the ADAMTS-13 activity. Severely deficient ADAMTS-13 alone is not sufficient to precipitate relapse of TTP, but rather it has been hypothesized to require a “second hit” in the context of severely deficient ADAMTS-13 activity to develop a clinical relapse. While our patient was found to have nearly normal ADAMTS-13 activity several months before her COVID-19 vaccine on one measurement, the finding of severely deficient ADAMTS-13 activity 6 days after her vaccine (but before overt iTTP relapse) suggests that she was likely severely deficient at the time of her vaccine.

PEX with the addition of immune suppressive therapy is an effective treatment for iTTP, but it is associated with potential morbidity and even mortality. Caplacizumab is a nanobody that targets the A1 domain of VWF to prevent the binding of platelets and the subsequent microvascular thrombosis. There are reports from our group and others suggesting that the use of caplacizumab alone with immune suppressive therapy may be a safe and effective alternative to PEX.

There are hypothesized risks for immune-mediated complications arising after any vaccine, and in this case report we describe very clearly a patient with a prior history of iTTP who developed an acute iTTP relapse after COVID-19 vaccination. Despite the potential risk from any vaccination, in general the potential benefit of vaccines to prevent infection in nearly all cases outweigh these risks. While we still recommend COVID-19 vaccination for our patients with iTTP, we now consider the timing of vaccination in the context of the patient’s serially monitored ADAMTS-13 activity. Our current approach to COVID-19 vaccination in survivors of iTTP is summarized in Figure 2. In patients whose ADAMTS-13 activity is >20%, we believe vaccination can proceed safely. However, if the ADAMTS-13 activity is <20% at the time of vaccination, the potential risk for triggering an iTTP relapse

*The risk of vaccination triggering and acute iTTP episode must be balanced against the greater risk of COVID-19 infection potentially doing the same.

**It must also be remembered that prophylactic therapy to increase the ADAMTS-13 activity (rituximab, cyclosporine) could blunt the response to the vaccination.

FIGURE 2  Proposed algorithm to determine relative safety of COVID-19 vaccination in patients with iTTP and follow-up for patients with iTTP at greater risk for recurrent iTTP. CBC, complete blood count; iTTP, Immune-mediated thrombotic thrombocytopenic purpura; LDH, lactate dehydrogenase
in that specific patient should be addressed. The decision to use 20% as the threshold as safe for vaccination was not specifically studied, but rather was extrapolated from recent consensus opinion in the field that uses an ADAMTS-13 activity of 20% as the threshold above which it is safe to stop caplacizumab. Further, the safety and efficacy of rituximab as a prophylactic therapy in remission to prevent relapse has led recently to using 20% as a threshold, below which prophylactic therapy to prevent relapse is strongly considered. The baseline risk for exposure to COVID-19 in the patient’s community should also likely be factored into this decision. Prophylactic treatments to raise the ADAMTS-13 activity (rituximab and cyclosporine) also have the potential to impair efficacy of the vaccine due to their immunosuppressant properties. Proceeding with vaccination and careful clinical monitoring would not be unreasonable, but delaying vaccination until successful prophylactic therapy has been administered and immune reconstitution has occurred would also be equally reasonable. The serial monitoring of the ADAMTS-13 activity is becoming increasingly important in the long-term care of patients with iTTP. In addition to the prediction of relapse risk, the ADAMTS-13 activity may also be useful as described in this case report to assess an individual iTTP survivor’s risk for adverse events following COVID-19 vaccination.

RELATIONSHIP DISCLOSURE
SRC has received research funding and consulting fees from Sanofi-Aventis, which markets caplacizumab. WD and SS have no conflicts to declare.

AUTHOR CONTRIBUTIONS
WD wrote and edited the manuscript; SS and SRC wrote and edited the manuscript and cared for the patient.

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