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Immune thrombocytopenia associated with COVID-19 mRNA vaccine tozinameran – a clinical case and global pharmacovigilance data

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Summary

We report the occurrence of immune thrombocytopenia (ITP) in a 77-year-old man a few days after receiving the first dose of the COVID-19 mRNA vaccine tozinameran (Comirnaty®). The patient was treated with systemic corticosteroids, intravenous immunoglobulins and eltrombopag. He elected to proceed with the second dose of tozinameran 14 weeks after the first and his platelet count remained stable under a tapered eltrombopag dose. To our knowledge, this is the first case in which a second tozinameran dose has been administered to a patient who developed presumed secondary ITP after the first vaccination. We also report global pharmacovigilance data for the occurrence of ITP after vaccination with tozinameran.

Introduction

Immune thrombocytopenia (ITP) is a condition resulting in the immunologically mediated destruction of platelets and typically an increased risk of bleeding. ITP frequently occurs following infections and resolves spontaneously. ITP has been reported as a complication of COVID-19 infection [1] and, rarely, following vaccination against influenza, measles, mumps and rubella [2]. Here we report a clinical case of a 77-year-old man with ITP diagnosed 8 days after vaccination with tozinameran.

Case description

A 77-year-old man (83 kg) with a history of coronary artery disease, atrial fibrillation and arterial hypertension was referred to the haematology outpatient clinic in January 2021 owing to unexplained macrocytic anaemia since 2017. During the previous year, his haemoglobin was 10.8–12.2 g/dl (normal range 14.0–18.0), and white blood cell counts were in the normal range. Mild thrombocytopenia (126 × 10^9/l, normal range 150–450) was documented shortly before (fig. 1). The patient had noticed small amounts of dry blood on his tissue after blowing his nose during the preceding days. He denied other signs of bleeding, weight loss, fever, or night sweats. No clinical signs of systemic autoimmune disease were present. His medication consisted of bisoprolol, tamsulosin, torasemide, atorvastatin and phenprocoumon, which were all taken at least since April 2018 (i.e., 33 months before consultation). Eight days previously, he had received the first dose of the COVID-19 messenger RNA (mRNA) vaccine tozinameran (Comirnaty®; Pfizer/BioNTech) [3].

Clinical examination revealed petechiae limited to the buccal mucosa. The ITP-specific bleeding assessment tool (ITP-BAT) score was 2/64 points [4]. Laboratory investigations showed severe thrombocytopenia (28 × 10^9/l), macrocytic anaemia with a mean corpuscular volume of 98 fl (normal 79–95) and mild neutrophilia (table 1). The immature platelet fraction was elevated (23.5%, normal <6.5%) as was the mean platelet volume (14 fl, normal 6.0–10.0) suggesting a high rate of destruction. A peripheral blood smear showed mild platelet anisocytosis, without schistocytes or platelet clumping, ruling out thrombotic thrombocytopenic purpura and pseudothrombocytopenia. Erythrocytes did not appear macrocytic and there was no abnormal segmentation of neutrophils or any other signs of haematologic neoplasia or dysplasia. Bone marrow aspiration and biopsy showed a high increase of megakaryocytes with a shift to immature forms. Dysplasia was not present. Serological testing was negative for human immunodeficiency virus (HIV), hepatitis C virus (HCV) and hepatitis B virus (HBV). Haematological neoplasia and acute infections (such as HIV, HCV and HBV) were therefore ruled out. In the

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absence of clinical suspicion for acute COVID-19, polymerase chain reaction testing for SARS-CoV2 was not performed. Due to their low sensitivity, antiplatelet antibody tests are not recommended and were therefore not carried out. We tested for vitamin B12 and folic acid deficiency, which were both absent, as well as haemolysis parameters (absolute reticulocytes 66 x 10^9/l (normal range 40–140), bilirubin 6.8 µmol/l (normal <24), lactate dehydrogenase 257 U/l (135–225). Protein electrophoresis did not show signs of a paraproteinaemia.

We stopped oral anticoagulation and administered oral vitamin K on two consecutive days, which normalised his INR (international normalised ratio). The remaining medication was continued. The following day the platelet count was 17 × 10^9/l. A diagnosis of ITP with severe thrombocytopenia was made. To prevent fatal bleeding in a high-risk situation the patient was started on oral prednisone 100 mg/day (1.2 mg/kg bodyweight) and given 40 g intravenous immunoglobulins (IVIG) (0.48 g/kg bodyweight) on two consecutive days. The platelet count then normalised (183 × 10^9/l) within 1 week (fig. 1 and table 1), accompanied by a neutrophilia attributable to steroids. As soon as the platelet count was >50 × 10^9/l, oral anticoagulation with apixaban 2.5 mg 2×/d was initiated. The

Figure 1: Time course of platelet counts in relation to tozinameran vaccination and treatment for immune thrombocytopenia. Arrows indicate the first and second vaccine dose and the * indicate intravenous immunoglobulin (IVIG) administration. Black dotted line = upper limit of normal platelet count, red dotted line = lower limit of normal platelet count, red shaded area = normal platelet count range. Grey shaded (and dark purple area where overlapping with eltrombopag) = prednisone (PDN) administration and dose (in mg/d), purple area = eltrombopag administration and dose.

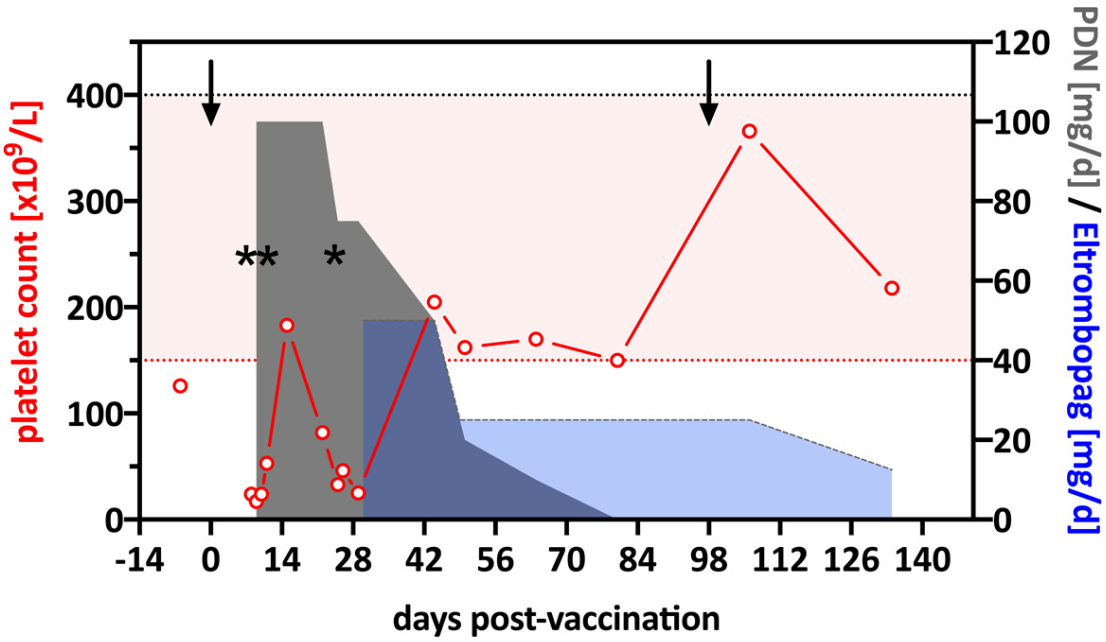


Table 1:
Time course of platelet count, haemoglobin, lymphocytes and neutrophilis before, during and after COVID-19 vaccination and ITP therapy. The second vaccination took place on day 98 in relation to the first vaccination.

Day in relation to 1 st vaccination	Day in relation to 2 nd vaccination	Platelets x 10 9 /l (normal range 150–450)	Hemoglobin g/dl (normal range 14.0–18.0)	Lymphocytes x 10 9 /l (normal range 0.9–3.3)	Neutrophils x 10 9 /l (normal range 1.3–6.7)
– 48		166	10.8	2.70	5.10
– 6		126	11.4	2.60	6.40
8		24	11.6	2.50	7.14
9		17	11.2	3.26	5.82
10		24	9.2	1.45	8.03
11		53	9.7	2.68	11.66
15		183	11.1	4.53	14.40
22		82	11.6	1.19	17.15
25		33	11.2	2.04	22.63
26		46	11.0	1.40	16.30
29		25	10.9	1.10	16.13
44		205	11.7	1.39	19.23
50		162	11.9	1.44	17.13
64		170	11.2	2.70	14.16
80	– 18	150	10.6	3.39	7.37
106	8	366	11.2	4.05	12.29
134	36	218	11.6	3.25	13.79

lower dose was chosen due to chronic renal insufficiency KDIGO G3b A1 with a baseline glomerular filtration rate (CKD-EPI) of approximately 40 ml/min/1.7 m^2. Even before the dose of prednisone was tapered, the platelet count was 82 × 10^9/l, suggesting refractoriness to steroids. This prompted us to give a third application of IVIG and to initiate treatment with the thrombopoietin-receptor agonist (TPO-RA) eltrombopag [5] on day 30 after vaccination (day 22 after ITP diagnosis). Eltrombopag was started at 50 mg/d and the platelet count rose to 205 × 10^9/l (target range 50–200) (fig. 1) [5]. Because the platelet count remained stable, the dose was reduced to 25 mg/d after 2 weeks, to 12.5 mg/d after a further 9 weeks and to 12.5 mg three times a week after a further 4 weeks, according to the license holder's recommendations [5].

To investigate SARS-CoV2 serostatus and anti-spike-antibody levels, we used the clinical assays (Elecsys® Roche Diagnostics, Switzerland), a commercial ELISA kit and a Luminex-based custom in-house assay. Using the Roche assay, anti-S(pike)-IgG/IgM (<0.7 U/ml) and anti-N(ucleocapsid)-IgG/IgM (0.074 COI, reference <0.7 = negative) were both negative at the first presentation. An independent commercial ELISA assay (EUROimmun IgG, Lübeck, Germany) was also negative, and showed anti-S1-IgG seroconversion over time. For the Luminex assay, we coated recombinant S1 or receptor binding domain (RBD) protein (both from eEnzyme LLC, Gaithersburg, MD, USA) on Luminex magnetic beads and incubated with patient plasma (d8 and d25 after vaccination). Serum from a non-infected person (COVID–, n = 1) and a convalescent serum ("conv. serum", n = 1) were used as controls. Anti-human IgG and IgM were used for detection (both from SouthernBiotech, Birmingham, USA).

Using the Luminex assay, anti-SARS-CoV2 spike(S1)- and anti-RBD-specific IgM and IgG were detectable at the time of ITP diagnosis (fig. 2). The negative anti-SARS-CoV-2 nucleocapsid protein IgG/M together with the absence of symptoms of a respiratory tract infection argued against a previous or current SARS-CoV2 infection. Anti-S1-IgG seroconversion was confirmed in the ELISA assay (EUROimmun IgG, Lübeck, Germany) at day 25 after vaccination.

The patient elected to proceed with a second vaccination 14 weeks after his first tozinameran dose and his platelet count remained stable (fig. 1). We reported the case and the patient`s clinical course to the pharmacovigilance unit of the national authority for therapeutic products (Swissmedic).

Global pharmacovigilance data

We examined data from VigiBase, the World Health Oganization (WHO) global database of individual case safety reports in the discussion of this case. A detailed description of VigiBase can be found in the publication by Lindquist [6]. We searched VigiBase using VigiLyze (https://vigilyze.who-umc.org/) for the following vaccine names "COVID-19 mRNA Vaccine BNT162b2", "Pfizer BioNTech COVID-19 vaccine", "Comirnaty", "Vacuna COVID-19 Pfizer BioNTech", "Vacuna Pfizer BioNTech COVID-19" and the following reaction term "Immune thrombocytopenia" (as given in the Medical Dictionary for Regulatory Activities – MedDRA – version 23.1). The vaccine names were coded according to WHODrug, the international reference for medicinal product information.

As of the dataset dated 30 May 2021, VigiBase contains a total of 26,454,272 reports from 152 countries. A total of 347,084 unique case reports were retrieved with the tozinameran vaccine names alone, and 199 (0.06%) with the vaccine names plus the preferred term "immune thrombocytopenia". The number of reports is higher than statistically expected (n = 96).

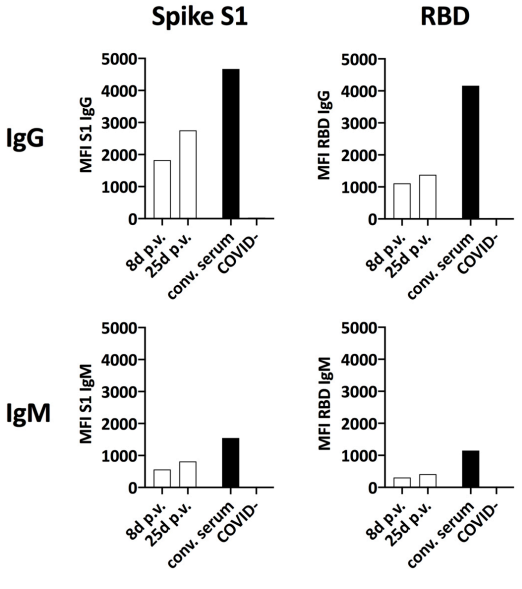
Discussion

ITP was not reported as an adverse event among 21,720 participants in the phase III BNT162b2 mRNA COVID-19 vaccine (tozinameran) trial [7]. However, the occurrence of rare adverse drug reactions (ADRs) that were not observed during vaccine development cannot be ruled out.

Given the temporal relationship between COVID-19 mRNA vaccination and the development of ITP, and exclusion of other causes of ITP in our patient, the WHO causality assessment of an adverse event following immunisation was judged as "indeterminate" on a three-point scale ("inconsistent-", "indeterminate-" or "consistent with a causal relationship"), as for all new vaccine-linked events [8].

A case report of ITP after the first dose of tozinameran in a healthy 22-year-old man without medication was published earlier this year [9]. Similar to our case, this patient had also experienced thrombocytopenia of unknown cause prior to vaccination. Lee and colleagues have summarised 20 patients hospitalised with thrombocytopenia after vaccination with an mRNA COVID-19 vaccine [10]. The authors observed a median time to presentation after vaccination of 5 days, and that all but one of the patients had developed significant thrombocytopenia (median 2 x 10^9/l, range 1–36) after the first vaccine dose. The authors noted that if the association between COVID-19 vaccina-

Figure 2: SARS-CoV2-specific anti-spike luminex assay. "conv. serum" = convalescent serum (n = 1), COVID- = negative control (serum from a non-infected person, n = 1); d: days; p.v.: post first vaccination; MFI: median fluorescence intensity; S1: SARS-CoV2 spike; RBD: receptor binding domain.



tion and ITP were due to chance alone, incident cases of ITP after the second vaccine dose would also be expected. However, it should be noted that the observation was made at a time when the number of people who had received both vaccine doses was likely to have been small (up until early February 2021). Among the cases described by Lee and colleagues, four patients had known previous ITP or thrombocytopenic episodes. Other case reports of ITP in association with COVID-19 mRNA vaccination have been reported in the literature during the past few months [11–13]. A report from the Vaccine Adverse Event Reporting System (VAERS) database of 28 patients with thrombocytopenia including ITP mentions two cases where ITP developed after the second dose [14]. Whether previous thrombocytopenic episodes are a risk factor for ITP after COVID-19 vaccination should be investigated further. The literature we cite here is current as of end of May 2021.

ITP often occurs in the context of an infection in the preceding days to weeks, and has been described in COVID-19 [1]. ITP associated with vaccination has been diagnosed in rare cases, especially with the MMR vaccine (1–3 in 100,000 vaccinated children) and usually has a mild course [15]. Vaccination may induce ITP by several mechanisms, most prominently molecular mimicry between viral and platelet proteins. Cross-reactive anti-viral antibodies act as autoantibodies by binding to platelets and inducing lysis through complement activation or cellular mechanisms. In our case, ITP occurred 8 days after vaccination when anti-S1 IgM and IgG were detectable in the serum only with a sensitive Luminex assay, and not with the clinical assay from Roche. Whether these vaccine-induced antibodies may have been enough to trigger ITP through cross-reactivity remains speculative.

Alternatively, unspecific vaccine-mediated immune stimulation may trigger ITP. The mRNA in the vaccine acts as an adjuvant by triggering toll-like receptors and inducing a type I interferon signature [16]. It is therefore plausible that this strong immune stimulation may induce immunological events in subjects with a – yet to be defined – background susceptibility.

Understanding the potential link between SARS-CoV2 antibodies and ITP will be important in defining what the best strategy is in patients with ITP occurring after a first dose of a COVID-19 vaccine. Furthermore, although our patient did not experience problems from the second dose of tozinameran 14 weeks after the first dose, further investigation of the safety of completing COVID-19 vaccination in patients who developed ITP after the first dose and the safety of a concurrent ITP treatment that includes TPO-RA is warranted. The risks of a subsequent SARS-CoV2 infection, and a potential infection-associated ITP episode, also need to be considered.

Although an early change to second-line therapy with TPO-RA does not represent standard care for patients with ITP, we elected this course of treatment in order to minimise exposure to steroids, maximise the chance of attaining a more stable platelet count in view of the patient's indication for oral anticoagulation, and in order to maintain the option of a second dose with the mRNA vaccine to fully establish protection from COVID-19. In our opinion, the benefits of this course of action outweighed the potential risks of thromboembolic events and eltrombopag-induced hepatoxicity [5], and its high costs were justified. The fact that the TPO-RA could be rapidly tapered and the platelet count even significantly increased on day 106 (8 days after the second vaccine dose) might indicate spontaneous resolution of the ITP and ‘overstimulation’ of megakaryopoesis by eltrombopag. Therefore – provided the patient's platelet count remains stable – we will consider stopping it in due course.

Concerning the macrocytic anaemia, our assessment ruled out haemolysis, substrate deficiencies and myeloma, leaving the anaemia unexplained. With a baseline GFR of 40 ml/min/1.7 m^2 (CKD-EPI), a renal component might play a role. We interpreted the initial neutrophilia as a reaction to the vaccination 8 days before. The bone marrow biopsy showed no explanation for the persisting neutrophilia after stopping the therapy with prednisone, which might suggest an underlying non-haematological aetiology.

Because data regarding the total number of administered doses is not collected in VigiBase, and ADR reporting is incomplete, the incidence of tozinameran-related ITP cannot be calculated. However, the known overall ITP incidence is approximately 3.3 per 100,000 adults/year [17]. It is important to continue being vigilant about severe adverse events that occur after vaccination and to report them to the national drug authorities. This essential step will allow discrimination between coincidence and causality through confluence of data.

Acknowledgment

Caveat Statement: Data from spontaneous ADR reporting are inhomogeneous as a result of different reporting policies worldwide and are vulnerable to underreporting and reporting bias. The information is therefore not homogeneous, at least with respect to origin and likelihood that the pharmaceutical product caused the adverse reaction. Conclusions drawn based on the post-marketing data in VigiBase are those of the authors and not those of the Uppsala Monitoring Centre, National Centres, or the World Health Organization.

Informed consent: The patient gave written informed consent for the anonymous publication of the case.

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Competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest was disclosed.

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