Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Therapie xxx (xxxx) xxx—xxx

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LETTER TO THE EDITOR

Immune thrombocytopenia following ChAdOx1 vaccine and positive rechallenge with BNT162b2 vaccine: A case report with pharmacovigilance analysis☆

Keywords Immune thrombocytopenia; COVID-19 vaccine; Adverse drug reaction; Cross-reactivity; Pharmacovigilance

Abbreviations

COVID-19	coronavirus disease 2019
CT	computed tomography
EBV	Epstein Barr virus
ICSR	individual case safety report
ITP	immune thrombocytopenic purpura
IV-Ig	polyvalent intravenous immunoglobulins
ROR	reporting odd ratio
SARS-CoV 2	severe acute respiratory syndrome coronavirus 2
WHO	World Health Organization

Introduction

Immune thrombocytopenic purpura (ITP) is a rare autoimmune disease, characterized by low platelet count (< 100 $\times$ 10^9/L) and risk of bleeding. ITP is caused by the production of autoantibodies against platelet surface glycoprotein and results in platelet destruction. It can either be idiopathic or secondary to an underlying medical condition. Pathogenesis of ITP is not completely understood but infections or vaccines might triggers ITP relapses [1]. It is believed that molecular mimicry may be one the prominent mechanisms of vaccine induced ITP. Here, we report a case of a patient with ITP flares induced by two different anti- severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines.

Case report

A 65-year-old man with a past medical history of resolved uveitis 30-year ago was admitted in the Emergency Department for epistaxis, petechiae in the upper thorax and gingiva and spontaneous hematomas and thrombocytopenia (9 $\times$ 10^9/L). In the current context of mass immunization against coronavirus disease 2019 (COVID-19), he had received a first dose of anti-SARS-CoV-2 vaccination with the ChAdOx1 nCoV-19 vaccine (Oxford / AstraZeneca) twelve days before. He didn't receive any medication, had no past medical history of thrombocytopenia and/or bleeding. No self-medication, including plants, was identified before admission to hospital. The patient was admitted in another hospital and an extensive work-up was performed to explore an underlying medical condition. Serologies for hepatitis C virus, hepatitis B virus, and HIV were negative. Epstein Barr virus (EBV) serology result suggested a resolved infection. Computed tomography (CT)-scan was normal. No other autoimmune disease (negative anti-nuclear antibodies), hematologic malignancy or primary immune deficiency was found. Bone marrow smear examination revealed numerous megakaryocytes supporting a peripheral origin of thrombocytopenia. No thrombosis was evidenced during hospital journey. Hence, the diagnosis of ITP was suspected and other diagnoses were ruled out. The patient received dexamethasone 40 mg/day for 4 days associated with polyvalent intravenous immunoglobulins (IV-Ig) (1 g/kg at day 1) with a good clinical and biological response.

The patient had two relapses (platelets < 30 $\times$ 10^9/L) during the following two months successfully treated by corticosteroids associated with IV-Ig for the first episode, and treated by IV-Ig alone for the second episode. The patient entered remission and platelets were stable between 50 and 75 $\times$ 10^9/L. Six months after the first dose, it was decided to complete the anti-SARS-CoV-2 immunization schedule with the BNT162b2 vaccine (BioNTech / Pfizer), another vaccine platform. On the day of vaccination, platelets were at 84 $\times$ 10^9/L. Four days later, he was referred to our hospital because of a platelet count at 8 $\times$ 10^9/L and an ITP relapse was diagnosed. Clinical examination revealed petechiae of the soft palate, of both legs, as well as an episode of unilateral epistaxis, rapidly recovering. He received dexamethasone for 4 days allowing a rise in platelet count at 49 $\times$ 10^9/L, which was stable for at least one month.

Discussion

We report here a case of ChAdOx1 nCoV-19 vaccine induced IPT, with further relapse with BNT162b2 vaccine, suggesting a role of these two vaccines. This observation supports the role of COVID-19 vaccines as an ITP triggering factor. Causality relationship between both vaccines and ITP was assessed as ''likely'' (C2S2, I2) using the French pharmacovigilance causality assessment tool [2].

Vaccines are suspected to trigger very rare autoimmune adverse events in some susceptible individuals, mainly

☆ This case has been declared to the French Pharmacovigilance System under the number FR-AFSSAPS-PV20213871 on 28th December 2021.

Please cite this article as: A. Murarasu, G. Bertoliatti-Fontana, N. Massy et al., Immune thrombocytopenia following ChAdOx1 vaccine and positive rechallenge with BNT162b2 vaccine: A case report with pharmacovigilance analysis, Therapies, https://doi.org/10.1016/j.therap.2022.05.006

Table 1 Immune thrombocytopenia reporting with COVID-19 vaccines and odds-ratios of reporting within the WHO pharmacovigilance database.

	Type of vaccine	ITP cases	Non-cases (other ADR)	ROR (95%CI) vs. all drugs
mRNA-1273	mRNA	352	609,833	1.9 (1.7—2.1)
BNT162b2	mRNA	1305	1,579,021	2.9 (2.7—3.0)
ChAdOx1	Adenovirus	721	720,334	3.3 (3.1—3.6)
Ad26.COV2-S	Adenovirus	139	136,110	3.3 (2.8—3.9)

95% CI: 95% confidence interval; ADR: adverse drug reaction; COVID-19: coronavirus disease 2019; ITP: immune thrombocytopenic purpura; ROR: ieporting odds-ratio; WHO: World Health Organization.

neurological events such as Guillain-Barre syndrome, multiple sclerosis or aseptic meningitis [3]. Hematological events such as ITP has already been related to the use of vaccines, specifically live attenuated vaccines such as measles, mumps and rubella [4]. The onset of vaccine-related ITP usually has a time relationship, occurring mainly within 42 days after vaccination [5]. Since the beginning of the COVID-19 mass immunization campaign, several case-reports or case-series of ITP following vaccination have been described in the literature [5—8]. In some cases, underlying autoimmune medical conditions may have contributed to the ITP occurrence but it appears infrequent [8]. For each of these cases, the authors brought out a temporal relationship with a reported time to onset after vaccination ranging from 12 hours to 23 days, similarly to what is observed in our case. The review of the IPT *de novo*cases reported to the French Pharmacovigilance Network showed unpredictable effect of rechallenge [8]. Although these cases cannot demonstrate a causal relationship between vaccination and ITP occurrence, their similarity supports a role of the vaccine. Like any ITP flare, post-vaccination ITP is usually successfully treated with IV-Ig and/or corticosteroids. In the literature, thrombocytopenia usually quickly resolves after a few days on treatment.

To date, post-marketing pharmacovigilance monitoring led the European Medicine Agency to mention IPT as an adverse drug reaction in the summary of product characteristics (SmPC) of the two adenovirus-based COVID-19 vaccines, ChAdOx1 nCoV-19 vaccine and Ad26.COV2-S vaccine [9]. Regarding mRNA-based vaccines, BNT162b2 and mRNA-1273, a safety signal has been raised. However, this safety signal is not confirmed yet. The review of the French nation-wide series suggested a possible higher frequency of ITP with ChadOx1-S nCoV-19 in comparison with BNT162b2 [8].

To provide further assessment of this risk, we reviewed VigiBase (https://who-umc.org/vigibase/), the World Health Organization (WHO) global individual case safety report (ICSR) database, which contains anonymized reports of suspected ADRs from more than 150 countries. We performed a disproportionality analysis, also called case/non-case study, that is a pharmacovigilance statistical approach used to identify safety signals [10]. Disproportionality analysis, based on a case/control design, estimates whether an adverse event is differentially reported for a specific drug compared to all other drugs, using the odds-ratio of reporting for each drug-adverse event combination and its 95% confidence interval. Cases are reports of IPT, whereas non-cases are reports including all other adverse drug reaction. Briefly, reporting odd ratio (ROR) [95% CI] are calculated as:

$$\frac{ad}{bc}\left[\frac{ad}{bc}\times e\pm 1.96\sqrt{\left(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}\right)}\right]$$

where a is the number of ITP cases with a COVID-19 vaccine of interest, b is the number of other reaction cases with a COVID-19 vaccine of interest, c is the number of ITP cases with all other drugs and d is the number of all other adverse drug reaction with all other drugs. Threshold for signal detection is defined as a ROR lower boundary 95% confidence interval ≥ 1. Hence, we assessed an association between ITP reporting and the use of COVID-19 vaccine.

Of 29,512,078 ICSRs registered in VigiBase up to February 2nd, 2022, 9,345 ITP cases were identified of which 2,524 were reported with a COVID-19 vaccine, including 1305 with BNT162b2, 721 with ChAdOx1 nCoV-19, 352 with mRNA-1273 and 139 with Ad26.COV2-S. All four COVID-19 vaccines, showed a significant disproportionate ITP reporting compared to the reporting of other adverse events (Table 1). The magnitude of disproportionality was similar between the four vaccines with an odds-ratio of reporting between 1.9 and 3.3. Altogether with previous published articles, this suggests a safety signal of ITP with COVID-19 vaccines, with a comparable risk between these four vaccines.

Conclusion

ITP may occur following COVID-19 vaccination. In these patients, the change of vaccine platform for further COVID-19 vaccination may be associated with ITP relapse, suggesting a shared adverse drug reaction between adenoviral-based and mRNA-based vaccines. Although this risk is established to date with adenoviral-based vaccines, our analysis suggests a similar risk with mRNA-based vaccines, with the same magnitude. Nevertheless, owing to the billions of COVID-19 vaccine doses administered worldwide, this risk appears to be very rare and does not balance the outstanding benefits of vaccination.

Acknowledgments

The authors would like to thank all the healthcare workers and the French Pharmacovigilance Network involved in the current large immunization campaign and in its safety monitoring.

VigiBase is a fully deidentified database maintained by the Uppsala Monitoring Center (UMC). The authors are indebted to the National Pharmacovigilance centres that contributed data. Information from VigiBase comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases. The information does not represent the opinion of the Uppsala Monitoring Center (UMC) or the World Health Organization and only reflects the authors' opinion. According to VigiBase access rules, no specific ethical approval is needed. VigiBase access is granted to national and regional pharmacovigilance centers such our teams.

Disclosure of interest

The authors declare that they have no competing interest.

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Received 13 March 2022;
accepted 19 May 2022

https://doi.org/10.1016/j.therap.2022.05.006