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Atypical thrombosis associated with VaxZevria® (AstraZeneca) vaccine: Data from the French Network of Regional Pharmacovigilance Centres

Keywords VaxZevria®; Covid-19 vaccine; Pharmacovigilance; Atypical thrombosis; Thrombopenia; Anti-PF4 antibodies

Abbreviations

ADRs	adverse drug reactions
ANSM	French Medicines Agency
COVID-19	coronavirus disease 2019
CRPV	French Regional Pharmacovigilance Network
CVT	cerebral venous thrombosis
DIC	disseminated intravascular coagulation
EMA	European Medicines Agency
SARS-CoV-2	severe acute respiratory coronavirus 2 syndrome
ST	splanchnic thrombosis
TTS	thrombosis with thrombocytopenia syndrome
VIPIT	vaccine-induced prothrombotic immune thrombocytopenia

Starting in late 2019, the initial cases of a previously unknown form of pneumonia, now referred to as coronavirus disease 2019 (COVID-19), led to a global pandemic. In response, most countries have sought to curb the spread of the virus by imposing periods of lockdown as a function of the national infection rates. By the end of 2020, the advent of vaccines against this severe acute respiratory coronavirus 2 syndrome (SARS-CoV-2) prompted new hope in the global fight against the COVID-19 pandemic. In Europe, mRNA vaccines and adenovirus vector vaccines have received conditional marketing authorizations for active immunization against SARS-CoV-2 in individuals aged 16 and over.

On January 29th, 2021, the European Medicines Agency (EMA) authorized VaxZevria®, the AstraZeneca adenovirus vector vaccine directed against SARS-CoV-2 and in France, the campaign officially started on February 6, 2021.

These new vaccine technologies are now considered to be the best option of countering the COVID-19 pandemic. Given the high level of population likely to be exposed to these drugs, vaccine safety is a critical issue. In order to promptly and accurately identify potential new signal, the French Medicines Agency (ANSM) oversees the assessment of vaccine safety and has initiated a specific strengthened surveillance system for adverse drug reactions (ADRs) related to COVID-19 vaccines in France. This system is based on the collaboration between the Regional Pharmacovigilance Network (CRPV) and the expert council of the specific ANSM/CRPV monitoring committee for vaccines [1].

In this letter, we describe and discuss the VaxZevria® associated-atypical thrombosis specific signal identified by this committee.

Table 1 Details of the 27 reported cases of atypical thrombosis following administration of the VaxZevria vaccine against COVID-19 between February 6th and April 15th, 2021.

N	Sex	Age	Onset period	Time to onset (days)	Cerebral venous thrombosis	Splanchnic thrombosis	Other thrombosis	Thrombo-cytopenia	Disseminated intravascular coagulation	Anti-PF4 antibodies	Causality assesment [6]
Brighton collaboration level 1											
1[a]	M	41	W15	17	Yes	Yes	Yes	Yes	Yes	Yes	I5
2[a]	M	63	W11	11	Yes	Yes	Yes	Yes	Yes	Yes	I5
3	F	21	W12	15	Yes	Yes	Yes	Yes	No	Yes	I6
4[a]	F	69	W14	12	Yes	No	Yes	Yes	Yes	Yes	I5
5	F	26	W8	9	No	Yes	Yes	Yes	Yes	Yes	I6
6	M	73	W15	12	No	Yes	Yes	Yes	No	Yes	I6
7[a]	F	61	W14	13	No	Yes	Yes	Yes	Yes	Yes	I5
8[a]	F	38	W12	8	Yes	Yes	No	Yes	Yes	No	I3
9	F	74	W14	15	No	No	Yes	Yes	Yes	Yes	I6
10	M	23	W12	9	Yes	No	No	Yes	Yes	Yes	I6
11	F	44	W12	9	Yes	No	No	Yes	Yes	Yes	I6
12	M	60	W14	11	Yes	No	No	Yes	No	Yes	I6
13[a]	M	60	W14	11	No	Yes	No	Yes	No	No	I3
14[a]	M	67	W14	8	No	Yes	No	Yes	Yes	No	I3
Other categories of interest											
15	F	67	W13	11	No	No	No	Yes	Yes	ND	I3
16	F	73	W12	10	No	No	No	Yes	Yes	Yes	I4
17	F	24	W11	35	Yes	No	Yes	No	No	ND	I2
18	M	51	W11	6	Yes	No	No	No	No	No	I2
19	F	53	W12	18	Yes	No	No	No	No	ND	I2
20	M	54	W14	25	No	Yes	No	No	No	ND	I2
21	M	56	W14	2	No	Yes	No	No	No	ND	I2
22	F	61	W15	17	No	Yes	No	No	No	ND	I2
23	M	68	W15	11	No	Yes	No	No	No	No	I2
24	M	73	W15	30	No	Yes	No	No	No	ND	I2
25[a]	M	24	W11	7	No	Yes	No	No	No	ND	I2
26	M	61	W12	2	No	Yes	No	No	No	ND	I2
27	F	58	W14	8	No	Yes	No	No	No	ND	I2

ND: not determine; W: calendar week.
[a] Fatal issue.

In France, VaxZevria® ADRs reporting was initially dominated by flu-like syndromes. In late February 2021, the first report of serious, unexpected, thrombotic events associated with coagulation disorders namely thrombocytopenia and disseminated intravascular coagulation (DIC) was identified by the two CRPV in charge of the survey, which alerted the French authorities.

This potential signal, also observed in other European countries, was confirmed by the EMA on March 18, 2021 and definitely validated on April 7th, 2021 [2]. Initially, the at-risk population, thought to be limited to young women, prompting member states to adapt their vaccination policy accordingly. Since then, various attempts have been made to define this new atypical thrombosis entity, with different entry points according to the presence of thrombocytopenia (thrombosis with thrombocytopenia syndrome [TTS] as proposed by the Brighton collaboration [3]), thrombosis (vaccine-induced prothrombotic immune thrombocytopenia [VIPIT] [4]) or anti-PF4 antibodies [5].

In the context of this signal, the ANSM/CRPV specific monitoring committee on vaccines considered 4 categories of interest:

- cerebral venous thrombosis (CVT) or splanchnic thrombosis (ST);
- multi-site thrombosis whether or not associated with thrombocytopenia or coagulation disorders;
- any other thrombosis associated with thrombocytopenia or coagulation disorders;
- isolated DIC.

In France, 11,206 ADR reports of which 2811 were serious have been received up to April 15th, 2021 from healthcare professionals and patients for a total of 3,263,188 injections of VaxZevria®. Of these, 360 mentioned venous and/or arterial thrombosis. According to the above defined categories, 27 cases fulfilled the criteria of the atypical thrombosis, i.e. a notification rate [95% confidence interval] of 0.8 [0.54—1.20] per 100,000 doses. These cases involved 13 women and 14 men, and the median (range) age was 60 years (21-74) (Table 1). There was no particular history or risk factor apart from long term well tolerated oral estroprogestative contraception in 4 patients. The median (range) time to onset was 11 days (2 to 35). Of the 16 patients tested for 12 were positive for anti-PF4 antibodies. There were 8 fatal issues, giving a mortality rate of 30%.

Fourteen of the 27 cases met the level 1 criteria of the Brighton collaboration, with a median (range) trough platelet count of 25 G/L (9—61), and 13 cases corresponded to other categories of interest defined by the ANSM/CRPV specific monitoring committee.

Of the 14 ''level 1'' cases, 9 corresponded to multiple thrombosis and thrombocytopenia and/or DIC, and 5 to isolated CVT ($n = 3$) or ST ($n = 2$) with thrombocytopenia. The 13 last cases included CVT ($n = 3$) and ST ($n = 8$) with no evidence of thrombocytopenia, and isolated DIC ($n = 2$).

These atypical thrombosis were not reported during the clinical trials of VaxZevria® [7], generally not powerful enough to identify rare ADRs, which emphasizes the importance of a close real time safety monitoring and scientific analysis by pharmacovigilance experts, as the risk was not identified after the first uses outside Europe.

Among the several possible explanations for these extremely rare thrombotic complications associated with thrombopenia and occurring within 1 to 2 weeks after vaccination with VaxZevria®, an autoimmune heparin-induced-like thrombocytopenia is the most frequently discussed. This well-known prothrombotic disorder is caused by platelet-activating antibodies that bind to multimolecular complexes between cationic PF4 and anionic heparin. However, anti-PF4 antibodies can be induced by substances other than heparin [5,8]. According to the German Society of Thrombosis and Haemostasis Research, vaccination is likely to induce the formation of antibodies against platelet antigens as a part of the inflammatory reaction and immune stimulation [9]. In line with previous reports from Norway [8] and Germany [5], 75% of our tested patients were positive for anti-PF4 antibodies. Screening must be performed under specific conditions, since, in our series, 6 of the 12 positive patients were initially seronegative with rapid screening assays.

Nevertheless, despite an adapted technique, in some of our patients sharing similar clinical and radiological pictures of those described as VIPIT/TTS, the anti-PF4 antibodies remained negative and in some of those cases no thrombocytopenia or coagulation disorders were observed suggesting other potential pathophysiological mechanisms justifying further investigation. Likewise, it is important to identify the causal determinant of these reactions:

- factors linked to the vaccine itself;
- factors linked to the induced immune reaction;
- factors linked to the patient himself.

To date, no particular risk factor has been identified in patients and although the incidence of cases was initially higher in young women [3], in the most recent data, atypical thrombosis equally affected men and patients above 60 years although the incidence of notification remains proportionately higher in younger patients.

Hence, all these points are essential to establish a diagnostic strategy allowing rapid identification of cases and to determine the most appropriate therapeutic attitude, notably on the choice of anticoagulants and the role of immunosuppressive therapies.

The existence of a similar confirmed signal for Johnson & Johnson vaccine [10,11], another adenovirus vector vaccines, may help guide further researches to answer those questions and more broadly on VaxZevria's place in COVID-19 immunization policy, even though this clinical picture remains rare and do not currently cast doubt on this vaccine risk/benefit ratio.

Disclosure of interest

The authors declare that they have no competing interest.

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COVID-19 vaccines and pregnancy: What do we know?

Keywords COVID-19; COVID-19 vaccine; Pregnancy; Adverse drug reaction

Abbreviations

ANSM	*Agence nationale de sécurité du médicament et des produits de santé* (French Drug Agency)
CDC	Centres for Disease Control and Prevention
COVACPREG	COvid VACcine PREGnancy
COVID-19	coronavirus disease 2019
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2

Since the start of the coronavirus disease 2019 (COVID-19) pandemic, concerns have been raised about how to manage and prevent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in pregnant women [1]. COVID-19 during pregnancy is associated with substantial risk of morbidity and mortality in mothers and in their infants [2,3], with for example preeclampsia, intensive care unit admission, infections, as well as preterm birth and low birth weight. These complications are more likely in women with pre-existing co-morbidities, such as overweight, diabetes, hypertension or cardiac and chronic respiratory diseases [4]. Moreover, detection of viral RNA in the placenta or in foetal membranes shows that vertical transmission of SARS-CoV-2 from mother to foetus is rare but possible [5]. Vaccination is therefore needed in this vulnerable population, and characterising vaccine adverse reactions in pregnancy is a major concern.

Animal studies conducted with the Pfizer, Moderna and Janssen vaccines have not found any teratogenic or fetotoxic effects for any of these vaccines [6,7]. Experimental studies on the AstraZeneca vaccine assessing the risk of malformation are still ongoing.

Some companies having developed COVID-19 vaccines may plan to include pregnant women in clinical trials in the future, but all current studies have excluded pregnant participants. Thus, very little information is currently available on safety and efficacy in pregnancy. During Pfizer and Moderna clinical trial, 12 and 6 pregnant women were respectively inadvertently enrolled in the vaccine groups. These vaccine-exposed pregnancies are ongoing without complications.

A recent Centres for Disease Control and Prevention (CDC) publication [8] reported that over 30,000 women have been exposed to mRNA vaccines in the United States, representing a roughly equal number of Pfizer and Moderna vaccines. Injection-site pain was reported more frequently among pregnant women than among non-pregnant women, whereas headaches, myalgia, chills and fever were reported less frequently. Pregnant women did not report having serious reactions more frequently than non-pregnant women, except for nausea and vomiting, which were reported slightly more frequently only after dose two. A total of 827 pregnancy outcomes were collected among the 5,230 pregnant women included in the v-safe prospective registry [8]. These pregnancies resulted in a live birth in 712 cases (86.1%), in spontaneous abortion in 104 cases (12.6%), in stillbirth in one case (0.1%) and in other outcomes (induced abortion and ectopic pregnancy) in 10 cases (1.2%). Among 724 live-born infants, including 12 sets of multiple gestation, 9.4% were born preterm (60 of 636 among those vaccinated before 37 weeks), 3.2% had a small size for gestational age and 2.2% major congenital anomalies; no neonatal deaths were reported at the time of interview. These incidences of spontaneous miscarriage, pregnancy complications, prematurity and birth defects were comparable to those expected in the general population.

Preliminary American data [9] demonstrated transmission of maternal antibodies to the foetus via the placenta, although it is too early to conclude that this will protect future newborns.

The mode of action of non-live vaccines makes a risk of malformation unlikely. Data on other non-live vaccines, such as that for influenza, are reassuring [10]. Based on what is known about how mRNA vaccines act locally (at the site of injection) and are rapidly degraded and removed by the lymphatic system, the likelihood of the vaccine reaching and crossing the placenta is believed to be low.

In view of this data, vaccination can be considered for pregnant women from the 2nd trimester (period carrying a lower risk of teratogenic effects and pregnancy termination), particularly in the presence of important risk factors (obesity, diabetes, etc.) for severe COVID-19 or if there is a high risk of contamination (medical profession, school environment, etc.). Moreover, on the recommendations of the French *Conseil d'orientation de la stratégie vaccinale* (Vaccine Strategy Steering Committee), the Directorate-General of Health extended priority access to COVID vaccination in France on 3 April 2021 to pregnant women with or without comorbidities from the 2nd trimester. The mRNA vaccines (Pfizer and Moderna) seem preferable for this population given the lack of animal data to date for the AstraZeneca vaccine and a higher frequency of post-vaccination influenza-like illnesses. Finally, for women wanting to fall pregnant, it may be preferable to suggest that they postpone the pregnancy until the end of the vaccination schedule, if this is not already the case.