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ORIGINAL RESEARCH ARTICLE

Cumulative Adverse Event Reporting of Anaphylaxis After mRNA COVID-19 Vaccine (Pfizer-BioNTech) Injections in Japan: The First-Month Report

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Abstract

Introduction In mid-February, the nationwide immunization plan for the prevention of coronavirus disease 2019 (COVID-19) started in Japan (at first primarily focused on health professionals) using an mRNA-based vaccine (Pfizer/BioNTech). During the phase-in period from February to March, attention was focused on post-vaccination anaphylaxis and anaphylactoid symptoms from the viewpoint of ensuring the safety of the vaccination program.

Objective The aim of this report was to provide an update on the status of anaphylaxis and anaphylactoid symptoms occurring after vaccination for COVID-19, as reported under the Adverse Event Following Immunization (AEFI) reporting system in Japan.

Methods The Pharmaceutical and Medical Devices Agency (PMDA) received AEFI reports from health professionals and manufacturers under the reporting system for AEFI after vaccination for COVID-19, which has been in operation since mid-February 2021. Reported AEFIs of anaphylaxis and anaphylactoid symptoms were assessed using the Brighton Collaboration Criteria to assess diagnostic certainty.

Results 1-month since Japan started the vaccination program for COVID-19 in February 2021, 578,835 doses have been administered to health professionals, with the PMDA receiving 181 suspected event reports of anaphylaxis and anaphylactoid symptoms. In 171 of these 181 cases, women developed these symptoms. Among 181 cases evaluated according to the Brighton Collaboration Criteria, 47 cases (26%) were classified as level 1–3 (reporting rate: 8.1/100,000 doses).

Conclusion The results appear similar to reported AEFIs in foreign studies of coronavirus vaccine administration to health professionals, although the reporting rate was higher. Further work is needed to examine the causal relationship of anaphylaxis reactions to coronavirus vaccine administration. Issues of multiple reporting and possible sex/age bias also remain to be analyzed.

1 Introduction

On 14 February 2021, The Ministry of Health, Labour and Welfare (MHLW) granted Special Approval for Emergency for the first coronavirus vaccine—Comirnaty (Pfizer/BioNTech; hereinafter referred to as the 'mRNA-based vaccine') intramuscular injection—for the prevention of coronavirus disease 2019 (COVID-19) in Japan. In mid-February, the nationwide immunization plan commenced, at first primarily focused on health professionals in the national hospital group network and other front-line hospitals. The program was expanded to other health professionals, followed by elderly populations, in May 2021. During the phase-in period from February to March, health professionals who initially received the vaccination were closely monitored for adverse events (AEs). In particular, anaphylaxis and anaphylactoid symptoms that developed after vaccinations were of high interest in terms of determining the safety of the vaccination.

The aim of this report was to update the status of anaphylaxis and anaphylactoid symptoms reported under the Adverse Event Following Immunization (AEFI) reporting

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Keypoints

In Japan, 1 month after starting the vaccination program using the mRNA coronavirus disease 2019 (COVID-19) vaccine (Pfizer-BioNTech), 578,835 doses have been administered. We provide an update of reported adverse events following immunization (AEFIs), focusing on anaphylaxis.

Forty-seven confirmed anaphylaxis cases were reported as AEFIs, corresponding to 8.1/100,000 doses. This is a higher rate than seen with conventional vaccines but is similar to rates reported in foreign studies of the coronavirus vaccine.

system in Japan, in order to assess the need for further safety measures as the vaccination program is extended.

2 Methods [Adverse Events Following Immunization (AEFI) Reporting System]

The Pharmaceutical and Medical Devices Agency (PMDA) is the operational body that, after vaccinations, receives AEFI reports from health professionals and manufacturers under the Immunization Act and the Pharmaceuticals and Medical Devices Act. Health professionals are obliged to report AEFIs when they encounter cases of AEs after vaccination, in accordance with these Acts. Anaphylaxis and anaphylactoid symptoms were designated as serious AEFIs to be reported. AEFI reporting after vaccination for COVID-19 has been in operation since the emergency authorization in mid-February 2021. The number of administered doses was collected from the vaccination sites through the nationwide vaccine supply information network, the Vaccination Facilitation System (V-SYS) [1], operated by the MHLW, which was used as the denominator for calculating the frequency of AEFI reporting. The reported AEFIs were assessed by PMDA/MHLW medical experts. The Brighton Collaboration Criteria were applied to classify event reports of suspected anaphylaxis and anaphylactoid symptoms according to diagnostic certainty (level 1 is the highest certainty and level 5 is the lowest) [2]. The widely used Brighton Collaboration Criteria were helpful in enabling comparison between different studies.

For comparison, we also calculated the reporting ratio of anaphylaxis and anaphylactoid symptoms in the adult population (over 16 years of age) for influenza HA vaccines, from data in the PMDA's AE reporting database (JADAR) during the 5 seasons from 2015 to 2019. The estimated total number of influenza HA vaccine doses over the five seasons was 262.48 million [3].

3 Results (Suspected Anaphylaxis Reporting)

As of 21 March 2021, 578,835 doses of the mRNA-based vaccine have been administered, and, to date, 733 (85 males [12%], 647 females [88%], 1 unknown [< 1%]) AEFIs have been reported from health care settings. Among these, there have been 181 (first dose: 177; second dose: 3; unknown: 1) suspected anaphylaxis reports [4], resulting in a reporting rate of 31.3/100,000 doses. In 171 of 181 cases, women developed suspected anaphylaxis and anaphylactoid symptoms. After 1 month of AEFI monitoring, the Committee on Drug Safety of the Pharmaceutical Affairs and Food Sanitation Council and the Vaccine Adverse Reaction Review Committee (hereinafter referred to as the 'Joint Committee') of the MHLW evaluated these cases using the Brighton Collaboration Criteria. Forty-seven of 181 (26%) cases reported by 21 March were evaluated as levels 1–3 cases (reporting rate: 8.1/100,000 doses) (Table 1).

Thirty-five of the 47 cases (74%) had a history of allergic disease or allergic reactions to medicines and/or food. In 44 of 47 cases (94%), women developed anaphylaxis. The overall characteristics of reported anaphylaxis are summarized in Table 2.

4 Discussion

In a summary of Yellow Card reporting of the coronavirus vaccine, the British Medicines and Healthcare Products Regulatory Agency (MHRA) reported 215 cases of anaphylaxis and anaphylactoid symptoms after administration of 11.5 million vaccine doses (reporting rate: approximately 1.9/100,000 doses) [5]. The experience in the UK is based mainly on adenovirus vaccine, and care is needed in comparing AEFIs of mRNA vaccines with those of adenovirus vaccines. Among mRNA vaccines, Shimabukuro et al. reported an anaphylaxis event rate of 0.47/100,000 doses for the Pfizer-BioNTech vaccine in the US, according to the Vaccine Adverse Event Reporting System (VAERS), during a 1-month period (14 December 2020–18 January 2021) [6].

Table 1 Confirmed anaphylaxis (Brighton level 1, 2 or 3) reaction reports after COVID-19 vaccination

No.	Age (years)	Sex	Lot no.	Onset after vaccination (mins)[b]	Background history of allergy	Other possible cause	Evaluation of the Brighton collaboration criteria	Treatment	Treatment outcome
1	36	F	EP2163	5	Bronchial asthma	Bronchial asthma	1	Adrenaline Corticosteroid SABA amino-phylline	Recovering
2	24	F	EP2163	25	–	None	1	Adrenaline	Recovered
3	29	F	EP9605	20	Urticaria	Urticaria	2	Adrenaline	Recovered
4	52	F	EP2163	5	Bronchial asthma, drug	None	3	Corticosteroid	Recovered
5	37	F	EP2163	22	Food, allergic disease	Unknown	2	Adrenaline Corticosteroid Anti-histaminic	Recovered
6	33	F	EP9605	5	Animals	None	2	Adrenaline	Recovered
7	27	F	EP2163	30	Food, drug	None	2	Adrenaline	Recovering
8	48	F	EP9605	Immediately after vaccination (1 min)	–	None	2	Adrenaline Corticosteroid	Recovering
9	55	F	EP2163	10	Bronchial asthma, anaphylaxis	None	2	Corticosteroid Anti-histaminic	Recovered
10	44	F	EP2163 second	13	Drug	None	2	Corticosteroid	Recovering
11	38	F	EP2163	3	Urticaria	None	2	Adrenaline Anti-histaminic	Recovering
12	29	F	EP9605	29	–	None	3	Unspecified	Recovered
13	51	F	EP2163	10	–	Unknown	2	No information	Recovering
14	44	F	EP2163 second dose	10	–	None	2	Adrenaline Corticosteroid	Recovered
15	33	F	EP9605	30	Bronchial asthma, drug	None	2	Corticosteroid Anti-histaminic	Recovering
16	55	F	EP9605	15	Food, drug	None	2	No information	Recovered
17	50	F	EP9605	9	Allergic disease	None	2	Adrenaline Corticosteroid Anti-histaminic	No information
18	34	F	EP9605	5	–	None	2	Adrenaline Anti-histaminic	Recovering
19	42	F	EP9605	7	Food, pollen	None	3	Adrenaline Corticosteroid Anti-histaminic SABA	Unrecovered[a]
20	37	F	EP9605	3	Food, drug	Unknown	2	Steroid Anti-histaminic	Recovered
21	43	F	EP9605	5	Food, drug	None	2	Adrenaline Corticosteroid	Recovered
22	35	F	EP9605	13	–	Unknown	2	Anti-histaminic	Recovering
23	24	F	EP9605	10	Bronchial asthma, animals, house dust	None	2	Corticosteroid Anti-histaminic	Recovering
24	46	F	EP9605	13	Food	None	2	Corticosteroid	Recovering
25	50	F	EP9605	15	Urticaria	None	1	Corticosteroid	Recovering
26	49	F	EP9605	10	Bronchial asthma	Unknown	1	Adrenaline Corticosteroid Anti-histaminic	Recovering

Table 1 (continued)

No.	Age (years)	Sex	Lot no.	Onset after vaccination (mins)[b]	Background history of allergy	Other possible cause	Evaluation of the Brighton collaboration criteria	Treatment	Treatment outcome
27	44	F	EP9605	10	Food	None	2	Corticosteroid Anti-histaminic	Recovering
28	24	M	EP9605	10	Food, pollen	None	3	Corticosteroid Anti-histaminic	Recovering
29	22	M	EP9605	15	–	None	2	Corticosteroid Anti-histaminic	Recovered
30	26	F	EP2163	5	–	None	2	Corticosteroid Anti-histaminic	Recovering
31	39	F	EP9605	7	Drug	Menstruation	3	No information	Recovering
32	38	F	EP9605	15	Bronchial asthma, food, metal	None	2	Corticosteroid Anti-histaminic	Recovered
33	25	F	EP9605	50	–	Chronic tonsilitis	1	Adrenaline Anti-histaminic	Recovered
34	55	F	EP9605	480	Drug	None	2	Corticosteroid Anti-histaminic	Recovering
35	48	F	EP9605	30	–	None	2	No information	Recovered
36	43	F	EP9605	5	Drug, pollen	None	2	Adrenaline Corticosteroid Anti-histaminic	Recovered
37	42	F	EP9605	10	Pollen	Unknown	3	Anti-histaminic	Recovering
38	50	F	EP9605	20	Drug	None	2	Adrenaline Corticosteroid	Recovered
39	42	F	EP2163	20	Drug, food, cosmetics, allergic disease	None	1	Adrenaline	Recovering
40	24	M	EP9605	30	Food, pollen	None	2	Anti-histaminic	Recovered
41	37	F	EP2163 second dose	2	Drug	None	2	Corticosteroid Anti-histaminic	Unrecovered[a]
42	38	F	EP9605	230	Bronchial asthma	None	2	Adrenaline Corticosteroid SABA	Recovered
43	54	F	EP9605	40	Bronchial asthma, drug	None	2	Adrenaline Anti-histaminic	Recovered
44	56	F	EP9605	60	Bronchial asthma	None	1	Corticosteroid Anti-histaminic Aminophylline	Recovering
45	41	F	EP9605	10	Bronchial asthma, drug, pollen	None	2	Adrenaline Corticosteroid Anti-histaminic	Recovering
46	31	F	EP9605	5	–	Unknown	3	Anti-histaminic	Recovered
47	47	F	EP2163	20	Urticaria, food, drug	None	2	Anti-histaminic	Recovered

COVID-19 coronavirus disease 2019, *F* female, *M* male, *SABA* short-acting β-agonists

[a]These cases were reported by 21 March 2021 and were evaluated for Brighton Collaboration Criteria by 25 March 2021

[b]Onset after vaccination' includes estimates of elapsed time before onset for cases where the exact time was not recorded

[c]The Brighton Collaboration Criteria are used to define the level of diagnostic certainty of reported cases of anaphylaxis and anaphylactoid symptoms, based on combinations of symptoms. Level 1 is the highest level of diagnostic certainty. Levels 4 and 5 do not meet the Brighton Collaboration Criteria definition of anaphylaxis

[d]Most cases received treatments (adrenaline and/or corticosteroid and/or anti-histaminic drug) in a hospital after the onset of anaphylaxis, and had recovered or been recovering by the cut-off date

Table 2 Characteristics of reported anaphylaxis (Brighton level 1, 2 or 3) after COVID-19 vaccination in Japan (14 February–21 March 2021)

Characteristics	No. of cases (%) [$n = 47$]
Age, years [median (range)]	41 (22–56)
Female sex	44 (94)
Time to onset, min [median (range)]	10 (< 1–480)
Symptom onset, min	
≤ 5	30 (64)
≤ 30	41 (87)
> 30	6 (13)
Prior allergic history	
Allergies and allergic reaction to food, drug, pollen, animals	34 (72)
Prior anaphylaxis	1 (2)
Vaccine doses	
First	45
Second	2
Brighton level	
1	7 (15)
2	33 (70)
3	7 (15)
Anaphylaxis reporting rate	8.1/100,000

Data are expressed as *n* (%) unless otherwise specified

COVID-19 coronavirus disease 2019

We have also reviewed the records of suspected anaphylaxis and anaphylactoid symptoms reported in the past for comparable influenza HA vaccines. Over the last 5 seasons (2015–2019), the reported number of suspected anaphylaxis and allergy-related reactions was 56, corresponding to a rate of 0.02/100,000 doses, in the PMDA's JADER database (electronic supplementary material). The most frequent rate of suspected anaphylaxis reporting for influenza HA vaccine was 1.0/100,000 doses in the 2009 season (H1N1) [7]. Among 118 cases of suspected anaphylaxis, 55 (46.8%) were level 1–3 according to the Brighton Collaboration Criteria.

In the 2009 H1N1 influenza vaccinations, the rate of female cases with suspected anaphylaxis was around 75% of the total, which is similar to the rate of development in women over the last 5 seasons of reporting after influenza vaccinations. Thus, the trend for a higher rate of reporting of anaphylaxis and anaphylactoid symptoms in women in the adult population after the influenza vaccination also appears to be the case for the COVID-19 vaccination in Japan.

The current Japanese rate of anaphylaxis and anaphylactoid symptom reporting (8.1/100,000 doses) [level 1–3 according to the Brighton Collaboration Criteria] seems relatively high. Multiple factors may be potentially associated with this high reporting rate. For example, the vaccinees were health professionals who were closely monitored and who were requested to report AEFIs. For comparison, Blumenthal et al. demonstrated that Mass General Brigham employees who received their first dose of a COVID-19 vaccine developed anaphylaxis at a rate of 25/100,000 doses [8]. There could also be other relevant factors, such as reporting bias, differences in the demography of the vaccinee population, etc. The possibility of anaphylaxis has been highly publicized in the context of the attention given to coronavirus vaccines by the media. We found that female cases accounted for 88% of the 733 AEFI reports, and the median age of cases reporting anaphylaxis AEFIs was 41 years, but these findings may simply reflect the demography of the vaccinee population.

The MHLW has been warning health professionals to exercise caution in the case of vaccinees who have a previous medical history of systemic allergic reactions, including anaphylaxis, allergy, or severe sensitivities to any vaccine, food, etc. [9]. When the vaccination program started, the joint committee of the MHLW recommended that for those who had encountered severe allergic symptoms in the past, including anaphylaxis, follow-up after vaccinations should be performed for 30 min, while for others, follow-up should be performed for at least 15 min [10].

5 Conclusion

One month after Japan started the vaccination program for COVID-19 in February 2021, 578,835 doses had been administered to health professionals. Among 181 AEFI cases of anaphylaxis and anaphylactoid symptoms evaluated according to the Brighton Collaboration criteria, 47 cases (26%) were classified as level 1–3 (reporting rate: 8.1/100,000 doses), which is similar to those AEFIs reported in foreign studies of coronavirus vaccine administration to health professionals, but higher than the rates reported for conventional scheduled vaccines.

Further work is needed to examine the causal relationship of anaphylaxis reactions to administration of the coronavirus vaccine. Furthermore, the issues of multiple reporting and reporting sex/age bias also remain to be analyzed. In addition, to date, only one type of coronavirus vaccine is available in Japan, therefore the comparison of AEFI reporting rates among different types of coronavirus vaccines will be a challenge for the future. At this point, we are not able to conclude that the characteristics of AEFI reporting of the coronavirus vaccine are different from those of other vaccines available on the market; however, they will be further assessed on the basis of the accumulation of AEFI reports in Japan and from the rest of the world.

We need to continue close monitoring of the reporting trend of suspected anaphylaxis and anaphylactoid symptom cases after vaccinations, as the target populations of vaccination were shifted from health professionals to the elderly

population in May 2021. The PMDA, in collaboration with the MHLW, will be regularly publishing the cumulative results of event reporting.

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Declarations

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Conflict of Interest Toyotaka Iguchi, Hikari Umeda, Michie Kojima, Yuri Kanno, Yuta Tanaka, Natsumi Kinoshita, and Daisaku Sato declare no competing interests.

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Consent to Participate Not applicable. All data are publicly available from the MHLW and PMDA websites.

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Code Availability Not applicable.

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