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Analysis of COVID-19 mRNA vaccine-induced mouth ulcers using the Japanese Adverse Drug Event Report database

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There are case reports of mouth ulcers caused by the coronavirus disease 2019 (COVID-19) messenger ribonucleic acid (mRNA) vaccine; however, the actual number and characteristics of cases are unknown. Therefore, we examined this issue using the Japanese Adverse Drug Event Report (JADER), a large Japanese database. We calculated the reported odds ratio (ROR) of drugs that may be specifically associated with mouth ulcers and assumed that a signal was present if the lower limit of the calculated ROR's 95% confidence interval (CI) was > 1. In addition, the time to symptom onset after administration of the COVID-19 mRNA and influenza HA vaccines was investigated. We found that the JADER database contained 4,661 mouth ulcer cases between April 2004 and March 2022. The COVID-19 mRNA vaccine was the eighth most common causative drug for mouth ulcers, with 204 reported cases. The ROR was 1.6 (95% CI, 1.4–1.9) and a signal was detected. There were 172 mouth-ulcer cases associated with the Pfizer-BioNTech's COVID-19 mRNA vaccine, 76.2% of which were female. The outcome was no unrecovered cases with the influenza HA vaccine, whereas the COVID-19 mRNA vaccine showed unrecovered cases (Pfizer-BioNTech: 12.2%, Moderna: 11.1%). The median time-to-onset of the mouth ulcers was two days for the COVID-19 mRNA vaccine and one day for the influenza HA vaccine, indicating that mouth ulcers caused by the COVID-19 mRNA vaccine were delayed adverse events. In this study, the COVID-19 mRNA vaccine was shown to cause mouth ulcers in a Japanese population.

1. Introduction

Severe mouth ulcers can cause acute pain and adversely affect oral function (Sonis 2004). Early detection and treatment of mouth ulcers are important for maintaining patients' quality of life (Cheng et al. 2010). Various causes of mouth ulcers have been reported, including drugs, infections, and inflammation (Sardana et al. 2014). Drug-induced mouth ulcers have been reported in many anticancer therapies, occurring in 20–90% of patients treated with anticancer agents (Curra et al. 2018). However, other drugs such as methotrexate and cocaine have also been reported to cause mouth ulcers (Sardana et al. 2014). Mouth ulcers are an important adverse event (AE) closely related to patients' quality of life; however, comprehensive studies on causative drugs have not been conducted.

The coronavirus disease 2019 (COVID-19) outbreak is one of the world's central health crises and affects people worldwide (Shanafelt et al. 2020). The COVID-19 messenger ribonucleic acid (mRNA) vaccine is an essential agent for the prevention of infection and severe disease resulting from COVID-19 virus infection (Mascellino et al. 2021). Therefore, the vaccine is administered to approximately one million people worldwide daily (Our World in Data 2022). However, there is a report of AE of palatal-mucosal ulceration after COVID-19 mRNA vaccination in Japanese patients (Maeda et al. 2022). It is unclear whether mouth ulcers are characteristic AEs of the COVID-19 mRNA vaccine. Since most Japanese people have been vaccinated with the COVID-19 mRNA vaccine, it would be useful to conduct a comprehensive survey of the number of reported mouth-ulcer cases caused by the COVID-19 mRNA vaccine to determine whether this is a characteristic AE.

In recent years, the number of reports from spontaneous reporting systems has increased, offering an important source of information as a large-scale database for the detection of drug-induced AEs (Kim et al. 2022). The Pharmaceuticals and Medical Devices Agency (PMDA), the Japanese regulatory authority, has comprehensively accumulated AE reports related to pharmaceuticals, and these have been published in the Japanese Adverse Drug Event Report (JADER) database. To date, the JADER database has been used to comprehensively investigate the relationship between drugs and adverse drug events (Tanaka et al. 2021).

Investigating the reported status of COVID-19 mRNA vaccine-induced mouth ulcers is important for predicting the onset of the disease, enabling early treatment, and improving patient quality of life. In this study, the JADER database was used to extensively investigate the occurrence of mouth ulcers and characteristics of these cases associated with the COVID-19 mRNA vaccine.

2. Investigations, results and discussion

2.1. Ten most frequently reported drugs for mouth ulcers

The total number of cases reported in the JADER database from April 2004 to March 2022 was 775,555, with 4,661 cases of mouth ulcers (Fig. 1). A total of 677 drugs were identified as causative drugs of mouth ulcers. The ten most frequently reported drugs were tegafur/gimeracil/oteracil potassium (498 cases), methotrexate (415 cases), everolimus (299 cases), lamotrigine (246 cases), fluorouracil (243 cases), cisplatin (232 cases), capecitabine (206 cases), COVID-19 mRNA vaccine (nucleoside-modified) (204 cases), doxorubicin hydrochloride (176 cases), and irinotecan hydrochloride hydrate (138 cases) (Table 1). Their reporting ratios

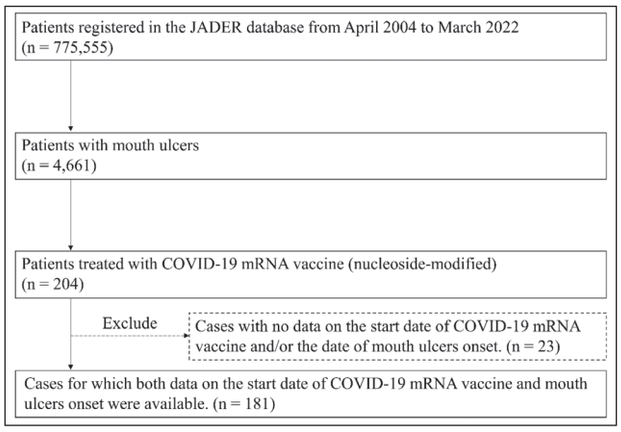

Fig. 1: Flowchart outlining the construction of the dataset used for analysis.

Table 1: Causative drugs of mouth ulcers in the JADER database

Causative drug[a]	Cases (n)	Non-Cases (n)	Total (n)	RR[b] (%)
Tegafur/gimeracil/oteracil potassium	498	7508	8006	6.2
Methotrexate	415	24800	25215	1.6
Everolimus	299	4324	4623	6.5
Lamotrigine	246	3898	4144	5.9
Fluorouracil	243	9493	9736	2.5
Cisplatin	232	10493	10725	2.2
Capecitabine	206	4427	4633	4.4
COVID-19 mRNA vaccine (nucleoside-modified)	204	21289	21493	0.9
Doxorubicin hydrochloride	176	5778	5954	3.0
Irinotecan hydrochloride hydrate	138	6843	6981	2.0
Recombinant-adsorbed-bivalent human papillomavirus-like particle vaccine (derived from *Trichoplusia ni* cells)	14	1911	1925	0.7
Influenza HA vaccine	12	3560	3572	0.3
Pneumococcal vaccine	8	1896	1904	0.4
Freeze-dried, cell-culture-derived Japanese encephalitis vaccine	4	608	612	0.7
Recombinant-adsorbed-quadrivalent human papillomavirus virus-like particle vaccine (yeast origin)	4	511	515	0.8
Recombinant-adsorbed hepatitis b vaccine (yeast-derived)	2	1246	1248	0.2
Freeze-dried BCG vaccine	1	452	453	0.2
Freeze-dried inactivated-tissue-culture rabies vaccine	1	23	24	4.2
Freeze-dried live-attenuated varicella vaccine	1	396	397	0.3
Inactivated poliomyelitis vaccine	1	76	77	1.3

[a] Drugs reported as "suspect drug" and "interaction" were newly defined as "causative drug". [b] RR: case/total×100. RR, reporting ratio.

(RRs) were 6.2%, 1.6%, 6.5%, 5.9%, 2.5%, 2.2%, 4.4%, 0.9%, 3.0%, and 2.0%, respectively. Eight of the top ten drugs are cancer treatments but also include mRNA vaccines, for the prevention of COVID-19 infection, and lamotrigine.

A systematic review of mouth ulcers caused by the COVID-19 mRNA vaccine until June 18, 2022, reported 11 case reports and a case series describing 16 cases (Di Spirito et al. 2022). This number of reports seems small considering that 68.2% of the global population has received at least one dose of the COVID-19 mRNA vaccine (Our World in Data 2022). However, despite the short amount of time since its launch, 204 cases of mouth ulcers caused by the COVID-19 mRNA vaccine were reported in the Japanese database, suggesting that more cases may be reported worldwide. Further studies using a global AE database are needed to determine whether these AEs are unique to the Japanese population.

2.2. Signal analysis of vaccines by reporting odds ratio

In addition to the COVID-19 mRNA vaccine, ten other vaccines were identified as causative drugs of mouth ulcers in this study (Table 1). The reporting odds ratio (ROR) of the COVID-19 mRNA vaccine was 1.6 (95% confidence interval [CI], 1.4–1.9) and a signal was detected. However, no signal was detected for the ten other vaccines. The number of reports and RORs (95% CI) for each of these vaccines were as follows: recombinant-adsorbed-bivalent human papillomavirus-like particle vaccine (derived from *Trichoplusia ni* cells) (14 cases, 1.2 [95% CI, 0.7–2.1]); influenza HA vaccine (12 cases, 0.6 [95% CI, 0.3–1.0]); pneumococcal vaccine (eight cases, 0.7 [95% CI, 0.3–1.4]); freeze-dried, cell culture-derived Japanese encephalitis vaccine (four cases, 1.1 [95% CI, 0.4–2.9]); recombinant-adsorbed-quadrivalent human papillomavirus virus-like particle vaccine (yeast origin) (four cases, 1.3 [95% CI, 0.5–3.5]); recombinant-adsorbed hepatitis b vaccine (yeast-derived) (two cases, 0.3 [95% CI, 0.1–1.1]); freeze-dried Bacille Calmette-Guerin (BCG) vaccine (one case, 0.4 [95% CI, 0.1–3.0]); freeze-dried inactivated-tissue-culture rabies vaccine (one case, 7.2 [95% CI, 1.0–53.3]); freeze-dried live-attenuated varicella vaccine (one case, 0.4 [95% CI, 0.1–2.6]); and inactivated poliomyelitis vaccine (one case, 2.2 [95% CI, 0.3–15.7]).

The number of people vaccinated against influenza HA in Japan from 2004 to 2020 was approximately 273,000,000 (Ministry of Health, Labour and Welfare 2022). The number of people who received COVID-19 mRNA vaccine from the start of vaccination on 2/17/2021 to 3/31/2022 was approximately 255,000,000 (Prime Minister's Office of Japan 2022). The COVID-19 mRNA vaccine had a higher number of mouth-ulcer reports compared with that of the influenza HA vaccine, even though fewer people were vaccinated. A case of Stevens-Johnson syndrome with mouth ulcers after influenza vaccination has been previously reported (Oda et al. 2017). However, there are no reports of an increased occurrence of mouth ulcers with the ten vaccines detected in this study. Currently, reports of mouth ulcers caused by COVID-19 mRNA vaccines are primarily case reports (Maeda et al. 2022; Caggiano et al. 2022; Sharda et al. 2022). This is due to the fact that the vaccine is a new mRNA vaccine that has just been launched, and further clinical reports may follow. On the other hand, mouth ulcers caused by COVID-19 mRNA vaccines has been reported more frequently now due to the Weber phenomenon and may decrease over time (Wallenstein et al. 2001). Therefore, there are insufficient data on oral lesions after vaccination. Further clinical reports and mechanistic analyses of COVID-19 mRNA vaccines focusing on mouth ulcers are needed.

2.3. Characteristic cases of COVID-19 mRNA and influenza HA vaccines

Data on characteristic cases of COVID-19 mRNA and influenza HA vaccines are presented in Table 2. Among COVID-19 mRNA vaccines, Comirnaty (Pfizer-BioNTech, NY, USA and Magonza, Germany) and Spikevax (Moderna, Cambridge, MA, USA) had 172 and 9 cases of mouth ulcers, respectively. However, the JADER database study cannot be compared by incidence rate because the population of reported cases is not known. There are reports that Moderna's vaccine has twice as many reports of AEs compared with Pfizer-BioNTech's vaccine; however, few reports compare the incidence of mouth ulcers (Beatty et al. 2021). Large multicenter-clinical studies are needed to elucidate the incidence of mouth ulcers resulting from different-manufacturer COVID-19 mRNA vaccines.

Table 2: Characteristics of the COVID-19 mRNA or influenza HA vaccine cases from the JADER database

	COVID-19 mRNA vaccine (nucleoside-modified)		Influenza HA Vaccine (n = 11)
	Pfizer-BioNTech (n = 172)	Moderna (n = 9)	
Sex, No. (%)			
Male	38 (22.1)	5 (55.6)	4 (36.4)
Female	131 (76.2)	4 (44.4)	7 (63.6)
Unknown	3 (1.7)	0 (0.0)	0 (0.0)
Age (years old), No. (%)			
< 10	0 (0.0)	0 (0.0)	0 (0.0)
10–19	19 (11.0)	1 (11.1)	0 (0.0)
20–29	25 (14.5)	3 (33.3)	2 (18.2)
30–39	27 (15.7)	0 (0.0)	1 (9.1)
40–49	34 (19.8)	1 (11.1)	3 (27.3)
50–59	24 (14.0)	3 (33.3)	3 (27.3)
60–69	17 (9.9)	0 (0.0)	0 (0.0)
70–79	11 (6.4)	1 (11.1)	1 (9.1)
80–89	6 (3.5)	0 (0.0)	0 (0.0)
90–99	2 (1.2)	0 (0.0)	1 (9.1)
Unknown	7 (4.1)	0 (0.0)	0 (0.0)
Outcome, No. (%)			
Recovery	71 (41.3)	2 (22.2)	5 (45.5)
Improvement	47 (27.3)	5 (55.6)	4 (36.4)
Sequelae	3 (1.7)	0 (0.0)	0 (0.0)
Unrecovered	21 (12.2)	1 (11.1)	0 (0.0)
Death	1 (0.6)	0 (0.0)	0 (0.0)
Unknown	29 (16.9)	1 (11.1)	2 (18.2)

In this study, Pfizer-BioNTech's COVID-19 mRNA vaccine was associated with a higher incidence of mouth ulcers in females than in males (76.2% vs. 22.1%). In previous studies, 68.8% of oral lesions and 90% of skin reactions due to vaccination were reported in females (Di Spirito et al. 2022; McMahon et al. 2021). Females usually exhibit stronger immune responses than males, with antibody titers twice as high as those of males. The exact mechanism of these sex differences is not fully understood, but it is believed to be as a result of sex hormones affecting the immune system (Klein et al. 2016). It has also been reported that higher immune reactivity in females is associated with vaccination-induced AEs (Italian Medicines Agency 2022). Thus, in Pfizer-BioNTech's vaccine, differences in immune response by sex may influence sex differences in mouth ulcers incidence. The incidence of mouth ulcers in males and females due to Moderna's vaccine was almost equal (44.4% of females vs. 55.6% of males); however, the small number of reports makes this difficult to identify gender differences in the incidence of mouth ulcers caused by the Moderna vaccine.

In the present study, the incidence of mouth ulcers was higher in those < 60 years-of-age than in those ≥ 60 years-of-age for both vaccines (incidence in cases < 60 years-of-age: Pfizer-BioNTech, 75.0%; Moderna, 88.9%). The number of cases also decreased with increasing age. Previous reports on AEs of COVID-19 mRNA vaccines have shown that younger patients have a higher incidence of systemic AEs, such as fever, than older patients (Izumo et al. 2021). This is thought to be due to an age-related decline in immune function (Goronzy et al. 2013). A similar trend was observed in this study, both for systemic symptoms and mouth ulcers, a local AE; this is a novel finding.

The trends in the incidence of mouth ulcers after influenza-HA vaccine administration by sex and age were similar to those of the COVID-19 mRNA vaccine. However, with regard to outcomes, there were no unrecovered cases with the influenza HA vaccine, whereas there were unrecovered cases with the COVID-19 mRNA vaccine (Pfizer-BioNTech, 12.2%; Moderna, 11.1%) (Table 2). Despite the few years that the COVID-19 mRNA vaccine has been on the market, several cases of severe symptoms with mouth ulcers such as toxic epidermal necrolysis and Stevens-Johnson syndrome have been reported (Marcelino et al. 2022; Mansouri et al. 2021; Bakir et al. 2021). One of the unrecovered patients in this study was also enrolled in the Stevens-Johnson syndrome group. Although detailed information on individual patients cannot be examined in this study because it is a database study, the possibility that the number of unrecovered cases of mouth ulcers increased due to complications of serious skin and mucous membrane diseases cannot be ruled out.

2.4. Mouth-ulcer onset time for the COVID-19 mRNA and influenza HA vaccines

Analysis of mouth-ulcer onset time for the COVID-19 mRNA and influenza HA vaccines showed that each vaccine tended to cause mouth ulcers within nine days for Pfizer-BioNTech, three days for Moderna, and six days for the influenza HA vaccine (Fig. 2). The median time-to-onset was two days for the COVID-19 mRNA vaccine and one day for the influenza HA vaccine. In a previous report, the duration of onset of oral lesions from the COVID-19 mRNA vaccine ranged from 1–30 days and has been reported as a delayed (>24 h) type of AE (Di Spirito et al. 2022). The results of this study are similar to a previous report, as the median time-of-onset of mouth ulcers for the influenza HA vaccine is an acute-type AE of one day, whereas for the COVID-19 mRNA vaccine it is a delayed-type AE of two days. A comparison of the time-of-onset of mouth ulcers with different vaccines may eliminate differences in the time interval between vaccination and the appearance of oral lesions. Therefore, the fact that mouth ulcers caused by the COVID-19 mRNA vaccine are a delayed AE is important information that may be useful in clinical practice.

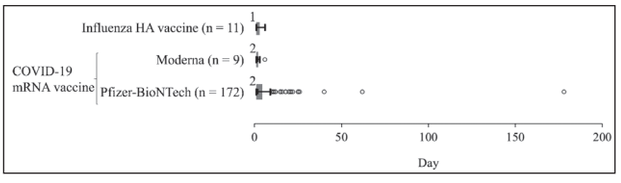

Fig. 2: Box chart for time-to-onset of mouse ulcers associated with COVID-19 mRNA and influenza HA vaccines. Vaccine-related mouth ulcers: Pfizer-BioNTech vaccine (n = 172), Moderna vaccine (n = 9), and influenza HA vaccine (n = 11). Box plots show the 25th quartile, 75th quartile, and median (Pfizer-BioNTech vaccine, 2; Moderna vaccine, 2; and influenza HA vaccine, 1). The whiskers present the maximum and minimum values within 1.5 times the inner-quartile point's length. The box's outside values represent the outliers.

The present study has several limitations. First, serious AEs may have been reported preferentially. Second, we excluded reports with missing data, such as date of administration initiation. Third, the COVID-19 mRNA vaccine has only recently been launched, and the number of cases is limited. Fourth, the influence of concomitant medications cannot be completely eliminated.

The COVID-19 mRNA vaccine ranks in the top ten in a survey of the causative drugs of mouth ulcers using the JADER database. COVID-19 mRNA vaccine mouth-ulcer cases were characterized by a higher number of female and young adult cases. In addition, unlike the influenza HA vaccine, unrecovered mouth ulcers and delayed AEs have been reported, possibly because it is a new form of mRNA vaccine. These findings indicate that mouth ulcers are one of the AEs to monitor for when administering the COVID-19 mRNA vaccine. This study will help improve the early detection and treatment of oral mucositis with COVID-19 mRNA vaccine administration.

3. Experimental

3.1. Data source

The JADER database is publicly available and can be downloaded from the PMDA website (https://www.pmda.go.jp; accessed on July 16, 2022). This study used data reported from April 2004 to March 2022. The data structure consists of four sets: patient demographic information, such as sex, age, and reporting year (DEMO); drug information, such as the name of the prescribed drug, pharmaceutical involvement, and start and end dates of administration (DRUG); AEs information, including the type, outcome, and date of onset (REAC); and medical history information (HIST). The DRUG file includes the role codes assigned to each drug: suspected, concomitant, and interacting drugs. Suspected and interacting drug records were extracted and newly defined as "causative drugs". Duplicate drug names in the DRUG file reported for the same case identification number (ID) were subsequently deleted.

3.2. Definition of mouth ulcers

The AEs in the JADER database were defined using the Medical Dictionary for Regulatory Activities/Japanese (MedDRA/J; https://www.jmo.pmrj.jp/ accessed on September 24, 2022). In the present study, mouth ulcers were defined using 20 preferred terms in MedDRA/J ver. 25.1 (Table 3). Duplicate mouth-ulcer cases in the REAC file reported for the same case ID were subsequently deleted.

Table 3: Definition of mouth ulcers

PT code	PT name
10002959	Aphthous ulcer
10018386	Glossitis
10024572	Lip ulceration
10028034	Mouth ulceration
10030094	Odynophagia
10030995	Oral mucosal blistering
10031009	Oral pain
10034834	Pharyngeal ulceration
10042128	Stomatitis
10042132	Stomatitis haemorrhagic
10042135	Stomatitis necrotising
10043942	Tongue blistering
10043991	Tongue Ulceration
10051992	Lip erosion
10062773	Pharyngeal erosion
10064594	Oral mucosa erosion
10065716	Pharyngeal inflammation
10067950	Oropharyngeal blistering
10068319	Oropharyngeal pain
10077519	Palatal ulcer

Mouth ulcers was defined as a condition associated with several Medical Dictionary for Regulatory Activities (MedDRA/J ver. 25.1) preferred terms. PT, Preferred terms.

3.3. RR and ROR

The RR for each drug is the number of mouth-ulcer cases divided by the total number of cases for that drug. Signal detection of the causative drug of mouth ulcers was performed using the ROR (van Puijenbroek et al. 2002). The ROR was calculated using a two-by-two contingency table divided by the presence or absence of drug use and the occurrence of specific AEs. A signal was considered to be present if the lower limit of the calculated ROR's 95% CI was > 1.

3.4. Time-to-onset analysis

COVID-19 mRNA and influenza HA vaccines were analyzed for time-to-onset of mouth ulcers. The number of days from the start of treatment to the onset of mouth ulcers was calculated using the date of treatment initiation and onset of AEs from the JADER dataset. Patients with no data on the date of treatment initiation and AE onset were excluded. If there was more than one start date for treatment, the first start date prior to AE onset was used in the analysis. Box-and-whisker plots were created to determine the relationship between each drug and the number of days before AE onset, and the median values were compared.

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