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ORIGINAL ARTICLE

Side Effects of COVID-19 Vaccines in Patients with Inflammatory Bowel Disease in Japan

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Abstract

Background Patients with inflammatory bowel disease (IBD) are recommended to receive the coronavirus disease 2019 (COVID-19) vaccine. However, a recent survey showed that patients with IBD are more hesitant to receive the vaccine than the general population. Detailed information on the side effects of the COVID-19 vaccine is necessary to encourage vaccination among patients with IBD.

Aim To investigate the frequency of side effects following COVID-19 vaccination in patients with IBD in Japan. Study design: a cross-sectional survey was conducted using a questionnaire administered to adult patients with IBD in a tertiary medical facility.

Results Among the participants who answered the questionnaire, 92.6%, 91.5%, and 41.5% of the participants had received their first, second, and third doses of the COVID-19 vaccine, respectively. Of the vaccinated participants, 88.3%, 86.3%, and 89.0% experienced side effects after receiving the first, second, and third doses of the vaccine, respectively. The incidences of fever, chills, and headaches were significantly higher among female participants than among male participants ($p < 0.05$). However, the frequencies of most side effects were comparable between the BNT162b2 mRNA and mRNA-1273 vaccines.

Conclusion The findings of our survey can help encourage patients with IBD to receive the COVID-19 vaccine.

Keywords COVID-19 vaccine · Inflammatory bowel disease · Side effects · Hesitancy

Introduction

A novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged at the end of 2019 in the City of Wuhan, China, causing an outbreak of an unusual viral pneumonia known as coronavirus disease 2019 (COVID-19) [1, 2]. Exposure to SARS-CoV-2 can result in clinical outcomes ranging from asymptomatic infection to severe acute respiratory distress and death [3]. COVID-19 is highly transmissible and has rapidly spread across the world [4, 5]. The first vaccinations approved by the United States Food and Drug Administration for mass immunization were the BNT162b2 mRNA (Comirnaty, Pfizer-BioNTech) and the mRNA-1273 (Spikevax, Moderna) vaccines. Health care workers (HCWs) received the first dose of these vaccines in December 2020 in the USA. To date, several vaccines have been developed against COVID-19, including the BNT162b2, mRNA-1273, and ChAdOx1 nCoV-19 (Vaxzevria, AstraZeneca) vaccines, which have efficacies of 95%, 94.1%, and 70.4%, respectively [6, 7].

The rapid development of multiple vaccines has contributed to the protection against SARS-CoV-2 infection worldwide. A recent study showed that either one dose of the BNT162b2 or ChAdOx1-S vaccine was associated with a significant reduction in symptomatic infections among older adults. It also offered enhanced protection against severe disease [8]. Both vaccines showed similar outcomes, and the vaccine effectiveness against SARS-CoV-2 infection remained competent for more than 6 weeks. In addition, a second dose of the BNT162b2 vaccine offered further protection against symptomatic disease.

However, short-term side effects related to these COVID-19 vaccines are frequently observed [9]. Participants in the registration trials for the BNT162b2 or ChAdOx1-S vaccine described pain at the injection site, fatigue, and headache as

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the most common side effects [10–13]. In addition, systemic symptoms, such as fatigue and headache, were reported in over 50% of the recipients who received the second dose [11, 12, 14]. Similarly, cross-sectional studies revealed that up to 66% of vaccinated recipients reported at least one generalized symptom, such as weakness, fatigue, headache, chills and fever [15, 16]. Moreover, due to the side effects related to the COVID-19 vaccine, 25% of HCWs had trouble performing their daily activities shortly after vaccination [16]. These issues can lead to hesitation in receiving vaccination against SARS-CoV-2 infection. The vaccine hesitancy or rejection rates are still high in Japan [17]. Furthermore, vaccine hesitancy has been linked to negative beliefs that vaccination is unsafe and could cause adverse side effects [18].

As per recommendations for the management of inflammatory bowel disease (IBD), all patients with IBD should receive the COVID-19 vaccine immediately, as several studies have shown that there is no increased risk of flares after vaccination [19]. However, information on the side effects of COVID-19 vaccination in patients with IBD is lacking. A novel technology deployed for the BNT162b2 mRNA and mRNA-1273 vaccines involves nucleic acid vaccines [20]. Nucleic acid-based vaccine technology employs either antigen-encoding plasmid DNA or RNA as messenger RNA or viral replicons. Technically, mRNA vaccines can encode any antigen of choice and allow a high degree of adaptability. Then, they can induce both humoral and cellular immune responses. Therefore, considering that patients with IBD have abnormal immune responses, it is natural that they have a fear of precipitating an IBD flare. Accordingly, a recent study showed that patients with IBD are more hesitant to receive vaccines than the general population [21]. This hesitancy stems mainly from the uncertainties surrounding the safety and efficacy of vaccines and government distrust [22].

Therefore, we aimed to investigate the frequency of side effects following COVID-19 vaccination in patients with IBD in Japan by conducting a cross-sectional questionnaire survey in a tertiary medical facility.

Methodology

Study Design

To assess the side effects of COVID-19 vaccines, we conducted a cross-sectional survey based on a questionnaire administered to patients with IBD at Kobe University from March 2022 to May 2022. We included patients who received Japanese medical care certificates for intractable diseases. The study participants were adults aged 20 years or older. Eligible participants were patients with IBD who had Japanese recipient certificates issued for specific disease treatment, such as ulcerative colitis (designated intractable disease No. 97 by the Japan Ministry of Health, Labor and Welfare) and Crohn's disease (designated intractable disease No. 96 by the Japan Ministry of Health, Labor and Welfare). We confirmed that all eligible patients had IBD symptoms or continued with medical treatment for IBD. Eligible participants were asked to take part in our study, and the questionnaires were distributed during regular visits to Kobe University Hospital. We excluded those who refused to participate. The self-administered questionnaire was written in Japanese and included the following items: (1) basic information (i.e., type of vaccine received and number of vaccine doses previously received) and (2) COVID-19 vaccine-related side effects after the first, second, or third doses. COVID-19 vaccine-related side effects in the questionnaire consisted of 12 items as follows: (1) No symptoms, (2) Pain at the site of injection, (3) Fever or Chills, (4) Fatigue, (5) Headache, (6) Muscle pain, (7) Joint pain, (8) Abdominal pain, (9) Nausea, (10) Allergy, (11) Myocarditis and (12) IBD exacerbation. The participants were given the questionnaires and instructed to check the symptoms that they experienced following COVID-19 vaccination. We retrieved general information, such as sex and disease type, from the medical records of the participants from Kobe University Hospital.

Data Analysis and Ethical Considerations

Descriptive statistics were used to generate summary tables for the study variables. A cross-tabulation analysis using the χ^2 test was performed to examine the associations between the frequencies of side effects following COVID-19 vaccination and sex or vaccine type. A two-tailed p value of less than 0.05 was considered statistically significant. The survey protocol was conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Ethical Committee of Kobe University Graduate School of Medicine (approval no. B210288).

Results

COVID-19 Vaccine-Related Side Effects in Patients with Inflammatory Bowel Disease

A total of 212 patients had Japanese recipient certificates issued for the treatment of ulcerative colitis or Crohn's disease at Kobe University Hospital; 146 patients had ulcerative colitis, and 66 patients had Crohn's disease. Of these 212 patients, 179 visited our hospital and completed the questionnaire; three questionnaires were excluded because they were incomplete. Among the 176 patients who answered the questionnaire, 92.6% (163/176), 91.5% (161/176), and 41.5% (73/176) of participants had received their first,

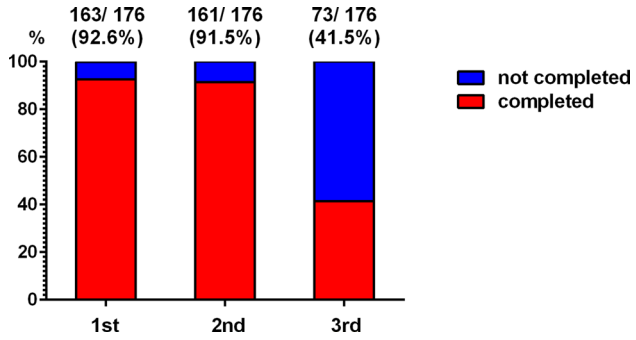

Fig. 1 The number of participants who received their first, second, and third doses of the COVID-19 vaccine

second, and third doses of the COVID-19 vaccine, respectively (Fig. 1).

Of the participants who had received the COVID-19 vaccine, 88.3% (144/163), 86.3% (139/161), and 89.0% (65/73) of the participants experienced side effects after receiving their first, second, and third doses of the vaccine, respectively (Table 1; Fig. 2). In addition, 116, 107, and 52 of the participants (71.2%, 66.5%, and 71.2%) experienced local side effects following their first, second, and third doses of the COVID-19 vaccine, respectively, while 61.3%, 68.9%, and 61.6% (100/163, 111/161, and 45/73) experienced systemic side effects following their first, second, and third doses of the COVID-19 vaccine, respectively (Table 1; Fig. 2).

Table 1 Frequencies of side effects in 1st to 3rd dose of COVID-19 vaccine

Side effects	Frequency		
	1st dose ($n=163$)	2nd dose ($n=161$)	3rd dose ($n=73$)
Local symptom			
Pain at the site of injection	116/163 (71.2%)	107/161 (66.5%)	52/73 (71.2%)
Systemic symptoms	100/163 (61.3%)	111/161 (68.9%)	45/73 (61.6%)
Fever or Chills	47/163 (28.8%)	72/161 (44.7%)	25/73 (34.2%)
Fatigue	50/163 (30.7%)	59/161 (36.6%)	20/73 (27.4%)
Headache	25/163 (15.3%)	35/161 (21.7%)	14/73 (19.2%)
Muscle pain	68/163 (41.7%)	61/161 (37.9%)	27/73 (37.0%)
Joint pain	21/163 (12.9%)	28/161 (17.4%)	10/73 (13.7%)
Abdominal pain	1/163 (0.6%)	2/161 (1.2%)	2/73 (2.7%)
Nausea	2/163 (1.2%)	3/161 (1.9%)	4/73 (5.5%)
Allergy	0/163 (0%)	0/161 (0%)	0/73 (0%)
Others			
Myocarditis	0/163 (0.0%)	0/161 (0.0%)	0/73 (0%)
Disease exacerbation in IBD	1/163 (0.6%)	2/161 (1.2%)	1/73 (1.4%)
Any side effects	144/163 (88.3%)	139/161 (86.3%)	65/73 (89.0%)

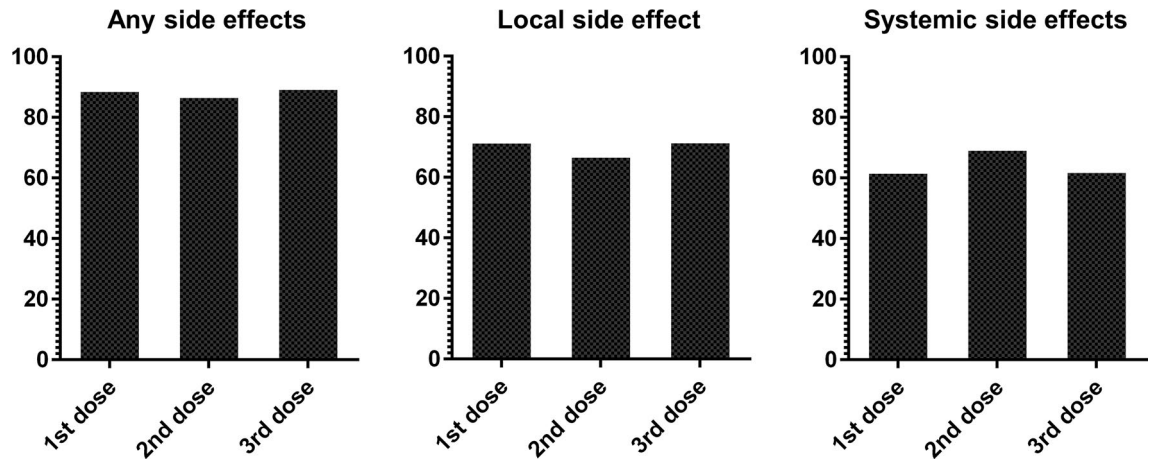

Fig. 2 The number of participants who experienced any local or systemic side effects following COVID-19 vaccination

Detailed data on the frequency of side effects for each dose are summarized in Table 1. Fever or chills, fatigue, and muscle pain were the most commonly reported systemic side effects among the study participants. Of the participants who answered the questionnaire, 28.8%, 44.7%, and 34.2% of participants who received their first, second, and third doses of COVID-19 vaccine reported fever or chills, respectively. Gastrointestinal symptoms, such as abdominal pain and nausea, were reported less frequently following COVID-19 vaccination. None of the participants experienced myocarditis, and only five participants reported IBD exacerbation following vaccination.

Correlation Between Reported Side Effects of the COVID-19 Vaccine and Sex

Data regarding the correlation between the side effects of the COVID-19 vaccine and sex are summarized in Table 2 and Fig. 3. Local symptoms (i.e., pain at the injection site) following the first and second doses of the COVID-19 vaccine were comparable between male and female participants (70.4% vs. 72.0% and 65.8% vs. 67.1%). On the other hand, the frequencies of several systemic symptoms following COVID-19 vaccination differed between male and female participants (Table 2; Fig. 3). For instance, the frequencies of fever, chills, and headaches were significantly higher among female participants than among male participants ($p < 0.05$). However, the frequency of

Table 2 Differences of side effects after COVID-19 vaccine between male and female

Side effects	Frequency					
	After 1st dose of COVID-19 vaccine			After 2nd dose of COVID-19 vaccine		
	Male	Female	*p*-value	Male	Female	*p*-value
Local symptom						
Pain at the site of injection	57/81 (70.4%)	57/82 (72.0%)	N.S	52/79 (65.8%)	53/82 (67.1%)	N.S
Systemic symptoms						
Fever or Chills	16/81 (19.8%)	31/82 (37.8%)	< 0.05	27/79 (34.2%)	45/82 (54.9%)	< 0.05
Fatigue	19/81 (23.5%)	31/82 (37.8%)	< 0.05	25/79 (31.6%)	33/82 (41.5%)	N.S
Headache	6/81 (7.4%)	19/82 (23.2%)	< 0.05	10/79 (12.7%)	25/82 (30.5%)	< 0.05
Muscle pain	32/81 (39.5%)	36/82 (43.9%)	N.S	28/79 (35.4%)	31/82 (30.2%)	N.S
Joint pain	7/81 (8.6%)	14/82 (17.1%)	N.S	8/79 (10.1%)	20/82 (24.4%)	< 0.05
Abdominal pain	0/81 (0%)	1/82 (1.2%)	N.S	1/79 (1.3%)	1/82 (1.2%)	N.S
Nausea	0/81 (0%)	2/82 (2.4%)	N.S	1/79 (1.3%)	2/82 (2.4%)	N.S
Any systemic side effects	43/81 (53.1%)	57/79 (69.5%)	< 0.05	49/79 (62.0%)	62/82 (75.6%)	N.S

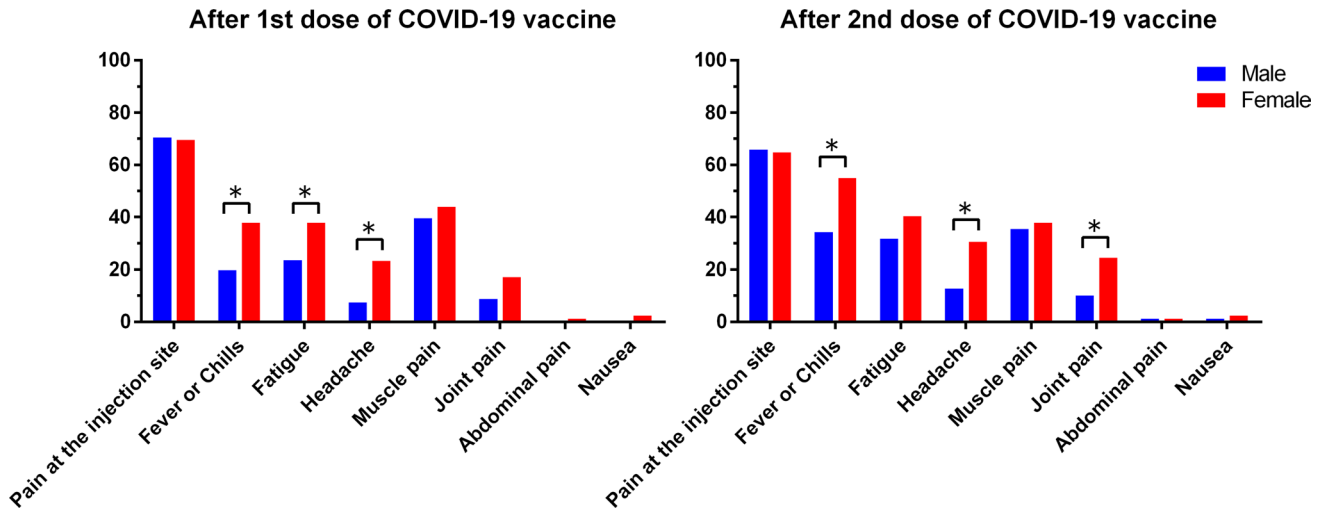

Fig. 3 Association of COVID-19 vaccine side effects with sex differences among patients with IBD

muscle pain was comparable between male and female participants (Table 2; Fig. 3).

Correlation Between Reported Side Effects of the COVID-19 Vaccine and Vaccine Type

Among the 212 participants, 126 (77.3%), 36 (22.1%), and 1 (0.6%) participant received the BNT162b2, mRNA-1273, and other types of vaccines as their first dose, respectively. A total of 125 (77.6%), 35 (21.7%) and 1 (0.6%) participant received a second dose of BNT162b2, mRNA-1273, and other types of vaccines, respectively. For the third dose, 39 (53.4%), 33 (45.2%), and 1 (1.4%) participant received BNT162b2, mRNA-1273, and other types of vaccines, respectively. The frequencies of local side effects reported by individuals who received their first and second doses of the BNT162b2 vaccine were comparable to those who received the mRNA-1273 vaccine (73.8% vs. 63.9% and 67.2% vs. 65.7%, respectively). However, fever or chills were more prevalent among participants who received a second dose of mRNA-1273 vaccine than among those who received the BNT162b2 vaccine. Other systemic side effects were not significantly associated with the first and second doses of either vaccine (Table 3).

Discussion

Although there are no data, the aberrant immune response that is usually present in patients with IBD can cause an unexpected side effect against COVID-19 vaccines, which may lead to anxiety in patients. Therefore, information about the side effects of COVID-19 vaccines is important. Previous meta-analyses showed that local and systemic side effects were observed in 66.7% and 46.2% of COVID-19 vaccinated individuals, respectively. Headache, fever, pain, fatigue, and nausea were the most common side effects [23, 24]. In the present study, most participants received the BNT162b2 vaccine, which is a messenger RNA vaccine that has a 95% efficacy against SARS-CoV-2 [12, 25]. It has been reported that the BNT162b2 vaccine is associated with high incidence rates of all types of side effects [26]. Following the BNT162b2 vaccine, the mRNA-1273 vaccine was the second most received vaccine. The most reported side effects following the mRNA-1273 vaccine include pain at the injection site, headache, fatigue, muscle pain, malaise, chills, joint pain, mucosal lesions, oral paresthesia, taste disturbance, pruritus, rash, itchy sensations in the mouth and throat, sensations of throat closure, muscle spasms, anorexia, decreased sleep quality, diarrhea, flushing, nasal stiffness, and respiratory symptoms [9]. Consistent with previous studies that showed a high incidence of side effects following COVID-19 vaccination, our survey also showed that most participants experienced several types of side effects.

Regarding the association between the frequency of side effects and sex of the participant, there are reports that demonstrated that female sex was associated with higher frequencies of side effects following vaccination [9, 23, 27]. However, a previous study reported a correlation between male sex and increased side effects of vaccination [28]. This study was conducted in Germany, where the two mRNA vaccines (i.e., the BNT162b2 and mRNA-1273 vaccines), as well as the vector vaccine (ChAdOx1 nCoV-19), were mainly administered [28]. Compared with our survey, the total frequency of documented side effects was low (i.e., 3.1% of all vaccinated individuals), which may explain the discrepancy between the results from our study and this study [28].

Table 3 Differences of side effects after COVID-19 vaccine among vaccine type

Side effects	Frequency					
	After 1st dose of COVID-19 vaccine			After 2nd dose of COVID-19 vaccine		
	Pfizer	Moderna	*p*-value	Pfizer	Moderna	*p*-value
Local symptom						
Pain at the site of injection	93/126 (73.8%)	23/36 (63.9%)	N.S	84/125 (67.2%)	23/35 (65.7%)	N.S
Systemic symptoms						
Fever or Chills	37/126 (29.4%)	10/36 (27.8%)	N.S	50/125 (40.0%)	22/35 (62.9%)	<0.05
Fatigue	43/126 (34.1%)	7/36 (19.4%)	N.S	48/125 (38.4%)	11/35 (31.4%)	N.S
Headache	21/126 (16.7%)	4/36 (11.1%)	N.S	27/125 (21.6%)	8/35 (22.9%)	N.S
Muscle pain	53/126 (42.1%)	14/36 (38.9%)	N.S	49/125 (39.2%)	11/35 (31.4%)	N.S
Joint pain	17/126 (13.5%)	3/36 (8.3%)	N.S	22/125 (17.6%)	5/35 (14.3%)	N.S
Abdominal pain	1/126 (0.8%)	0/36 (0%)	N.S	1/125 (0.8%)	1/35 (2.9%)	N.S
Nausea	2/126 (1.6%)	0/36 (0%)	N.S	2/125 (1.6%)	1/35 (2.9%)	N.S
Any systemic side effects	82/126 (65.1)	17/36 (47.2%)	N.S	85/125 (68.0%)	25/35 (71.4%)	N.S

Some reports have demonstrated that the type of vaccine leads to differences in the frequency of side effects following vaccination (e.g., between the BNT162b2 and mRNA-1273 vaccines). For instance, individuals who received the mRNA-1273 vaccine experienced side effects more frequently than those who received other vaccines [23, 29, 30]. However, our survey did not show the same results. Thus, further studies are needed to assess the association between the frequency of side effects and vaccine type.

Hesitancy for COVID-19 vaccination might pose a problem in protecting patients with IBD from COVID-19. All patients with IBD, including those taking immunosuppressants, are recommended to receive vaccination, as studies have shown that there is no increased risk of flares after immunization [19, 31]. Nevertheless, a recent study showed that patients with IBD were more hesitant to receive vaccination compared to the general population; 58.5% of patients with IBD planned to get vaccinated or were vaccinated, which was significantly lower than the percentage of control patients who planned to get vaccinated or were vaccinated (65.1%, $p=0.013$) [21]. Therefore, we examined the number of participants who had received the COVID-19 vaccine. Our survey showed that most participants had already received the first and second doses of a COVID-19 vaccine (92.6% and 91.5%), suggesting that most patients with IBD who visit Japanese tertiary centers believe that the vaccine is effective in protecting them against COVID-19.

One limitation of this study was its reliance on self-reporting for data collection. Recall bias may have affected the study because the participants were interviewed after receiving the vaccine. Second, the study was conducted only on participants who visited our Department at Kobe University Hospital. Third, the sample size of this study was small. Further investigations are needed to confirm the results of this study.

In conclusion, more than half of the patients with IBD experienced side effects associated with the COVID-19 vaccine. Our study suggested that female sex was associated with a higher incidence of side effects following COVID-19 vaccination, but there was no significant difference between the BNT162b2 and mRNA-1273 vaccines. The findings of our survey provide additional information on the side effects of the COVID-19 vaccine in patients with IBD, which clinicians can use to help encourage vaccination among patients with IBD.

Author's contribution HM, DW, YI, NO, ET, YK, MO, NH, and YK collected the data and wrote the manuscript.

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Declarations

Conflict of interest None.

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