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Note

Incidence of acute exacerbation in patients with interstitial lung disease after COVID-19 vaccination

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ABSTRACT

Acute exacerbations due to COVID-19 vaccination in patients with interstitial lung disease (ILD) have been reported, but their incidence is unknown. We investigated the incidence of exacerbations of ILD and respiratory symptoms due to the mRNA COVID-19 vaccines. A questionnaire survey was conducted on adverse reactions to the mRNA COVID-19 vaccination in 545 patients with ILD attending our hospital and retrospectively examined whether the eligible patients actually developed acute exacerbations of ILD induced by the vaccine. Of the 545 patients, 17 (3.1%) patients were aware of the exacerbation of respiratory symptoms, and four (0.7%) patients developed an acute ILD exacerbation after vaccination. Of the four patients who experienced exacerbations, two had collagen vascular disease-associated ILD, one had nonspecific interstitial pneumonia, another had unclassifiable idiopathic pneumonia, and none had idiopathic pulmonary fibrosis. Four patients were treated using steroid pulse therapy with a steroid taper, and two of the four also received intravenous cyclophosphamide pulse therapy. Tacrolimus was started in one patient with myositis-associated interstitial lung disease. Eventually, all patients exhibited improvement with immunosuppressive treatment and were discharged. COVID-19 vaccination for patients with ILD should be noted for developing acute exacerbations of ILD with low incidence, although manageable with early diagnosis and treatment.

1. Introduction

Coronavirus disease 2019 (COVID-19) is a disease that causes acute respiratory illness and is spreading worldwide. Symptoms of COVID-19 range from asymptomatic to fatal with severe acute respiratory syndrome. Alternatively, vaccines against COVID-19, proven to be highly effective and well-tolerated have been rapidly developed [1–3], and two or more doses of these COVID-19 vaccines have been promoted in several countries. However, in the real world, some patients and physicians are concerned about the safety of these vaccines. This is a particularly crucial issue in patients with interstitial lung disease (ILD) because while ILD is a risk factor for COVID-19 severity, the development or acute exacerbation of ILD (AE-ILD) after the COVID-19 vaccination has actually been reported [4–7]. So far, there have been only a few reports of the development or ILD exacerbations after COVID-19 vaccination, and the incidence of acute exacerbation after COVID-19 vaccination in patients with ILD in clinical practice remains unclear. The incidence of all adverse reactions to the COVID-19 vaccines in these patients is also unknown. Thus, we investigated the incidence of adverse reactions after COVID-19 vaccination in ILD patients, including AE-ILD.

2. Methods

This retrospective study was conducted from April to December 2021 at the Kanagawa Cardiovascular and Respiratory Center according to the ethical principles of the 1964 Helsinki Declaration and subsequent amendments. All procedures were approved by the Ethics Committee of the Kanagawa Cardiovascular and Respiratory Center (approval number KCRC-21-0006). Consecutive patients with ILD attending the outpatient clinic of ILD specialists at the hospital who have completed 2 doses of SARS-CoV-2 or discontinued after 1 dose due to adverse effects and agreed to complete the questionnaire for adverse reactions to the
vaccines were included. First, eligible patients were asked to complete a questionnaire about the adverse reactions of the COVID-19 vaccine within 6 months of vaccination. Questionnaire survey items were as follows: 1) Type of COVID-19 vaccine received, 2) Date of vaccination, 3) Adverse reactions to the COVID-19 vaccine (multiple-choice format), 4) The presence or absence of exacerbations of respiratory symptoms after COVID-19 vaccination and if so, details of their exacerbations (descriptive format). Next, patients’ clinical background and whether or not their ILD was exacerbated after the COVID-19 vaccination was obtained from their medical records. In cases where the patients had developed AE-ILD after COVID-19 vaccination, detailed patient background, treatment course, and outcomes of the acute exacerbation were also obtained. AE-ILD in relation to COVID-19 vaccination was defined as worsening of respiratory symptoms owing to COVID-19 vaccination, with worsening of oxygenation and appearance of new ground grass opacity/consolidation on computed tomography (CT) not caused by pulmonary edema or other causes within one month after vaccination, referring to the acute exacerbation of idiopathic pulmonary fibrosis (IPF) criteria suggested by the international working group in 2016 [8]. The eligible patients were classified into two groups: those who reported worsening respiratory symptoms because of COVID-19 vaccination (the deterioration group) and those who reported no worsening of respiratory symptoms after COVID-19 vaccination (the stable group), and a comparative analysis was conducted between the two groups regarding differences in all adverse reactions to the COVID-19 vaccine, types and ILD treatment. All statistical analyses were conducted using JMP® pro 13.2.0 software (SAS Institute Inc. Cary, NC, USA). Fisher’s exact test was used for categorical data, and the Mann-Whitney U test was not used for continuous data. A p-value of <0.05 was considered statistically significant for all analyses.

3. Results

Five hundred and forty-five patients with ILD who have received the COVID-19 vaccine responded to the survey. All but one patient who developed AE-ILD after first dose of the COVID-19 vaccine had received two doses. Of the 545 patients, 17 (3.1%) reported that COVID-19 vaccination caused an adverse reaction of worsening respiratory symptoms (classified as the deterioration group), and the remaining 528 patients remained unchanged (classified as the stable group). Regarding adverse reactions related to respiratory symptoms in the deterioration group, coughing the most common (14/17, 82.4%), followed by dyspnea (8/17, 47.1%) and increased sputum (2/17, 11.8%). Patients’ characteristics, including the vaccine type and treatment of ILD, are shown in Table 1. The deterioration group tended to be younger than the stable group, but there were insignificant sex differences. The type of ILD in the deterioration group included nonspecific interstitial pneumonia (NSIP) and collagen vascular disease-associated ILD (CVD-ILD) more frequently, with no IPF. Although there were no significant differences between the two groups regarding the baseline ILD treatment, the use of long-term oxygen therapy tended to be more common in the deterioration group.

The common adverse reactions other than respiratory symptoms due to COVID-19 vaccines are indicated in Table 2. Adverse reactions other than respiratory symptoms were observed to be significantly higher in the deterioration group than in the stable group (94.1% in the deterioration group vs. 52.1% in the stable group, p < 0.001). The most common adverse reaction was fatigue in both groups (70.6% in the deterioration group and 29.9% in the stable group, p < 0.001), followed by headache (52.9%), fever (47.1%) in the deterioration group, and muscle pain (22.5%) and fever (15.3%) in the stable group. All adverse reactions were more common in the deterioration group than in the stable group, and several of these varied statistically. Furthermore, significantly more patients in the deterioration group had two or more adverse reactions than those in the stable group (76.5% in the deterioration group vs. 26.1% in the stable group, p < 0.001). Four of the total 545 cases (0.7%) or 17.6% of the deterioration group developed AE-ILD in relation to COVID-19 vaccination. The clinical course of these four cases is shown in Table 3. Of the four cases, two were CVD-ILD (myositis-associated ILD), one was NSIP, and the other was unclassifiable idiopathic interstitial pneumonia. No obvious cause of acute exacerbation other than COVID-19 vaccination was identified in any of the four cases. The baseline percent predicted forced vital capacity (%FVC) and percent predicted diffusing capacity of carbon monoxide (%DLOCO) were markedly low. Baseline KL-6 was elevated in all patients, and honeycomb on CT was found in two of four patients. All patients were hospitalized and received steroid pulse therapy (intravenous methylprednisolone 500-mg for three days) with steroid taper. Two of the four patients also received intravenous cyclophosphamide pulse therapy, and tacrolimus was

| Table 1 | Patients’ characteristics in this study. |
|---|---|
| | All patients (n = 545) | Stable group (n = 528) | Deterioration group (n = 17) |
| Age, median (range) | 72 (22–91) | 72 (22–91) | 64 (40–84) |
| Male, n (%) | 314 (58%) | 304 (58%) | 10 (59%) |
| Type of vaccine | | | |
| BNT162b2 (BioNTech/Pfizer) | 478 (87.7%) | 461 (87.3%) | 17 (100%) |
| mRNA-1273 (Moderna) | 53 (9.7%) | 53 (10.0%) | 0 |
| unknown | 14 (2.6%) | 14 (2.7%) | 0 |
| Treatment for ILD | | | |
| Steroid | 167 (30.6%) | 161 (30.5%) | 6 (35.3%) |
| Immunosuppressant | 117 (21.5%) | 113 (21.4%) | 4 (23.5%) |
| Nintedanib | 52 (9.5%) | 49 (9.3%) | 3 (17.6%) |
| Pirfenidone | 60 (11.0%) | 58 (11.0%) | 2 (11.8%) |
| Supplemental oxygen | 63 (11.6%) | 59 (11.2%) | 4 (23.5%) |

Table 2 | Adverse reactions other than respiratory symptoms to COVID-19 vaccination in patients with interstitial lung disease in this study.

| | All patients (n = 545) | Stable group (n = 528) | Deterioration group (n = 17) | P |
|---|---|---|---|---|
| Fever | 89 (16.3%) | 81 (15.3%) | 8 (47.1%) | 0.002 |
| 37.5–37.9°C | 45 (8.3%) | 42 (8.0%) | 3 (17.7%) | 0.158 |
| 38.0°C | 48 (8.8%) | 42 (8.0%) | 6 (35.3%) | 0.002 |
| Fatigue | 170 (31.2%) | 158 (29.9%) | 12 (70.6%) | <0.001 |
| Headache | 65 (11.9%) | 56 (10.6%) | 9 (52.9%) | <0.001 |
| Chill | 23 (4.2%) | 20 (3.8%) | 3 (17.7%) | 0.030 |
| Nausea | 12 (2.2%) | 10 (1.9%) | 2 (11.8%) | 0.050 |
| Diarrhea | 12 (2.2%) | 11 (2.1%) | 1 (5.9%) | 0.31 |
| Muscle pain | 126 (23.1%) | 119 (22.1%) | 7 (41.2%) | 0.082 |
| Asthagia | 40 (7.3%) | 35 (6.6%) | 5 (29.4%) | 0.005 |
| Rash | 23 (4.2%) | 21 (4.0%) | 2 (11.8%) | 0.157 |
| Any adverse effects | 291 (53.4%) | 275 (52.1%) | 16 (94.1%) | <0.001 |
| ≥2 adverse effects | 151 (27.7%) | 138 (26.1%) | 13 (76.5%) | <0.001 |
| No adverse effects | 254 (46.6%) | 253 (47.9%) | 0 (5.9%) | 0.001 |

Footnote: Describing adverse reactions that appeared in any of vaccinations.
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| Case* | Age  | Sex  | BMI  | Type of ILD | Date of admission | Prior treatment | Baseline data | Other adverse reactions | Treatment for AE-ILD | Outcome |
|-------|------|------|------|-------------|-------------------|-----------------|--------------|----------------------|---------------------|---------|
| 1     | 60   | M    | 28.7 | CVD-ILD    | 19 days after 1st vaccination | none           | NA           | no fever, cough, dyspnea | mPSL pulse, Tac            | improve |
| 2     | 43   | M    | 25.6 | NSIP       | 21 days after 2nd vaccination | PSL, Tac       | 31/1 min    | fever, fatigue, headaches | IVCY + Tac                 | improve |
| 3     | 62   | M    | 22.3 | CVD-ILD    | 17 days after 2nd vaccination | PSL, Tac       | 31/1 min    | dyspnea, headache, myalgia | mPSL pulse               | improve |
| 4     | 73   | M    | 29.9 | unclassifiable | 30 days after 2nd vaccination | PSL, Tac       | 31/1 min    | nausea, cough, fatigue, headache | mPSL pulse               | improve |

Maximum oxygen administration: FiO₂ 80% in HFOEC

Baseline data: FVC 56.5, DLCO 25.6, KL-6 4233

Other adverse reactions: No fever, cough, dyspnea

Treatment for AE-ILD: IVCY, mPSL pulse

Outcome: Improve

Abbreviations and footnote: *all patients received the BNT162B2 (BioNTech/Pfizer) vaccine.**

Conclusion: The incidence of adverse reactions to the COVID-19 vaccine, including AE-ILD, was 0.7% in the population studied. The majority of cases occurred within 30 days of vaccination, and the symptoms were primarily respiratory. AE-ILD was seen in patients with various types of ILD, including CVD-ILD and NSIP. The incidence of AE-ILD in patients with ILD was similar to the general population. Further studies are needed to better understand the etiology and mechanisms of AE-ILD related to COVID-19 vaccination.
difficult to diagnose. However, based on the clinical course and the absence of any other apparent causes after searching as much as possible, it was considered that the cases in this study were AE-ILD related to COVID-19 vaccination. As this study included only four patients who developed AE-ILD and was unable to identify the risk factors to develop AE-ILD after vaccination, further large-scale investigation is required.

In conclusion, COVID-19 vaccination in patients with ILD can cause AE-ILD in less than 1% and should be administered with caution. Particular attention may be needed in patients with pulmonary function impairment or autoimmune disease-related ILD. Most ILD patients benefit the vaccination with low incidence of AE-ILD which, even if occur, is manageable with early diagnosis and treatment.

Author contributions

MS had full access to all of the data in the study and responsibility for its integrity and the accuracy of the data analysis. MS, TB, AS and TO contributed to the study concept and design. MS and EH drafted the manuscript. MS, HK, SI, ET and TO contributed to data collection. MS, ET, SY and KF contributed to data analysis. All authors revised the manuscript critically for important intellectual content and approved the final manuscript.

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