COVID-19 Vaccine in Patients with Exacerbation of Idiopathic Pulmonary Fibrosis

To the Editor:

Between the end of 2020 and the beginning of 2021, the first mRNA vaccines against coronavirus disease (COVID-19) received approval for emergency use by the World Health Organization. Patients affected by fibrotic interstitial lung disease (ILD) were granted priority access to vaccination because these patients may develop severe complications after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and carry a higher risk of death, with in-hospital mortality estimated to be approximately 50% (1–3).

Acute exacerbations of idiopathic pulmonary fibrosis (AE-IPF) are defined as acute, clinically significant respiratory deteriorations characterized by new bilateral ground-glass opacification/consolidation at chest imaging not fully explained by cardiac failure or fluid overload. These events are characterized by poor prognosis and have limited therapeutic options (4). A role for viral infections, including SARS-CoV-2, as triggers of AE-ILD has been suggested, although the pathobiological mechanisms driving the acute lung injury remains largely unknown (5, 6). Cases of acute interstitial pneumonia or exacerbation of existing fibrosing ILD developed after vaccination for influenza viruses such as H1N1 have also been reported in the past (7, 8); however, there is limited knowledge about the risk of these events in relation to COVID-19 vaccination (9, 10).

Between January and December 2021, a total of 26 patients with a diagnosis of IPF were hospitalized for respiratory worsening at our center, a large referral center for ILD. In 16 patients, such deterioration was explained by a range of conditions, including progression of the underlying fibrotic disease, pulmonary embolism, infection, or fluid overload from congestive heart failure. Ten patients were diagnosed with AE-IPF on the basis of radiological findings and the exclusion of alternative causes of respiratory worsening, according to current adjudication criteria (4, 11). Data including demographics, medical history, type and date of the last dose of COVID-19 vaccine, laboratory tests performed on hospital admission, comorbidities, and the last available pulmonary function tests performed before hospitalization were retrospectively collected from the medical records of patients with AE-IPF.

In the selected cohort, 4 (40%) of 10 patients were referred to the emergency room for worsening of dyspnea occurring a few days after COVID-19 vaccination. All patients received the Pfizer-BioNTech Comirnaty vaccine. The deterioration occurred after receiving the first dose of the vaccine in one patient, after the second dose in one patient, and after the third dose in the two remaining patients. None of these patients experienced previous episodes of AE-IPF. The temporal proximity between COVID-19 vaccination and the onset of symptoms (between 3 and 5 d; median time interval, 3.5 d) indicated the vaccine as the most likely trigger of AEs, as compared with the six patients for whom such a relationship could be reasonably excluded (median time interval, 54.5 d). However, neither influenza nor pneumococcal vaccinations were reportedly performed in these patients in the weeks before hospitalization.

Among the patients who experienced respiratory worsening after COVID-19 vaccination, three patients had a usual interstitial pneumonia pattern on the high-resolution computed tomography (CT) scan at diagnosis, whereas for one patient, the CT pattern was classified as probable usual interstitial pneumonia. Baseline lung function tests were available for three patients: FVC was preserved (90% and 94% predicted) in two patients who had coexistent signs of emphysema on CT scans, whereas it was severely reduced in one patient (36% predicted). On hospital admission, C-reactive protein concentrations (median, 84.8 mg/L) and leukocyte counts (median, 12.14×10^9/L) were increased. The findings regarding serum IgM concentrations for respiratory viruses and atypical pulmonary bacteria were negative, as were the results of SARS-CoV-2 real-time PCR testing. On high-resolution CT scans performed during hospitalization, two patients had bilateral ground-glass opacities with a lower-lobe predominance, whereas one patient had multifocal ground-glass and consolidative areas in the upper right, upper left, and lower left lobes. One patient had bilateral signs of alveolar involvement on chest radiography. (He could not undergo a CT scan because of rapid respiratory deterioration.) All patients were started on treatment with high-dose intravenous methylprednisolone (1 g/d) within the first days of hospitalization. The dosage was halved every 3 days and progressively titrated with a maintenance dose of 0.75–1 mg/kg until death or discharge. Two patients' condition deteriorated rapidly, and they died of respiratory failure despite treatment (one patient on the first day of admission to hospital and the other 14 d after hospitalization); two patients gradually recovered and were discharged after 2 weeks. Once discharged, they continued steroid treatment with oral prednisone with progressive dosage reduction.

The observation that a significant proportion (40%) of patients hospitalized for AE-IPF in our cohort had a close temporal relationship with COVID-19 vaccination suggests that the immune response induced by the vaccine may activate pathobiological cascades leading to the AEs in susceptible patients. COVID-19 vaccination produces a T-cell response with a predominant T-helper cell type 1 phenotype (12), releasing proinflammatory cytokines such as IL-2, tumor necrosis factor-α, and IFN-γ, which could be responsible for the diffuse alveolar damage via upregulation of macrophage activation pathways. Notably, vaccines are not currently recognized as being among the potential triggers of AE-IPF (4). Despite being limited to our single-center experience, our findings add to previous reports of AE-IPF after influenza vaccination (7, 8) and a recent case report of AE-IPF after COVID-19 vaccination (10), thus warranting further investigation of the relationship between vaccines and AE-IPF. Still, vaccine-associated AEs should be considered as rare events occurring in a small minority of vaccinated patients with IPF.

Author Contributions: Conception and design: G.S., A.C., and L.R. Data collection, analysis, and interpretation: G.S., T.M., M.L., and A.C. Drafting the manuscript: G.S., T.M., and M.L. Manuscript review: G.S., A.C., and L.R. Supervision: G.S. and L.R.

Originally Published in Press as DOI: 10.1164/rccm.202112-2765LE on April 12, 2022

Table 1. Baseline Characteristics of Patients with Acute Exacerbations of Idiopathic Pulmonary Fibrosis, Grouped by Potential Relationship with COVID-19 Vaccine

	Vaccine-associated AE-IPF (*n* = 4)	Idiopathic AE-IPF (*n* = 6)
Age, yr	71.5 (62–72)	67.5 (40–79)
Sex		
Male	3 (75)	4 (67)
Female	1 (25)	2 (33)
Smoking history*		
Former smoker	1 (25)	1 (20)
Never smoker	3 (75)	4 (80)
BMI, kg/m^2	23.7 (21–26)	27 (22–31)
Use of long-term oxygen therapy	2 (50)	4 (66)
Antifibrotic treatment	1 (25)	5 (83)
FVC, L*	1.9 (1.4–2.9)	1.9 (1.8–2.6)
FVC, % predicted*	90 (36–94)	65.5 (60–70)
D_{LCO}, % predicted*	22 (19–59)	25 (14–33)
Comorbidities		
COPD	1 (25)	1 (17)
OSAS	0 (0)	2 (33)
Chronic heart disease	1 (25)	2 (33)
PH	2 (50)	2 (33)
GERD	0 (0)	3 (50)
Cancer	1 (25)	1 (17)
Time from last vaccine dose, d*	3.5 (3–5)	54.5 (23–117)
WBC count, $\times 10^9$/L	12.1 (9.9–23.0)	10.7 (6.3–15.8)
Neutrophils, %	87 (74.4–92.1)	83 (78.7–85.6)
Lymphocytes, %	7.2 (5.1–17.8)	11.7 (8.2–15.3)
Monocytes, %	5.2 (2.2–6.5)	3.6 (3.0–7.6)
CRP, ml/L	84.8 (40.2–177.3)	133.2 (32.5–234.2)
In-hospital deaths	2 (50)	5 (83)
Duration of steroid therapy, d	11 (1–15)	11 (2–46)

Definition of abbreviations: AE-IPF = acute exacerbations of idiopathic pulmonary fibrosis; BMI = body mass index; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease; CRP = C-reactive protein; GERD = gastroesophageal reflux disease; OSAS = obstructive sleep apnea syndrome; PH = pulmonary hypertension; WBC = white blood cells.
Data are expressed as count (percent) or as median with minimum and maximum values.
*Some observations were not available.

Patients with either "triggered" or "idiopathic" AE-IPF had known risk factors for AE-IPF, including low D_{LCO} at baseline (median values, 22% and 25% predicted, respectively) and use of supplemental oxygen (50% and 66% of patients, respectively) (Table 1). The two groups were too small to assess whether any demographic or clinical features could be associated with an increased susceptibility to vaccine-associated AEs. Interestingly, though, only one patient of those who had AEs after vaccination was receiving treatment with antifibrotics (among the three untreated patients, one had a recent diagnosis of IPF and was about to start treatment, one was undiagnosed before hospital admission, and one patient could not be prescribed antifibrotics because of advanced disease), as compared with five (83%) of six patients in the idiopathic AE-IPF group. Recently, a role for antifibrotic therapy (nintedanib and pirfenidone) in reducing the fibrotic sequelae of COVID-19 pneumonia has been postulated and is currently being investigated in clinical trials (13). However, whether antifibrotics could exert a protective role toward an aberrant reaction to COVID-19 vaccines remains merely speculative.

In our cohort, we report a numerically lower in-hospital mortality rate in the group with AEs after COVID-19 vaccination than in the patients with idiopathic AE-IPF (50% and 83%, respectively). It is possible that vaccine-associated AEs are characterized by better steroid responsiveness than idiopathic AEs through activation of pathways more similar to those activated by SARS-CoV-2 itself. Although no firm conclusions can be drawn from our clinical observations, we anticipate that this important topic will be further explored in future longitudinal, prospective studies.

In conclusion, our observations suggest that COVID-19 vaccination may act as a potential trigger of AE-IPF, warranting a close monitoring strategy in patients with IPF after vaccination to ensure early detection of worsening of symptoms or oxygen desaturation requiring immediate clinical referral. Although COVID-19 vaccination remains strongly advised in the general IPF population, further evidence is required to clarify whether a clinical phenotype of IPF could be at higher risk of AEs after vaccine administration. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Giacomo Sgalla, M.D., Ph.D.*
Fondazione Policlinico Universitario A. Gemelli Istituto di Ricovero e Cura a Carattere Scientifico
Rome, Italy

Tonia Magrì, M.D.
Marialessia Lerede, M.D.
Alessia Comes, M.D.
Università Cattolica del Sacro Cuore
Rome, Italy

Luca Richeldi, M.D., Ph.D.
Fondazione Policlinico Universitario A. Gemelli Istituto di Ricovero e Cura a Carattere Scientifico
and
Università Cattolica del Sacro Cuore
Rome, Italy

ORCID ID: 0000-0003-3130-9388 (G.S.).

*Corresponding author (e-mail: giacomo.sgalla@policlinicogemelli.it).

References

1. Aveyard P, Gao M, Lindson N, Hartmann-Boyce J, Watkinson P, Young D, *et al.* Association between pre-existing respiratory disease and its treatment, and severe COVID-19: a population cohort study. *Lancet Respir Med* 2021;9:909–923.
2. Drake TM, Docherty AB, Harrison EM, Quint JK, Adamali H, Agnew S, *et al.*; ISARIC4C Investigators. Outcome of hospitalization for COVID-19 in patients with interstitial lung disease. An international multicenter study. *Am J Respir Crit Care Med* 2020;202: 1656–1665.
3. Esposito AJ, Menon AA, Ghosh AJ, Putman RK, Fredenburgh LE, El-Chemaly SY, *et al.* Increased odds of death for patients with interstitial lung disease and COVID-19: a case-control study. *Am J Respir Crit Care Med* 2020;202:1710–1713.
4. Collard HR, Ryerson CJ, Corte TJ, Jenkins G, Kondoh Y, Lederer DJ, *et al.* Acute exacerbation of idiopathic pulmonary fibrosis. An international working group report. *Am J Respir Crit Care Med* 2016;194:265–275.
5. Saraya T, Kimura H, Kurai D, Tamura M, Ogawa Y, Mikura S, *et al*. Clinical significance of respiratory virus detection in patients with acute exacerbation of interstitial lung diseases. *Respir Med* 2018; 136:88–92.
6. Fonseca M, Summer R, Roman J. Acute exacerbation of interstitial lung disease as a sequela of COVID-19 pneumonia. *Am J Med Sci* 2021; 361:126–129.
7. Umeda Y, Morikawa M, Anzai M, Sumida Y, Kadowaki M, Ameshima S, *et al.* Acute exacerbation of idiopathic pulmonary fibrosis after pandemic influenza A (H1N1) vaccination. *Intern Med* 2010;49: 2333–2336.
8. Okusaki T, Fukuhara K. Exacerbation of connective tissue disease-associated interstitial lung disease due to influenza vaccination. *Respir Med Case Rep* 2021;33:101463.
9. Park JY, Kim JH, Lee IJ, Kim HI, Park S, Hwang YI, *et al.* COVID-19 vaccine-related interstitial lung disease: a case study. *Thorax* 2022;77: 102–104.
10. Bando T, Takei R, Mutoh Y, Sasano H, Yamano Y, Yokoyama T, *et al.* Acute exacerbation of idiopathic pulmonary fibrosis after SARS-CoV-2 vaccination. *Eur Respir J* 2022;59:2102806.
11. Andrade J, Schwarz M, Collard HR, Gentry-Bumpass T, Colby T, Lynch D, *et al.*; IPFnet Investigators. The Idiopathic Pulmonary Fibrosis Clinical Research Network (IPFnet): diagnostic and adjudication processes. *Chest* 2015;148:1034–1042.
12. Keech C, Albert G, Cho I, Robertson A, Reed P, Neal S, *et al.* Phase 1-2 trial of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine. *N Engl J Med* 2020;383:2320–2332.
13. Sgalla G, Comes A, Lerede M, Richeldi L. COVID-related fibrosis: insights into potential drug targets. *Expert Opin Investig Drugs* 2021; 30:1183–1195.

Check for updates

Comparison of Lung Function in Healthy Nigerian Children Living in Nigeria and in the United Kingdom

To the Editor:

Early-life determinants, such as passive smoking, indoor air pollution, childhood infections, nutritional status, and socioeconomic status (SES), affect lung development and the subsequent lung function trajectory throughout life (1). However, the interaction between environmental exposures and genetics in determining lung function in healthy children is yet to be established, in part because of the paucity of comparative data in subjects with common genetic ancestry living in very different environments. Sonnappa and colleagues previously reported lower dynamic lung volumes in Indian semiurban and rural children than in U.K.-Indian children, whereas spirometric outcomes between Indian urban children and U.K.-Indian children were virtually identical (2).

We explored the hypothesis that Nigerian children would have lower lung function than children of Nigerian origin in the United Kingdom (henceforth referred to as U.K.-Nigerian children) because of socioeconomic disadvantage. This prospective cross-sectional study was conducted in Nigeria and the United Kingdom using the same equipment, techniques, and quality control criteria (3). Healthy children were recruited in Nigeria in private and public urban schools in Kaduna city (north-central Nigeria) and in rural schools within 50 km from Kaduna city in April 2017 (Barau Dikko Teaching Hospital Ethics Committee, Kaduna, HREC 16-0017) (4). U.K.-Nigerian children were enrolled as part of the SLIC (Size and Lung Function in Children) study (London-Hampstead REC 10/ H0720/53) (3) between December 2010 and July 2013. Parental written consent and verbal assent from each participant were obtained.

Children aged 6–11 years were eligible. Exclusion criteria were children unwell on the test day, prematurity, and current asthma or chronic disease/congenital abnormalities likely to affect lung function (3). The child's respiratory history, tribal group (only in Nigeria), family SES, and tobacco and biomass smoke exposures were investigated via a questionnaire administered to the child by the researchers. SES was evaluated using the Family Affluence Scale (FAS), based on the collated score for number of computers, vehicle ownership, and whether the child had his or her own bedroom, on a scale from 0 to 6 (3).

The Size and Lung Function in Children study was funded by the Wellcome Trust (WT094129MA). For data collection in Nigeria, the Sickle Cell Cohort Research Foundation (www.scorecharity.com) and Associazione Allergie Pneumopatie Infantile (https://www.alpiassociazione.it/) offered financial support to refund travel expenses to Nigeria for two investigators (M.A. and C.Z.).

Author Contributions: M.A. conceived the study, performed data collection, performed analyses, interpreted data, and wrote the manuscript; S.L., P.C., and B.I. conceived the study, interpreted data, and contributed to the manuscript; C.Z., L.G.D., R.Z., E.R., and A.D.S. performed data collection and revised the manuscript; L.C. performed statistical analysis, interpreted data, and revised the manuscript. All the authors approved the final draft of the manuscript.

Originally Published in Press as DOI: 10.1164/rccm.202201-0093LE on April 15, 2022