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

Giacomo Sgalla, MD, PhD[1], Tonia Magrì[2], Marialessia Lerede[2], Alessia Comes[2], Luca Richeldi[1,2]

[1]UOC Pneumologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italy;

[2]Università Cattolica del Sacro Cuore, Roma, Italy

Corresponding author:

Giacomo Sgalla, MD PhD

UOC Pneumologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Agostino Gemelli 8, 00168, Rome, Italy.

E-mail: giacomo.sgalla@policlinicogemelli.it

Word count: 1221

Sources of funding: none

Authors' contributions: Conception and design: GS, AC, LR; Data collection, analysis and interpretation: GS, TM, ML, AC; Drafting the manuscript: GS, TM, ML; Manuscript review: GS, AC, LR; Supervision: GS, LR.

AJRCCM Articles in Press. Published April 12, 2022 as 10.1164/rccm.202112-2765LE

To the editor

Between the end of 2020 and the beginning of 2021, the first mRNA vaccines against COVID-19 received approval for emergency use by the World Health Organization (WHO). Patients affected by fibrotic interstitial lung disease (ILD) were granted priority access to vaccination, as these patients may develop severe complications after SARS-CoV-2 infection and carry a higher risk of death, with in-hospital mortality estimated to be around 50% (1)(2, 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 acute exacerbation of 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 have been 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 an acute exacerbation of IPF, based on radiological findings and the exclusion of alternative causes of respiratory worsening, according to current adjudication criteria (11)(4). Data including demographics,

AJRCCM Articles in Press. Published April 12, 2022 as 10.1164/rccm.202112-2765LE

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 out of 10 patients (40%) were referred to the Emergency Room for worsening of dyspnea occurring few days after COVID-19 vaccination: all patients received the Pfizer-BioNtech Comirnaty® vaccine. In one patient the deterioration occurred after receiving the first dose of the vaccine, in one patient after the second dose, while in the two remaining patients after the third dose. None of these patients experienced previous episodes of AE-IPF. The temporal proximity between COVID-19 vaccination and onset of symptoms (between 3 and 5 days, median time interval 3.5 days) indicated the vaccine as the most likely trigger of acute exacerbation, as compared to the 6 patients for whom such relationship could be reasonably excluded (median time interval 54.5 days). On the other hand, neither influenza nor pneumococcal vaccinations were reportedly performed by these patients in the weeks prior to hospitalization.

Among the patients who experienced respiratory worsening following COVID-19 vaccination, 3 patients had a Usual Interstitial Pneumonia (UIP) pattern on high-resolution CT (HRCT) scan at diagnosis, while for one patient the CT pattern was classified as probable UIP. Baseline lung function tests were available for 3 patients: forced vital capacity (FVC) was preserved (90% and 94% of percent predicted) in 2 patients who had coexistent signs of emphysema on CT scans, while it was severely reduced in one patient (36% of percent predicted). On hospital admission, C-reactive protein levels (median 84.8 mg/L) and leukocyte counts (median 12.14 $x10^{\wedge 9}$/L) were increased. Serum IgM levels for respiratory viruses and atypical pulmonary

AJRCCM Articles in Press. Published April 12, 2022 as 10.1164/rccm.202112-2765LE

bacteria were negative as well as SARS-CoV-2 real-time PCR testing. On HRCT scan performed during hospitalization, 2 patients had bilateral ground glass opacities with a lower-lobe predominance, while 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 perform CT scan due to the rapid respiratory deterioration). All patients were started treatment with high dose intravenous methylprednisolone (1 g daily) within the first days of hospitalization. The dosage was halved every 3 days and progressively titrated with a maintaining dose of 0.75-1 mg/kg until death or discharge. Two patients deteriorated rapidly and died from respiratory failure despite treatment (one patient on the first day of admission to hospital, the other 14 days after hospitalization); two patients gradually recovered and were discharged after two 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 acute exacerbation in susceptible patients. COVID-19 vaccination produces a T-cell response with a predominant Th1 phenotype (12) , releasing proinflammatory cytokines such as IL-2, TNF-α and INF-γ which could be responsible for the diffuse alveolar damage via upregulation of macrophage activation pathways. Notably, vaccines are not currently recognized among potential triggers of AE-IPF (4): despite being limited to our single center experience, our findings add to previous reports of AE-IPF following influenza vaccination (7)(8) and a recent case report of AE-IPF following COVID-19 vaccination (10), thus warranting

AJRCCM Articles in Press. Published April 12, 2022 as 10.1164/rccm.202112-2765LE

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 IPF patients.

Patients with either “triggered” or “idiopathic” AE-IPF had known risk factors for AE-IPF, including low DLco at baseline (median values 22% and 25% of predicted, respectively), and use of supplemental oxygen (50% and 66% of patients) (Table 1). The two groups were too small to assess whether any demographic or clinical feature could be associated with an increased susceptibility to vaccine-associated acute exacerbation. Interestingly though, only one patient of those who exacerbated after vaccination was receiving treatment with antifibrotics (among the 3 untreated patients, one had a recent diagnosis of IPF and was about to start treatment; one was undiagnosed before hospital admission; one patient could not be prescribed antifibrotics due to advanced disease), as compared to 5 out of 6 patients (83%) in the idiopathic AE-IPF group. Recently, a role for antifibrotic therapy (nintedanib and pirfenidone) in reducing the fibrotic sequalae of COVID-19 pneumonia has been postulated and is currently being investigated in clinical trials (13). However, whether antifibrotics could exert a protective role towards 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 exacerbating after COVID-19 vaccination as compared to the patients with idiopathic AE-IPF (50% and 83%, respectively). It is possible that vaccine-associated AE are characterized by better steroid responsiveness, as compared to “idiopathic” AE, through activation of pathways more similar to those activated by SARS-COV-2 itself. Although no firm conclusions

AJRCCM Articles in Press. Published April 12, 2022 as 10.1164/rccm.202112-2765LE

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 of IPF patients after vaccination to early detect worsening of symptoms or oxygen desaturation, requiring immediate clinical referral. While 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 acute exacerbation following vaccine administration.

AJRCCM Articles in Press. Published April 12, 2022 as 10.1164/rccm.202112-2765LE

REFERENCES

1. Aveyard P, Gao M, Lindson N, Hartmann-Boyce J, Watkinson P, Young D, Coupland CAC, Tan PS, Clift AK, Harrison D, Gould DW, Pavord ID, Hippisley-Cox J. 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, Babu S, Barber CM, Barratt S, Bendstrup E, Bianchi S, Villegas DC, Chaudhuri N, Chua F, Coker R, Chang W, Crawshaw A, Crowley LE, Dosanjh D, Fiddler CA, Forrest IA, George PM, Gibbons MA, Groom K, Haney S, Hart SP, Heiden E, Henry M, Ho L-P, *et al.* 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, Goldberg HJ, Baron RM, Hunninghake GM, Doyle TJ. 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, Lee JS, Maher TM, Wells AU, Antoniou KM, Behr J, Brown KK, Cottin V, Flaherty KR, Fukuoka J, Hansell DM, Johkoh T, Kaminski N, Kim DS, Kolb M, Lynch DA, Myers JL, Raghu G, Richeldi L, Taniguchi H, Martinez FJ. 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, Sada M, Oda M, Watanabe T, Ohkuma K, Inoue M, Honda K, Watanabe M, Yokoyama T, Fujiwara M,

AJRCCM Articles in Press. Published April 12, 2022 as 10.1164/rccm.202112-2765LE

Ishii H, Takizawa H. 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, Ishizaki T. Acute exacerbation of idiopathic pulmonary fibrosis after pandemic influenza A (H1N1) vaccination. *Intern Med* 2010;49:2333–6.

8. Okusaki T, Fukuhara K. Exacerbation of connective tissue disease-associated interstitial lung disease due to influenza vaccination. *Respir Med Case Reports* 2021;33:101463.

9. Park JY, Kim J-H, Lee IJ, Kim H Il, Park S, Hwang Y Il, Jang SH, Jung K-S. COVID-19 vaccine-related interstitial lung disease: a case study. *Thorax* 2021;doi:10.1136/thoraxjnl-2021-217609.

10. Bando T, Takei R, Mutoh Y, Sasano H, Yamano Y, Yokoyama T, Matsuda T, Kataoka K, Kimura T, Kondoh Y. Acute Exacerbation of Idiopathic Pulmonary Fibrosis after SARS-CoV-2 Vaccination. *Eur Respir J* 2022;doi:10.1183/13993003.02806-2021.

11. Andrade J de, Schwarz M, Collard HR, Gentry-Bumpass T, Colby T, Lynch D, Kaner RJ, IPFnet Investigators for the Ipf. 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, Plested JS, Zhu M, Cloney-Clark S, Zhou H, Smith G, Patel N, Frieman MB, Haupt RE, Logue J, McGrath M, Weston S,

AJRCCM Articles in Press. Published April 12, 2022 as 10.1164/rccm.202112-2765LE

Piedra PA, Desai C, Callahan K, Lewis M, Price-Abbott P, Formica N, Shinde V, Fries L, Lickliter JD, Griffin P, Wilkinson B, Glenn GM. 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;1–13.doi:10.1080/13543784.2021.2010188.

AJRCCM Articles in Press. Published April 12, 2022 as 10.1164/rccm.202112-2765LE

Table 1. Baseline characteristics of patients with acute exacerbation of IPF (AE-IPF), grouped by potential relation with COVID-19 vaccine. Data are expressed as counts (%) or median with minimum and maximum values. BMI=body mass index; FVC=forced vital capacity; DLco= diffusing capacity of the lung for carbon monoxide; COPD=chronic obstructive pulmonary disease; OSAS= obstructive sleep apnea syndrome; PH=pulmonary hypertension; GERD=gastroesophageal reflux disease; WBC=white blood cells; CRP= C reactive protein. *= some observations were not available.

AJRCCM Articles in Press. Published April 12, 2022 as 10.1164/rccm.202112-2765LE

Table 1

	Vaccine-associated AE-IPF (n=4)	Idiopathic AE-IPF (n=6)
Age, years	71.5 (62-72)	67.5 (40-79)
Sex		
Male	3 (75)	4 (67)
Female	1 (25)	2 (33)
Smoking history*		
Former	1 (25)	1 (20)
Never smoker	3 (75)	4 (80)
BMI	23.7 (21-26)	27 (22-31)
Use of long-term oxygen therapy	2 (50)	4 (66)
Anti-fibrotic 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)
DLco % 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 (days)*	3.5 (3-5)	54.5 (23-117)
WBC count (x109/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 (days)	11 (1-15)	11 (2-46)

AJRCCM Articles in Press. Published April 12, 2022 as 10.1164/rccm.202112-2765LE