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COVID-19 mRNA Vaccines and Interstitial Lung Disease Exacerbation: Causation or Just a Temporal Association?

To the Editor:

We read the recent paper by Sgalla and colleagues reporting the potential relationship between coronavirus disease (COVID-19) vaccination and idiopathic pulmonary fibrosis (IPF) (1) with great interest.

We would also like to cautiously share our experience with a patient who developed interstitial lung disease (ILD) exacerbation after receiving COVID-19 vaccination. The patient, a 72-year-old man, had slowly progressive pleuroparenchymal fibroelastosis. He presented 5 days after his second COVID-19 vaccine dose (mRNA, Moderna) with cough, dyspnea, and hypoxia. Computed tomography showed new diffuse ground-glass opacities with patchy areas of consolidation. A detailed history, physical exam, and workup including bronchoscopy did not reveal any causes for the exacerbation. He progressed rapidly to respiratory failure requiring invasive mechanical ventilation. He did not respond to high-dose corticosteroids and tocilizumab, and eventually died.

However, we would like to point out that a temporal relationship between the COVID-19 vaccine and ILD exacerbation does not equate to causality in the previously published case reports (2–5), those described by Sgalla and colleagues (1), and the case we describe. There will be a small number of ILD exacerbations that appear to be temporally related to the COVID-19 vaccine but are in fact random occurrences simply because of the finite background rate of ILD exacerbations and the large numbers of patients with ILD who have received the COVID-19 mRNA vaccine.

These cases do however raise an interesting and important question that can only be answered by larger and likely prospective studies comparing the rate of ILD exacerbations between vaccinated and unvaccinated groups. Until these definitive data are available, we suggest caution in attributing uncertain adverse effects to the COVID-19 vaccines because of the additional risk of misrepresentation of this data in the lay or social media in context of the current antipathy to vaccines (COVID-19 and others) in a subset of the population. ■

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References

1. Sgalla G, Magrì T, Lerede M, Comes A, Richeldi L. COVID-19 vaccine in patients with exacerbation of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2022;206:219–221.
2. Kono A, Yoshioka R, Hawk P, Iwashina K, Inoue D, Suzuki M, *et al.* A case of severe interstitial lung disease after COVID-19 vaccination. *QJM* 2022;114:805–806.
3. So C, Izumi S, Ishida A, Hirakawa R, Kusaba Y, Hashimoto M, *et al.* COVID-19 mRNA vaccine-related interstitial lung disease: two case reports and literature review. *Respirol Case Rep* 2022; 10:e0938.
4. Amiya S, Fujimoto J, Matsumoto K, Yamamoto M, Yamamoto Y, Yoneda M, *et al.* Case report: acute exacerbation of interstitial pneumonia related to messenger RNA COVID-19 vaccination. *Int J Infect Dis* 2022;116: 255–257.
5. Yoshikawa T, Tomomatsu K, Okazaki E, Takeuchi T, Horio Y, Kondo Y, *et al.* COVID-19 vaccine-associated organizing pneumonia. *Respirol Case Rep* 2022;10:e0944.

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Reply to Huang and Wei, Kang *et al.*, and Ehteshami-Afshar and Raj

From the Authors:

We read with interest the pertinent comments to our recent paper, "COVID-19 Vaccine in Patients with Exacerbation of Idiopathic Pulmonary Fibrosis" (1), in which we described a small cohort of patients with acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) potentially triggered by coronavirus disease (COVID-19) vaccination.

Kang and colleagues raised concerns regarding the size of the study population and potential biases influencing the findings of our research. Our study involved 10 patients admitted to our hospital in 2021 because of AE-IPF. In another 16 patients with IPF who were hospitalized within this time frame, acute exacerbation was excluded on the basis of clinical presentation and imaging or laboratory findings supportive an alternative cause of respiratory deterioration. Indeed, our study was not powered to demonstrate a causal link in such a small population, whose size should be viewed in the context of rare events (AE-IPF) in a rare disease (IPF). Furthermore, we acknowledge that our cases were too few to identify peculiar features of vaccine-related AE-IPF; matching four and six patients in the "idiopathic" and "triggered" groups, respectively, was not feasible, nor was it to make statistical inference via between-group comparisons.

Some concerns were also raised regarding disease homogeneity in our cohort. We confirm that subclinical autoimmune diseases were ruled out by performing comprehensive serological panels for

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detection of autoantibodies as part of the diagnostic work up of all patients with IPF included in our cohort, as recommended by current guidelines (2).

With regard to adjudication of AE-IPF, we believe that a proper discrimination of idiopathic acute exacerbation events from those triggered by respiratory infection would in theory require a thorough investigation, as suggested by Huang and colleagues. Nevertheless, as often happens in clinical practice, invasive procedures such as BAL were not safely feasible owing to the severe impairment of gas exchange at hospital admission and the need for high-flow oxygen supplementation.

Because there is no validated temporal cutoff to establish a direct relationship of an acute exacerbation event with a putative trigger, in our study we arbitrarily identified a cluster of four cases with a close temporal relationship with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination (onset of symptoms from 3 to 5 days after vaccination). On the other hand, the idiopathic cases described in our cohort developed respiratory symptoms ranging from 23 days to 117 days after receiving the last dose of vaccine (median time interval, 54 d), which can reasonably exclude a link between vaccination and the respiratory deterioration.

We agree with Huang and colleagues that it would be extremely useful to classify patients with AE-IPF using biomarkers of disease activity and/or severity. Unfortunately, validated biomarkers of AE-IPF are not available yet for routine clinical use. In our cohort, all patients with AE-IPF had normal blood eosinophil counts before starting steroid treatment. Ferritin concentrations were evaluated in one patient and were normal. KL-6 (Krebs von den Lungen-6) and SP-D (surfactant protein D) concentrations were not assessed, as such tests are not part of routine management of these patients. Although we recognize this as a potential limitation of our retrospective, descriptive study, we believe that dosing these biomarkers could have been of little help in discriminating the pathobiological features of triggered and idiopathic AE-IPF in such a small cohort of patients.

Although we postulated that triggered AEs may be more sensitive to high-dose steroid treatment during hospitalization, we would like to stress that no firm conclusions can be drawn from our limited dataset. In particular, in-hospital mortality for AE-IPF has been reported upward of 50% (3); as such, mortality in the vaccine-related AE-IPF group is still in line with the currently available evidence. Huang and colleagues seem to point out that further administration of ciclosporin A or cyclophosfamide could have affected survival. However, currently there are no proven effective therapies for AE-IPF. In fact, a recent double-blind, placebo-controlled trial showed that adding intravenous cyclophosphamide pulses to glucocorticoids increases mortality in patients with AE-IPF (3). Even the most recent international guideline document on treatment of IPF simply indicates that "acute exacerbations may be treated with corticosteroids" (4). Indeed, the optimization of AE-IPF treatment and the identification of effective preventive strategies, including personalized antifibrotic therapies and vaccination approaches, require much deeper insights into AE-IPF complex pathobiology and identification of novel molecular targets. This goes well beyond the scope of our work and will hopefully be clarified in future studies.

Finally, we completely agree with Ehteshami-Afshar and colleagues that a temporal relationship does not equate to causality, and we endorse their invitation to a cautious reporting of new potential adverse events to COVID-19 vaccines owing to their resonance in the current social context. On the other hand, we believe that the findings from our research and other recently published case reports highlight the need for further investigation on this relevant topic of respiratory medicine. ■

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References

1. Sgalla G, Magrì T, Lerede M, Comes A, Richeldi L. COVID-19 vaccine in patients with exacerbation of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2022;206:219–221.
2. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, *et al.*; American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2018;198: e44–e68.
3. Naccache J-M, Jouneau S, Didier M, Borie R, Cachanado M, Bourdin A, *et al.*; EXAFIP investigators and the OrphaLung network. Cyclophosphamide added to glucocorticoids in acute exacerbation of idiopathic pulmonary fibrosis (EXAFIP): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med* 2022;10:26–34.
4. Raghu G, Remy-Jardin M, Richeldi L, Thomson CC, Inoue Y, Johkoh T, *et al.* Idiopathic pulmonary fibrosis (an update) and progressive pulmonary fibrosis in adults: an official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2022;205: e18–e47.