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Postvaccination Acute Exacerbations of Idiopathic Pulmonary Fibrosis?

To the Editor:

We appreciate Dr. Sgalla and colleagues for their recent study (1) on 26 acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) cases from the interstitial lung disease (ILD) referral center in Italy. Ten patients were further divided into "vaccine-associated" and "idiopathic" acute exacerbation (AE). Lower in hospital mortality, better steroid response, and lower ratio of antifibrotic treatment was noticed in vaccine-associated AE. We anticipate further discussion on several points.

First, exclusion of connective tissue disease–ILD by seronegative detection of antinuclear antibody (ANA), anti-neutrophil cytoplasmic antibody (ANCA), rheumatoid factor (RF) should be performed to guarantee homogeneous disease phenotype. The division rationale for the two groups based on time point between coronavirus disease (COVID-19) vaccination and onset of symptoms (median time interval, 3.5 vs. 54.5 d) might be questionable. A recent case reported AE-IPF gradually onset 9 days after the second vaccination (2).
It would be crucial to determine whether the two groups merely belong to early and later phase of postvaccination events. Furthermore, infection of opportunistic pathogens should also contribute to AE and should be excluded.

Second, besides older age, male sex, and Asian ethnicity, eosinophil might act as a risk factor for AE and was not described in the study. Ferritin, Krebs von den Lungen-6 (KL-6), and surfactant protein (SP-D) (2–4) could be identified from both groups to calculate the cutoff for evaluation of disease activity and severity.

Third, mortality was lower in vaccine-associated AE (50%) than in idiopathic AE (83%). Nonetheless, two died despite steroid treatment without further administration of cyclophosphamide or cyclosporin A. Treatment strategy optimization might benefit from clarification of AE-IPF pathogenesis and identification of novel antiinflammatory and antifibrotic targets. It is speculated that antifibrotic drugs might be helpful. AE-IPF risk was reduced greater for pirfenidone than for nintedanib (5), suggesting that antifibrotic treatment should also be individualized.

Finally, in severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) mice study, recombinant vaccine expressing S protein or TH1-skewing adjuvants might develop protective immunity via T-helper cell type 1 (Th1) regulation and avoid Th2-induced eosinophil-associated lung pathology (6). SARS-CoV-1 and SARS-CoV-2 share more than 80% identity and might have similar underlying postvaccine mediated mechanisms. Future vaccine development could take advantage of this strategy to avoid postvaccination AE-IPF events. ■

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