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Early View

Research letter

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Reduced immunogenicity of the mRNA vaccine BNT162b2 in patients with IPF

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Take home message: Patients with IPF did not mount appreciable antispike antibody responses to two doses of SARS-CoV-2 mRNA vaccine compared to general population. National authorities should prioritize patients with IPF for booster doses.

To the editor:

The emergence and spread of 2019 coronavirus disease (COVID-19) are causing a growing global public health crisis. Despite advances in treatment, vaccination remains the best way to contain the pandemic[1]. Vaccines are currently available by means of conditional marketing approval, full approval and emergency use authorization pathways[2]. Evidence suggest that immunocompromised individuals including solid organ transplants recipients and patients under immunosuppressive treatment may have increased mortality from SARS-CoV-2 infection despite double dose messenger RNA (mRNA) vaccine regimens[3]. This is partially attributed to blunted immune responses to vaccination since only 38-54% of kidney and liver transplant recipients developed detectable SARS-CoV-2 antibodies following the second dose of mRNA vaccines [3,4].

Patients with Idiopathic Pulmonary Fibrosis (IPF) present with disrupted cellular and humoral immune responses[5]. In view of previous data during the first waves of the pandemic indicating increased risk of death from COVID-19 in unvaccinated patients with fibrotic ILDs[6], we aimed to determine humoral responses to two doses of SARS-CoV2 BNT162b2 mRNA vaccine in patients with IPF and compare them to those seen in the general population.

Therefore, we conducted a multicenter, prospective study between 22/7/2021 and 31/10/2021 including patients who received a multidisciplinary diagnosis of IPF in 5 Interstitial Lung Disease centers in Greece and aged-matched controls. Prospective data collection and analysis was approved by the Institutional Review Board and the Local Ethics Committee (protocol number 18482/21-7-21). IPF was diagnosed based on ATS/ERS 2018 Guidelines[7].

We compared anti–SARS-CoV-2 antibodies three months after the second dose of the mRNA vaccine BNT162b2 in three subgroups: 1) patients with IPF receiving antifibrotics, 2) patients with IPF under no treatment, 3) aged-matched controls. Patients receiving corticosteroids or steroid sparing agents and patients with malignancies were excluded from the analysis. Subjects with history of prior SARS-CoV-2 infection were also excluded. The recruitment period was between 22/7/2021 and 31/10/2021. All measurements were performed using the authorized Abbott SARS-CoV-2 IgG assay. Positivity cut-off threshold for this assay was 50 AU/ml.

With regards to summary statistics, categorical data were presented as absolute numbers and relative frequencies. Continuous data were demonstrated as mean± standard deviation (SD) or medians with 95% Confidence Interval (95% CI) based on Kolmogorov-Smirnov test for normality. Kruskal-Wallis test was used to detect differences in the aforementioned three subgroups. P-values < 0.05 were considered statistically significant.

Sixty-seven (n=67) subjects were included in the analysis (patients with IPF receiving antifibrotics: 32, patients with IPF under no treatment: 10, controls: 25). Groups were age and gender balanced [median age- IPF/treatment: 72.5 (95% CI: 69.9 to

75.0) vs IPF/no treatment: 73.0 (95% CI: 67.9 to 80.5) vs controls: 69.0 (95% CI: 65.5 to 74.2), p=0.15), gender- IPF/treatment: males 78.1% (n=25/32), IPF/no treatment: males 80% (n=8/10), controls: males 76% (n=19/25)]. Median Forced Vital Capacity% predicted and diffusing capacity of the lung for carbon monoxide %predicted were 81.0 (95% CI: 68.8 to 89.4) and 47.0 (95% CI: 40.9 to 57.4), 106.9 (95% CI: 66.1 to 121.1) and 60.7 (95% CI: 50.7 to 85.1), as well as 91.5 (95% CI: 87.0 to 97.8) and 87.0 (95% CI: 80.0 to 97.0) in the IPF/treatment, IPF/no treatment and control groups, respectively. The majority of subjects were current or ex-smokers in all groups [81.3% (n=26/32), 80% (n=8/10) and 76% (n=19/25), respectively]. Arterial hypertension was the most common comorbidity among all groups [43.8% (n=14/32), 40% (n=4/10) and 40% (n=10/25), respectively], while proportions of all comorbidities including obesity were balanced among groups. Both groups of patients with IPF whether receiving or not antifibrotic compounds exhibited similarly reduced levels of anti–SARS-CoV-2 antibodies after two doses of the mRNA vaccine BNT162b2 compared to general population [666.1, (95%: 540.1 to 900.0) vs 579.5 (95% CI: 232.4 to 4054.2) vs 2118.6 (95% CI: 1248.3 to 4035.5), p=0.002] **(Figure 1)**. The prevalence of anti–SARS-CoV-2 antibodies above the suggested cut-off threshold of 1000 AU/ml was 21.9%, 40% and 72% in the IPF/treatment, IPF/no treatment and control groups, respectively.

To the best of our knowledge, this is the first study showing that patients with IPF did not mount appreciable antispike antibody responses to two doses of SARS-CoV-2 mRNA vaccine compared to general population. Importantly, impaired immunogenicity was observed irrespective of anti-fibrotic treatment further adding to the knowledge that current anti-fibrotics do not cause further

immunosuppression but rather confer protection to disease acute exacerbations including those infection-mediated[8,9]. This is report is of interest given that impaired immune response following vaccination in most diseases has not been attributed to the disease per se but to the compounds used to treat the disease. Our findings are in line with mechanistic data showing blunted cellular and humoral immune responses in patients with IPF potentially contributing to fibrosis development and progression. In particular, patients with IPF and poor disease outcomes present with T-cell exhaustion as indicated by down-regulation of T-cell co-stimulatory markers. Impressively, the same high-risk genomic profile was also associated with increased mortality in patients with COVID-19[10], indicating that similar aberrant immune responses predispose to severe SARS-CoV-2 pneumonitis and fibrotic ILD. The relationship between B cells and IPF remains largely speculative, given the conflicting results of previous studies. On the one hand, increased detection of CD20+ B cells has been reported in lungs of patients with IPF[11]. Detection of B lymphocyte stimulator, denominated B-cell-activating factor (BAFF), is enriched in the peripheral blood and pulmonary parenchyma of patients with IPF, while neutralization or genetic ablation of BAFF attenuated pulmonary fibrosis[12]. On the other hand, data derived from other animal models demonstrated that B cells may suppress fibrotic response[13].

Limitations of our study include a moderate sample size that may lack generalizability, lack of serial measurements and underpowered arm of patients with IPF under no treatment. However, treatment-naive patients with IPF represent only a small minority in the era of antifibrotics and thus our sample size of non-treated IPF patients is representative of the everyday clinical practice. Moreover, we had not

measured anti-SARS-CoV2 antibody levels prior to vaccination; yet, we excluded subjects with history of SARS-CoV-2 infection. Another limitation is that we used Abbott test which quantifies IgG directed against an epitope of the spike protein, but we did not investigate specific immune responses such as specific T cell responses. We did not also record the exact time of the day that vaccination was performed to adjust for the effect of circadian rhythm. Finally, there is a small age difference between patients with IPF and controls; nonetheless, this is not statistically significant.

Our findings are of important value and should prompt national authorities to prioritize those subgroups of patients for booster doses and stringent precautions at the level of other groups of immunosuppressed individuals considering that reduced levels of anti-SARS-CoV-2 protective antibodies as well as fibrotic lung diseases per se are independent risk factors for increased mortality following SARS-CoV-2 infection [6,14]. Additional precautionary measures should include personal protective approaches such as protective facial masks and awareness of physical distancing, that played a beneficial role in the early phases of the pandemic[15]; yet, emergence of highly contagious variants of concerns mandate vaccination approaches to boost effectiveness and encourage fully vaccinated household contacts to offer optimal protection for at risk individuals.

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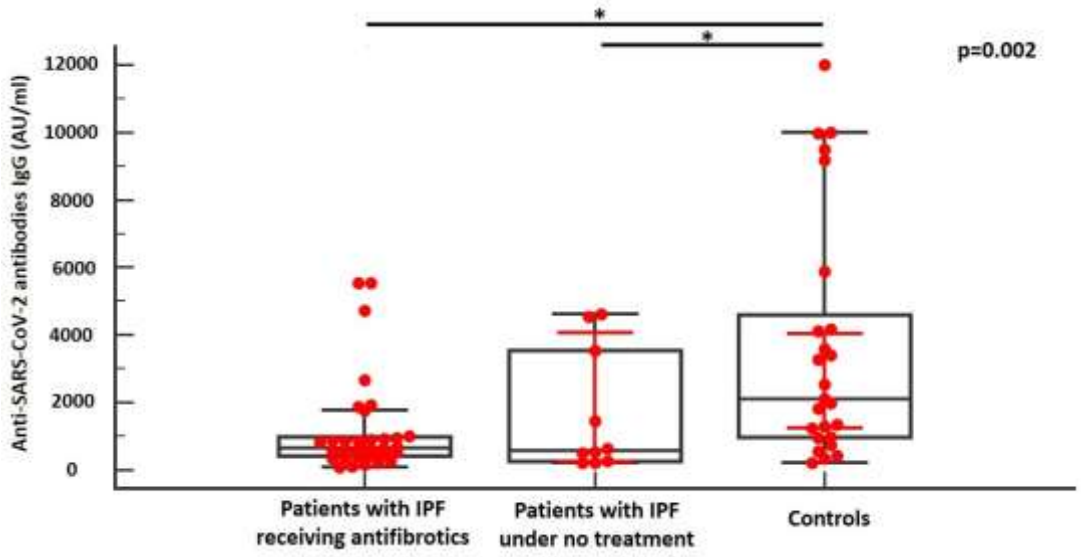

Figure 1. Both patients with IPF receiving antifibrotics and patients with IPF under no treatment had reduced levels of anti–SARS-CoV-2 antibodies after two doses of SARS-CoV-2 mRNA vaccine compared to general population (Kruskal-Wallis test, p=0.002).