COVID-19 in patients with pulmonary alveolar proteinosis: a European multicentre study

To the Editor:

Granulocyte–macrophage colony-stimulating factor (GM-CSF) signalling is essential in both alveolar macrophage (AM) differentiation and activation of lung immune cells [1]. Differentiated AMs are crucial in both the elimination of alveolar microbes and surfactant clearance. The disruption of the GM-CSF axis in AMs leads to the development of pulmonary alveolar proteinosis (PAP) [1]. In the majority of patients, this relates to the presence of autoantibodies against GM-CSF (autoimmune (a)PAP) but there are multiple other causes [1–3]. GM-CSF-deficient animals may have impaired lung inflammatory response to commensal microbes and humans with PAP may occasionally develop opportunistic lung infections [4]. The mainstay of pharmacological treatment in aPAP is inhaled GM-CSF (iGM-CSF), which is off-label but increasingly used worldwide [5–9].

SARS-CoV-2, a new infection that causes COVID-19, is clearly associated with worse prognosis in adults with pre-existing lung disorders and might represent an additional risk factor for severe pneumonia in PAP patients [10, 11]. However, controversy exists regarding the relationship between GM-CSF signalling and outcome of COVID-19 [12] (figure 1). There have been no studies in patients with PAP who also have COVID-19. We hypothesised that patients with PAP would be at increased risk and have poor outcomes. This European collaborative study aimed to investigate prevalence and clinical consequences of COVID-19 in PAP patients and the impact of prior iGM-CSF treatment on outcome.

This multicentre, observational, retrospective, European collaborative study includes all adult and paediatric PAP patients with COVID-19 diagnosed in referral centres from 11 European countries from 24 January 2020 to 31 August 2021. PAP diagnosis was based on chest computed tomography findings and the results of either lung biopsy or cytologic analysis of bronchoalveolar lavage fluid. Further characterisation of aPAP or hereditary PAP was based on increased levels of GM-CSF autoantibodies or a positive genetic analysis for CSF2RA, CSF2RB or MARS mutations respectively [1]. PAP patients were eligible if COVID-19 was confirmed either by reverse transcriptase (RT)-PCR or by compatible clinical (acute onset of fever, influenza-like symptoms, headache and anosmia), radiological and serological findings [10]. Generally, hospitalisation was considered in patients with dyspnoea or increased respiratory rate (≥30 breaths per min), or oxygen saturation ≤94% on room air or decrease in saturation to <90% with ambulation, and also on the basis of overall clinical concern by emergency department staff, including perceived risk of high risk for complications from severe COVID-19 [13]. The prevalence of COVID-19 in PAP patients was calculated, and demographic, clinical and functional characteristics closest to the time of COVID-19 infection and outcomes were collected using anonymised data forms. Since the prevalence of COVID-19 has differed between countries during the pandemic, the median prevalence (interquartile range (IQR)) of COVID-19 in all European countries participating in the study was calculated at 14.8% (11.09–17.15%), taking into consideration the population of each country and the cumulative cases of COVID-19 officially reported (https://www.ecdc.europa.eu/en/covid-19/data) (table 1). The study was approved by all medical ethics committees, primarily that of the General University Hospital “Attikon”, Athens, Greece (BΠΕΥΜ, EBΔ67/30–11–2021).

Normality of distributions was checked with the Kolmogorov–Smirnov test. Categorical variables are presented as n (%), whereas numerical variables are presented as median (interquartile range (IQR)) or as
mean (range) for the results in the adult and child populations respectively. Comparisons between groups were performed using Chi-squared tests for categorical data and the Mann–Whitney U-test for numerical data. Cox regression univariate and multivariate analyses were performed to evaluate predictors of outcome. Data were analysed using SPSS 18.0 for Windows (SPSS Inc., Chicago, IL, USA) and p-values <0.05 were considered statistically significant.

COVID-19 infection was diagnosed in 34 out of 255 PAP patients (13.3%). 31 out of 34 were adults (91.2%), 30 out of 31 with aPAP; 19 out of 31 (61.3%) were male with a median (IQR) age at inclusion of 47 (35–56) years and median disease duration 57 (35–115) months. 61.3% were ever-smokers. Median forced vital capacity was 78% (64.3–86%) predicted and median diffusing capacity of the lung for carbon monoxide ($D_{LCO}$) was 62.9% (48.8–70.75%) predicted. Long-term oxygen therapy (LTOT) was administered to seven out of 31 (22.6%), Whole-lung lavage (WLL) had been performed in 27 out of 31 (87.1%) and iGM-CSF was prescribed in 15 (48.4%) (table 1).

In aPAP patients, COVID-19 presented mostly with fever (77.4%) and dyspnoea (61.3%). All patients were infected before the preventive option of vaccination was available. 11 out of 31 patients (35.5%) needed hospitalisation, five out of 31 patients (16.1%) in the ICU. All patients with mild disease treated at home survived. Among hospitalised patients, two died and one patient underwent lung transplantation (three out of 11, 27%). These three patients had worse $D_{LCO}$ % predicted (p=0.019) and had more often arterial hypertension (p=0.012) and a smoking history (p=0.002). Treatment with iGM-CSF was withheld during hospitalisation in all patients. Sex, age, disease duration, spirometry results, LTOT, comorbidities, and history of WLL and of iGM-CSF treatment had no impact upon hospitalisation or outcome. Among seven children (five with hereditary PAP), three developed COVID-19 (two with hereditary PAP); all needed hospitalisation and all survived (table 1).

To our knowledge, this is the only study of COVID-19 disease in PAP. The major findings are: 1) COVID-19 developed in 13.3% of patients, the majority were adults (91.2%), all with aPAP and all unvaccinated; 2) one third needed hospitalisation (35.5%), almost 50% in the ICU; 3) although the numbers are small, 27% hospitalised patients either died or were lung-transplanted, whereas all patients with mild disease treated at home survived; 4) poor prognosis was related to lower $D_{LCO}$ % predicted, arterial hypertension and smoking history; 5) previous treatment with iGM-CSF had no impact upon hospitalisation or outcome; and 6) all paediatric patients were hospitalised but survived.

The prevalence of COVID-19 in PAP patients was found to be similar to the calculated median prevalence of COVID-19 in the general population of participating European Countries (13.3% versus 14.8%, 14.8%).
TABLE 1 Demographic, clinical, functional characteristics and outcomes of patients with pulmonary alveolar proteinosis (PAP) who had COVID-19 (n=34)\(^a\)

| All | Non-hospitalised | Hospitalised | p-value |
|-----|------------------|--------------|---------|
| Adults | | | |
| Patients | 34 | 20 | 14 | |
| Males | 19 (61.3%) | 12 (60.0%) | 7 (63.6%) | 0.700 |
| Age at inclusion, years, median (IQR) | 47 (35.0–56.0) | 40 (38.5–50.7) | 51 (45.0–56.0) | 0.060 |
| Duration of disease, months, median (IQR) | 57 (36.0–115.0) | 74.5 (38.0–127.5) | 43 (28.0–98.0) | 0.256 |
| Autoimmune PAP¶ | 30 (96.8%) | 19 (95%) | 11 (100%) | 0.451 |
| GM-CSF autoantibody level, μg·mL\(^{-1}\), median (IQR) | 89.5 (52.3–154.7) | 69.01 (21.1–187.7) | 107.6 (62.3–125.2) | 0.625 |
| PAP documented by lung biopsy | 9 (29%) | 3 (15%) | 6 (54.5%) | 0.020 |
| Never-/current/ex-smokers | 38.7%/9.7%/51.6% | 45%/5%/50% | 27.3%/18.2%/54.5% | 0.391 |
| BMI, kg·m\(^{-2}\), median (IQR) | 26.9 (23.5–30.0) | 26.9 (23.4–29.3) | 27 (22.6–34.0) | 0.714 |
| LTOT | 7 (22.6%) | 2 (10%) | 5 (45.5%) | 0.029 |
| Arterial hypertension | 8 (25.8%) | 2 (10%) | 6 (54.5%) | 0.007 |
| History of treatment with WLL | 27 (87.1%) | 18 (90%) | 9 (81.8%) | >0.950 |
| Number of WLLs, median (IQR) | 2 (1–4) | 2 (1–3) | 3 (1–11) | 0.283 |
| History of treatment with iGM-CSF | 15 (48.4%) | 10 (50%) | 5 (45.5%) | 0.809 |
| FVC, % predicted, median (IQR) | 78 (64.3–86.0) | 81.5 (71.0–89.0) | 73 (55.0–81.0) | 0.175 |
| DL\(_{CO}\), % predicted, median (IQR) | 62.9 (48.5–70.7) | 69.4 (53.0–75.5) | 53 (35.5–69.3) | 0.137 |
| SpO\(_2\) at rest, median (IQR) | 96.0% (95.5–98%) | 97.0% (94.0–98.0%) | 95.5% (94.5–96.2%) | 0.257 |
| Distance walked in 6MWT, m, median (IQR) | 481 (360–525) | 501 (437.5–560.0) | 407 (333.7–483.3) | 0.060 |
| Fever | 24 (77.4%) | 14 (70%) | 10 (90.9%) | 0.053 |
| Dyspnoea | 19 (61.3%) | 10 (50%) | 9 (81.8%) | 0.032 |
| Fatigue | 18 (58.1%) | 8 (40%) | 8 (72.7%) | 0.114 |
| Cough | 16 (51.6%) | 8 (40%) | 8 (72.7%) | 0.038 |
| Anosmia | 9 (29%) | 6 (30%) | 3 (27.3%) | 0.090 |
| Oxygen therapy or increase of oxygen | 24 (77.4%) | 14 (70%) | 10 (90.9%) | <0.001 |
| HFNC | 7 (22.6%) | 2 (10%) | 5 (45.5%) | 0.007 |
| Systemic corticosteroids | 18 (58.1%) | 8 (40%) | 8 (72.7%) | 0.001 |
| Macrolides | 14 (45.2%) | 6 (30%) | 8 (72.7%) | 0.001 |
| Anticoagulants | 13 (40%) | 4 (20%) | 9 (81.8%) | 0.020 |
| Remdesivir | 3 (9.4%) | 1 (6.3%) | 2 (18.2%) | 0.038 |
| Other treatment§ | 5 (16.1%) | 2 (50%) | 3 (27.3%) | 0.027 |
| iGM-CSF | 1 (6.4%) | 1 (6.3%) | 0 (0%) | 0.027 |
| ICU admission | 5 (16.1%) | 2 (50%) | 3 (27.3%) | 0.003 |
| Death or lung transplantation | 3 (9.7%) | 0 (0%) | 3 (27.3%) | 0.037 |

Children

| Patients | 7 | 4 | 3 |
| Males | 4 (57.1%) | 1 (25%) | 3 (100%) | 0.100 |
| Age at inclusion, years, mean (range) | 12 (5–17) | 6 (11–17) | 9 (5–14) | 0.108 |
| Duration of disease, months, mean (range) | 33 (3–36) | 23 (3–26) | 22 (14–36) | 0.154 |
| Autoimmune PAP | 2 (28.6%) | 1 (25%) | 1 (33.3%) | 0.809 |
| Congenital PAP¶ | 5 (71.4%) | 3 (75%) | 2 (66.7%) | 0.809 |
| BMI, kg·m\(^{-2}\), mean (range) | 11.1 (4.4–27.5) | 13.1 (11.4–27.5) | 7 (14.6–21.6) | 0.724 |
| LTOT | 5 (71.4%) | 3 (75%) | 2 (66.7%) | 0.809 |
| History of treatment with WLL | 5 (71.4%) | 3 (75%) | 2 (66.7%) | 0.809 |
| Number of WLLs, mean (range) | 96 (0–96) | 96 (0–96) | 0 (0–13) | 0.372 |
| History of treatment with iGM-CSF | 1 (14.3%) | 1 (25%) | 0 (0%) | 0.325 |
| Other treatment§ | 5 (71.4%) | 3 (75%) | 2 (66.7%) | >0.950 |
| FVC, % predicted, mean (range) | 47 (35–82) | 19 (35–58) | 47 (35–82) | >0.950 |
| DL\(_{CO}\), % predicted, mean (range) | 61 (31–92) | 18 (31–49) | 0 (92) | 0.221 |
| SpO\(_2\) at rest, mean (range) | 92% (75–97%) | 92% (75–97%) | 12% (85–97%) | >0.950 |

Hospitalisation\(^{1}\) | 3 (42.9%) | 3 (100%) | }
The median (prevalence (interquartile range, IQR) of COVID-19 for European countries participating in the study was calculated taking into consideration the population of each country and the cumulative cases of COVID-19 officially reported for each one as per 7 January 2022 and was found to be 14.8% (11.09–17.15%) (https://www.ecdc.europa.eu/en/covid-19/data): Greece 14.02%, Italy 11.74%, Germany 8.85%, Denmark 15.68%, France 17.14%, Turkey 10.81%, Poland 11.09%, Spain 14.8%, Ireland 18.13%, UK 20.74% and Portugal 15.15%. Regarding adult PAP patients, the prevalence was calculated by taking into account the patients followed-up in each centre (Italy 10/50, Greece 3/27, Turkey 3/11, Poland 3/9, Germany 2/38, France 3/38, Spain 2/9, UK 2/50, Denmark 1/10, Ireland 1/4, Portugal 1/2); overall prevalence 31 (12.5%) out of 255. Children included in the study were as follows: four in Germany, one in the UK, one in France and one in Greece; three children (Germany) presented with COVID-19; overall prevalence: 34 out of 255 (13.3%). GM-CSF: granulocyte–macrophage colony-stimulating factor; BMI: body mass index; LTOT: long-term oxygen therapy; WLL: whole-lung lavage; iGM-CSF: inhaled granulocyte–macrophage colony-stimulating factor; FVC: forced vital capacity; $D_{LCO}$: diffusing capacity of the lungs for carbon monoxide; $S_{pO2}$: oxygen saturation measured by pulse oximetry; 6MWT: 6-min walk test; HFNC: high-flow nasal cannula; ICU: intensive care unit. $\dagger$: 21 out of 31 adult patients had SARS-CoV-2 infection documented by reverse transcriptase (RT)-PCR, only one adult patient had received one dose of the vaccine against SARS-CoV-2 before developing COVID-19 and three out of three children had SARS-CoV-2 infection documented by RT-PCR. $\ddagger$: in adults, only one patient had disease related to CSF2RA (GM-CSF receptor subunit α) mutation; in children, one had disease related to CSF2RA mutation, one related to CSF2RB (GM-CSF receptor subunit β) mutation and three to MARS1; out of them, two brothers with MARS1 mutation contracted SARS-CoV-2 infection. $\S$: plasma therapy or bamlanivimab; $\|$: methionine, azithromycin, simvastatin or bromhexine. $^{\circ}$: details of treatment upon hospitalisation were available for one child, and included HFNC oxygen treatment, systemic corticosteroids and anticoagulants, but no iGM-CSF. Bold indicates statistically significant p-values (p<0.05).

During the pandemic, it soon became clear that adults with chronic respiratory diseases, especially ILD, were at increased risk of developing severe COVID-19 and dying [10, 11]. There are very few data regarding COVID-19 and ultrarare diffuse parenchymal lung diseases. Lymphangioleiomyomatosis patients with COVID-19, compared to an age-matched general population (30–59 years), had increased rates of hospitalisation but not mortality [15]. In the present study, PAP patients showed increased rates of mortality and lung transplantation, but similar to the upper limits of in-hospital mortality ranges recently reported for certain European countries [16]. This could be explained by the presence of known risk factors, such as arterial hypertension and smoking, and possibly also due to macrophage immunosuppression in PAP [4, 10]. It is known that GM-CSF facilitates AMs and other immune cells in clearing pathogens, including viruses. Based on positive results from animal models, recombinant forms of iGM-CSF are under investigation in patients with COVID-19-related acute hypoxic respiratory failure (www.clinicaltrials.gov identifier number NCT04326920). Conversely, inhibition of GM-CSF pathways could reduce the exuberant lung inflammation in COVID-19. This study cannot distinguish between these possibilities.

Only a small number of children were included in the study because of the rarity of pediatric PAP [3]; half of the patients had COVID-19 with good outcome. The effects of COVID-19 on children are less severe than in adults but the effects on children with chronic rare respiratory diseases are unknown [17].

The present study has limitations. The number of PAP patients with COVID-19 might be underestimated because asymptomatic or newly diagnosed patients could have been missed; however, the close contact of patients with this ultrarare disease with specialised centres means that it is likely that at least all patients with a known diagnosis were included. Multivariate analysis was not performed to investigate predictors of mortality because univariate analysis did not demonstrate any significant association, probably due to the limited number of patients and events. Finally, the level of enforcement of prophylactic measures may have varied between countries, and determining the effects of this on the interpretation of the data is challenging and beyond the scope of the present study. However, this collaboration permitted the analysis of data from multiple specialised centres for both children and adults, providing a unique opportunity for examining COVID-19 in this ultrarare disease.

In conclusion, PAP patients experienced similar rates of COVID-19 to the general population and high rates of hospitalisations and deaths, underscoring the vulnerability of this population and the necessity of preventive measures to avoid infection. If infected, secondary prophylaxis with monoclonal antibodies and the impact of iGM-CSF must be considered.

**TABLE 1 Continued**

| All | Non-hospitalised | Hospitalised | p-value |
|-----|-----------------|--------------|---------|
| Death or lung transplantation | 0 (0%) | 0 (0%) | >0.256 |

| All | Non-hospitalised | Hospitalised | p-value |
|-----|-----------------|--------------|---------|
| Death or lung transplantation | 0 (0%) | 0 (0%) | >0.256 |

p=0.256. However, previous studies demonstrated that other groups with interstitial lung disease (ILD) experienced lower than expected COVID-19, most probably due to better use of prophylactic measures and remote contact with physicians for electronic prescription of treatment [14]. The younger age of PAP patients and presumably their higher sociability might partly explain discrepancy.

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