



HAL
open science

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

Spyros Papiris, Ilaria Campo, Francesca Mariani, Maria Kallieri, Lykourgos Kolilekas, Andriana Papaioannou, Efsun Gonca Chousein, Erdogan Cetinkaya, Francesco Bonella, Raphael Borie, et al.

► To cite this version:

Spyros Papiris, Ilaria Campo, Francesca Mariani, Maria Kallieri, Lykourgos Kolilekas, et al.. COVID-19 in patients with pulmonary alveolar proteinosis: a European multicentre study. *ERJ Open Research*, 2023, 9 (1), pp.00199-2022. 10.1183/23120541.00199-2022 . hal-04066597

HAL Id: hal-04066597

<https://univ-rennes.hal.science/hal-04066597>

Submitted on 30 May 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License



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

Copyright ©The authors 2023

This version is distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0. For commercial reproduction rights and permissions contact permissions@ersnet.org

Received: 26 April 2022
Accepted: 23 May 2022

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 $\leq 94\%$ 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 (BΠINEYΜ, ΕΒΔ657/30–11-2021).

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



Shareable abstract (@ERSpublications)

Adult PAP patients experience similar #COVID19 rates to the general population, and high rates of hospitalisation and deaths, underscoring their vulnerability and the need for measures to prevent infection. The impact of iGM-CSF must be considered. <https://bit.ly/3M0wKnZ>

Cite this article as: Papiris SA, Campo I, Mariani F, *et al.* COVID-19 in patients with pulmonary alveolar proteinosis: a European multicentre study. *ERJ Open Res* 2023; 9: 00199-2022 [DOI: 10.1183/23120541.00199-2022].



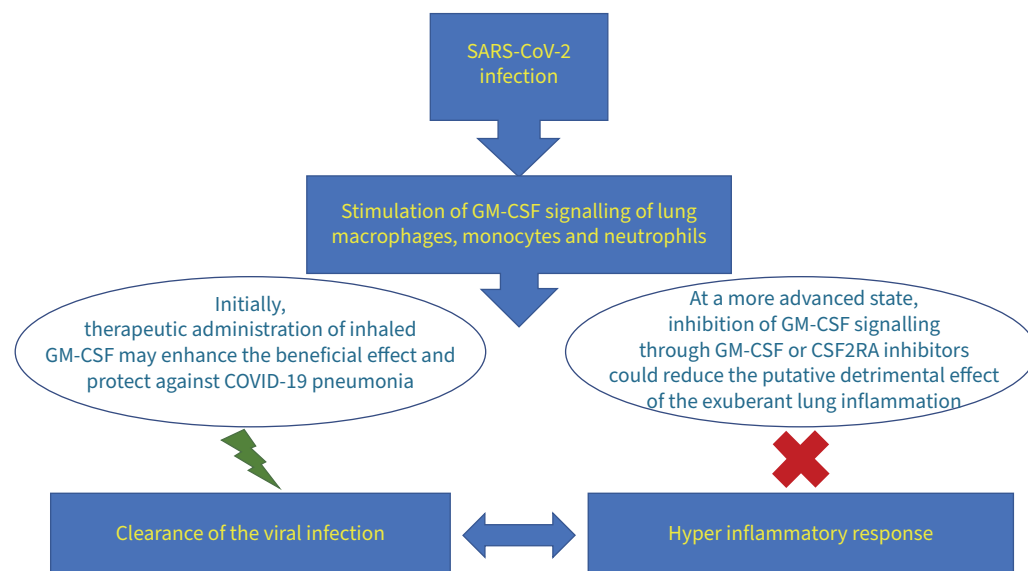


FIGURE 1 Potential relationship between granulocyte–macrophage colony-stimulating factor (GM-CSF) signalling, and the early and late inflammatory response to COVID-19. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; CSF2RA: granulocyte–macrophage colony-stimulating factor receptor subunit α .

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%,

TABLE 1 Demographic, clinical, functional characteristics and outcomes of patients with pulmonary alveolar proteinosis (PAP) who had COVID-19 (n=34)[#]

	All	Non-hospitalised	Hospitalised	p-value
Adults				
Patients	31	20	11	
Males	19 (61.3%)	12 (60.0%)	7 (63.6%)	0.700
Age at inclusion, years, median (IQR)	47 (35.0–56.0)	40 (28.5–50.7)	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, $\mu\text{g}\cdot\text{mL}^{-1}$, 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, $\text{kg}\cdot\text{m}^{-2}$, 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
D_{LCO} , % predicted, median (IQR)	62.9 (48.8–70.7)	69.4 (53.0–75.5)	53 (35.5–69.3)	0.137
S_{pO_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%)	10 (50%)	8 (72.7%)	0.114
Cough	16 (51.6%)	8 (40%)	8 (72.7%)	0.038
Anosmia	9 (29%)	6 (30%)	3 (27.3%)	>0.950
Oxygen therapy or increase of oxygen	11 (35.5%)	0 (0%)	11 (100%)	<0.001
HFNC	7 (22.6%)	0 (0%)	7 (63.6%)	p<0.001
Systemic corticosteroids	18 (58.1%)	8 (40%)	11 (100%)	0.001
Macrolides	14 (45.2%)	6 (30%)	8 (72.3%)	0.031
Anticoagulants	13 (40%)	4 (20%)	9 (81.8%)	0.020
Remdesivir	2 (6.4%)	0 (0%)	2 (18.2%)	0.118
Other treatment [†]	2 (6.4%)	0 (0%)	2 (18.2%)	0.118
iGM-CSF	2 (6.4%)	2 (10%)	0 (0%)	0.527
ICU admission	5 (16.1%)	0 (0%)	5 (45.5%)	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, $\text{kg}\cdot\text{m}^{-2}$, mean (range)	13.1 (14.4–27.5)	13.1 (14.4 (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)	13 (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 (39–58)	47 (35–82)	>0.950
D_{LCO} , % predicted, mean (range)	61 (31–92)	18 (31–49)	0 (92)	0.221
S_{pO_2} at rest, mean (range)	22% (75–97%)	22% (75–97%)	12% (85–97%)	>0.950
Hospitalisation ^f	3 (42.9%)		3 (100%)	

Continued

TABLE 1 Continued

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

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 COVID-19 patients/active PAP 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 lung for carbon monoxide; S_{pO_2} : oxygen saturation measured by pulse oximetry; 6MWT: 6-min walk test; HFNC: high-flow nasal canula; ICU: intensive care unit. [#]: 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. [†]: 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. ^{*}: plasma therapy or bamlanivimab; [§]: methionine, azithromycin, simvastatin or bromhexine. [‡]: 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).

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.

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. Lymphangiomyomatosis 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 of 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.

Spyros A. Papiris¹, Ilaria Campo², Francesca Mariani², Maria Kallieri¹, Lykourgos Kolilekas³, Andriana I. Papaioannou¹, Efsun Gonca Chousein⁴, Erdogan Cetinkaya⁴, Francesco Bonella⁵, Raphael Borie⁶, Maria Kokosi⁷, Thomas Pickworth⁸, Maria Molina-Molina⁹, Mercè Gasa⁹, Elżbieta Radzikowska¹⁰, Justyna Fijolek¹⁰, Stéphane Jouneau¹¹, Emmanuel Gomez¹², Cormac McCarthy¹³, Elisabeth Bendstrup¹⁴, Wojciech J. Piotrowski¹⁵, Rishi Pabary¹⁶, Alice Hadchouel¹⁷, Nathalie Coolen-Allou¹⁸, Tiago Alfaro¹⁹, Carlos Robalo Cordeiro¹⁹, Elvira-Markela Antonogiannaki¹, Ioannis P. Tomos¹, Despoina Papakosta²⁰, Theodoros Kontakiotis²⁰, Panagiota Panagiotou²¹, Konstantinos Douros²², Andrea Schams²³, Sara Lettieri², Vassiliki Papaevangelou²², Christina Kanaka-Gantenbein²¹, Anna Karakatsani¹, Stelios Loukides¹, Ulrich Costabel⁵, Bruno Crestani⁶, Cliff Morgan⁷, Ryushi Tazawa²⁴, Andrew Bush¹⁶, Matthias Griese²³ and Effrosyni D. Manali¹

¹General University Hospital “Attikon”, Medical School, National and Kapodistrian University of Athens, Athens, Greece. ²Laboratorio di Biochimica e Genetica, UOC Pneumologia, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy. ³7th Pulmonary Dept, Athens Chest Hospital “Sotiria”, Athens, Greece. ⁴University of Health Sciences Turkey, Yedikule Chest Diseases and Thoracic Surgery Research and Training Hospital, Istanbul, Turkey. ⁵Center for Interstitial and Rare Lung Diseases, Pneumology Dept, Ruhrlandklinik, University Hospital, University of Essen, Essen, Germany; European Reference Network (ERN)-LUNG, ILD Core Net. ⁶Université de Paris, INSERM UMR 1152, APHP, Hôpital Bichat, Service de Pneumologie A, FHU APOLLO, Centre de référence des maladies pulmonaires rares, Paris, France. ⁷Interstitial Lung Disease Unit, Royal Brompton Hospital & Harefield NHS Foundation Trust and Interstitial Lung Disease Unit, Guy’s and St Thomas’ Hospital NHS Foundation Trust, London, UK. ⁸Dept of Anaesthesia, Royal Brompton Hospital, London, UK. ⁹ILD Multidisciplinary Unit, Hospital Universitari de Bellvitge-IDIBELL, L’Hospitalet del Llobregat, Barcelona, Spain. ¹⁰3rd Dept of Lung Diseases and Oncology, National Tuberculosis and Lung Diseases Research Institute, Warsaw, Poland. ¹¹IRSET UMR 1085, Université de Rennes Service de Pneumologie, CHU de Rennes, Rennes, France. ¹²Pneumologie, CHU de Nancy, Nancy, France. ¹³University College Dublin School of Medicine Education and Research Centre, St Vincent’s University Hospital, Dublin, Ireland. ¹⁴Center for Rare Lung diseases, Dept of Respiratory Diseases and Allergy, Aarhus University Hospital, Aarhus, Denmark. ¹⁵Dept of Pneumology, 2nd Chair of Internal Medicine, Medical University of Lodz, Lodz, Poland. ¹⁶Paediatrics and Paediatric Respiriology, Imperial College and Imperial Centre for Paediatrics and Child Health, Royal Brompton & Harefield NHS Foundation Trust, London, UK. ¹⁷AP-HP, Hôpital Necker-Enfants Malades, Service de Pneumologie Pédiatrique, Centre de Référence pour les Maladies Respiratoires Rares de l’Enfant and INSERM U1151, Institut Necker Enfants Malades, Université de Paris, Faculté de Médecine, Paris, France. ¹⁸Service de Pneumologie Hôpital Félix Guyon, CHU Réunion, Reunion, France. ¹⁹Dept of Pulmonology, Coimbra University Hospital, University of Coimbra, Coimbra, Portugal. ²⁰Dept of Pulmonary Medicine, Aristotle University of Thessaloniki, “G. Papanikolaou” Hospital, Exochi, Thessaloniki, Greece. ²¹First Dept of Paediatrics, Agia Sophia Children’s Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece. ²²Third Dept of Pediatrics “Attikon” University Hospital, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece. ²³Dept of Pediatric Pneumology, Dr von Hauner Children’s Hospital, Ludwig-Maximilians-University, German Center for Lung Research, Munich, Germany. ²⁴Health Administration Center, Tokyo Medical and Dental University, Tokyo, Japan.

Corresponding author: Effrosyni Manali (fmanali@otenet.gr)

Provenance: Submitted article, peer reviewed.

Author contributions: S.A. Papiris made major contribution to the concept and design of the study, to the acquisition, analysis and interpretation of data, had access to all data and wrote the manuscript with E.D. Manali. I. Campo, F. Mariani, M. Kallieri and L. Kolilekas made major contribution to the acquisition and interpretation of data, and revised critically the work for important intellectual content. A.I. Papaioannou performed the statistical analysis of the data, contributed substantially to the interpretation of data for the work and drafted part of the manuscript. E.G. Chousein, E. Cetinkaya, F. Bonella, R. Borie, M. Kokosi, T. Pickworth, M. Molina-Molina, M. Gasa, E. Radzikowska, J. Fijolek, S. Jouneau, E. Gomez, C. McCarthy, E. Bendstrup, W.J. Piotrowski, R. Pabary, A. Hadchouel, N. Coolen-Allou, T. Alfaro, C. Robalo Cordeiro, E-M. Antonogiannaki, I.P. Tomos, D. Papakosta, T. Kontakiotis, P. Panagiotou, K. Douros, A. Schams, S. Lettieri, V. Papaevangelou, C. Kanaka-Gantenbein, A. Karakatsani, S. Loukides, U. Costabel, B. Crestani, C. Morgan, A. Bush and M. Griese made major contribution to the acquisition and interpretation of data, and revised critically the work for important intellectual content. R. Tazawa contributed in interpreting the data and revised critically the work for important intellectual content.

E.D. Manali made major contribution to the concept and design of the study, to the acquisition, analysis and interpretation of data, had access to all data, supervised the accuracy and integrity of any part of the work and wrote the manuscript with S.A. Papiris. All authors read and approved of the final version of the submitted publication.

Conflict of interest: S.A. Papiris reports grants, personal fees and nonfinancial support from La Roche Hoffman and Boehringer Ingelheim, and other support from Savara, outside the submitted work. F. Bonella reports grants and personal fees from Savara Pharma outside the submitted work. R. Borie has received consulting fees from Boehringer Ingelheim, Roche and Sanofi, outside the submitted work; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Boehringer Ingelheim and Roche, outside the submitted work; support for attending meetings and/or travel received from Boehringer Ingelheim, Roche and Chiesi outside the submitted work; and participation on a data safety monitoring or advisory board for Savara, outside the submitted work. M. Molina-Molina reports personal fees and grants from Esteve-Teijin, Roche and Boehringer Ingelheim, outside the submitted work. E. Jouneau reports personal fees and other support from Actelion, AIRB, AstraZeneca, Bellerophon Therapeutics, Biogen, BMS, Boehringer Ingelheim, Chiesi, FibroGen, Galecto Biotech, Genzyme, Gilead, GlaxoSmithKline, LVL, Mundipharma, Novartis, Pharm-Olam, Pfizer, Pliant Therapeutics, F. Hoffmann-La Roche, Ltd, Sanofi and Savara-Serendex, outside the submitted work. C. McCarthy is a scientific advisory board member of Savara Inc. unrelated to this work and has not received any payment from Savara Inc. for any work to date. E. Bendstrup reports grants and personal fees from Boehringer Ingelheim and Hofmann la Roche, and personal fees from Galapagos, outside the submitted work. M. Griese has received grants or contracts from Boehringer Ingelheim, outside the submitted work; has participated on a data safety or advisory board for Boehringer Ingelheim, outside the submitted work; and is the Head of chILD-EU, outside the submitted work. E.D. Manali reports personal fees and nonfinancial support from La Roche Hoffman; grants, personal fees and nonfinancial support from Boehringer Ingelheim; and other support from Savara, all outside the submitted work. The remaining authors have nothing to disclose.

References

- 1 Trapnell BC, Nakata K, Bonella F, *et al.* Pulmonary alveolar proteinosis. *Nat Rev Dis Primers* 2019; 5: 16.
- 2 Hadchouel A, Wieland T, Griese M, *et al.* Biallelic mutations of methionyl-tRNA synthetase cause a specific type of pulmonary alveolar proteinosis prevalent on Réunion Island. *Am J Hum Genet* 2015; 96: 826–831.
- 3 Bush A, Pabary R. Pulmonary alveolar proteinosis in children. *Breathe (Sheff)* 2020; 16: 200001.
- 4 Tazawa R, Hamano E, Arai T, *et al.* Granulocyte-macrophage colony-stimulating factor and lung immunity in pulmonary alveolar proteinosis. *Am J Respir Crit Care Med* 2005; 171: 1142–1149.
- 5 Tazawa R, Trapnell BC, Inoue Y, *et al.* Inhaled granulocyte/macrophage-colony stimulating factor as therapy for pulmonary alveolar proteinosis. *Am J Respir Crit Care Med* 2010; 181: 1345–1354.
- 6 Papiris SA, Tsigiotis P, Kolilekas L, *et al.* Long-term inhaled granulocyte macrophage-colony stimulating factor in autoimmune pulmonary alveolar proteinosis: effectiveness, safety, lowest-effective dose. *Clin Drug Invest* 2014; 34: 553–564.
- 7 Papiris SA, Tsigiotis P, Kolilekas L, *et al.* Pulmonary alveolar proteinosis: time to shift? *Expert Rev Respir Med* 2015; 9: 337–349.
- 8 Tazawa R, Ueda T, Abe M, *et al.* Inhaled GM-CSF for pulmonary alveolar proteinosis. *N Engl J Med* 2019; 381: 923–932.
- 9 Trapnell BC, Inoue Y, Bonella F, *et al.* Inhaled molgramostim therapy in autoimmune pulmonary alveolar proteinosis. *N Engl J Med* 2020; 383: 1635–1644.
- 10 Gallay L, Uzunhan Y, Borie R, *et al.* Risk factors for mortality after COVID-19 in patients with preexisting interstitial lung disease. *Am J Respir Crit Care Med* 2021; 203: 245–249.
- 11 Beltramo G, Cottinet J, Mariet AS, *et al.* Chronic respiratory diseases are predictors of severe outcome in COVID-19 hospitalized patients: a nationwide study. *Eur Respir J* 2021; 58: 2004474.
- 12 Bonaventura A, Vecchié A, Wang TS, *et al.* Targeting GM-CSF in COVID-19 pneumonia: rationale and strategies. *Front Immunol* 2020; 11: 1625.
- 13 Boston University School of Medicine. COVID19 clinical criteria for discharge. <https://www.bumc.bu.edu/id/covid-19-response/clinical-algorithms-for-admission-and-discharge/> Date last updated: 2 December 2020.
- 14 Papiris SA, Bouros D, Markopoulou K, *et al.* Early COVID-19 lockdown in Greece and idiopathic pulmonary fibrosis: a beneficial “impact” beyond any expectation. *Eur Respir J* 2021; 57: 2003111.
- 15 Baldi BG, Radzikowska E, Cottin V, *et al.* COVID-19 in lymphangioleiomyomatosis: an international study of outcomes and impact of mTOR inhibition. *Chest* 2021; 161: 1589–1593.
- 16 Gray WK, Navaratnam AV, Day J, *et al.* COVID-19 hospital activity and in-hospital mortality during the first and second waves of the pandemic in England: an observational study. *Thorax* 2022; 77: 1113–1120.
- 17 Rasmussen SA, Thompson LA. Coronavirus disease 2019 and children: what pediatric health care clinicians need to know. *JAMA Pediatr* 2020; 174: 743–744.