Bridges of Pulmonology 2023 proceedings: Highlights in the field of interstitial lung diseases

Vasilina Sotiropoulou[1]*, Panagiota Tsiri[1]*, Athena Gogali[2], Vasileios Tzilas[3], Demosthenes Bouros[4], Argyris Tzouvelekis[1]

The first patient-centered scientific congress in the field of Greek respiratory medicine, Bridges of Pulmonology 2023, took place on June 2023, in Patras. The congress welcomed over 1000 participants on its hybrid platform 'bridging' specialized professionals from different medical fields and highlighting the importance of a modern holistic approach in the management of the respiratory patient. A wide spectrum of topics was discussed, some of which were focused on interstitial lung diseases (ILDs). We aim to summarize the scientific highlights of Bridges of Pulmonology 2023 in the field of ILDs, enriched with the latest literature review.

Despite their similar clinical presentation, fibrotic lung diseases of different cause may have different prognosis and management. Grouping ILDs with progressive fibrosing behavior remains challenging, given that the response to treatment and the risk of further progression may differ according to the underlying disease entity[1]. On the other hand, splitting pulmonary fibrosis in order to apply personalized medicine has been hampered by the lack of clinically applicable molecular biomarkers linking endotypes with clinical phenotypes. Shedding light on the cellular and molecular mechanisms that generate and regulate fibrosis would be of great importance[2]. Recently, single cell profiling data have revealed cellular changes and immune aberrations in the usual interstitial pneumonia (UIP) lung. Several cell populations, such as alveolar epithelial cells and endothelial capillary cells, are substantially reduced in the fibrotic lung parenchyma samples[3]. In contrast, aberrant basaloid cells, a previously unknown cell type co-expressing epithelial, basal, mesenchymal and senescence genes and highly expressing genes typically related to idiopathic pulmonary fibrosis (IPF), have been identified in the fibroblastic foci, but not in control donor lungs[3]. Ectopic bronchial vascular endothelial cells abound in the affected alveolar regions of remodeling in IPF, while these cells are limited to the normal airway circulation. This finding is consistent with the already described histological observation of 'proximalization' of the distal airways in IPF[3]. Moreover, peripheral blood and lung single-cell RNA data from patients with IPF demonstrated that the immune elements and the chemokine signaling pathways could differentiate progressors from non-progressors. Classical monocytes and regulatory T-cells are increased, while other lymphocytic populations are decreased in progressive IPF compared to stable. Combined evidence from lung and blood samples, associated specific cytokines receptors (CCR) and their ligands (CCL) with the accumulation of these cell types, such as CCR2/CCL7 for monocytes and CCR4/CCL17 and CCR8/CCL18 for regulatory T-cells, and a mechanism of lung-blood recruitment has been suggested[4]. Despite promising data, the future taxonomy of pulmonary fibrosis based on sequencing technology is still in its infancy.

The recently-introduced term 'progressive pulmonary fibrosis' (PPF) encompasses certain non-IPF ILDs that develop a progressive phenotype, as defined by clinical, functional and radiological criteria[5]. Both anti-fibrotic agents can decelerate disease progression, as measured by forced vital capacity (FVC) decline from baseline, but only nintedanib has received conditional recommendation for the treatment of PPF[6]. The identification of the predictors of disease progression, to integrate an individually tailored management approach

AFFILIATION
1 Department of Respiratory Medicine, University Hospital of Patras, Patras, Greece
2 Department of Respiratory Medicine, University Hospital of Ioannina, Ioannina, Greece
3 5th Department of Respiratory Medicine, 'Sotiria' General Hospital of Chest Diseases, Athens, Greece
4 1st University Department of Respiratory Medicine, 'Sotiria' General Hospital of Chest Diseases, Athens, Greece
* Co-first authors

CORRESPONDENCE TO
Argyrios Tzouvelekis. Department of Respiratory Medicine, University Hospital of Patras, 26504, Rion, Achaia Patras, Patras, Greece.
E-mail: atzouvelekis@upatras.gr
ORCID iD: https://orcid.org/0000-0002-6295-1384

KEYWORDS
interstitial lung diseases, Bridges of Pulmonology, progressive pulmonary fibrosis, REMAP-ILD, ILD genetic screening

Received: 2 January 2024
Revised: 9 February 2024
Accepted: 21 February 2024

Pneumon 2024;37(1):15
https://doi.org/10.18332/pne/183960

in the context of personalized medicine is of paramount importance. UIP pattern is an independent predictor of acute exacerbations and disease progression in non-IPF ILDs[7]. In a cohort of 167 patients with rheumatoid arthritis-ILD (RA-ILD), the gradual decline of pulmonary function is worse in UIP pattern than nonspecific interstitial pneumonia[8]. Moreover, the extent of fibrotic features, the presence of honeycombing and traction bronchiectasis, as well as the elevated systolic pulmonary artery pressure >36.5 mmHg, are independent risk factors for mortality in IPF and other fibrosing ILDs[9,10]. A substantial minority of patients with scleroderma-related-ILD (SSc-ILD) may present with a rapid, continuous pattern of FVC decline with several consecutive episodes of deterioration. The phenotype of rapid progressors includes early-onset diffuse cutaneous SSc, with elevated acute-phase markers and topoisomerase I antibody positivity[11].

With regard to recent advances in non-IPF ILDs treatment, both mycophenolate mofetil (MMF) and cyclophosphamide presented favorable results in lung function, imaging, and clinical presentation in symptomatic/progressive SSc-ILD, while MMF had a better toxicity profile[12]. Additionally, improvement of skin thickening and FVC measurements were noticed in patients with SSc treated with rituximab[13]. Towards this direction, the RECITAL study showed non-superiority of rituximab compared to cyclophosphamide in progressive connective-tissue disease-ILDs (CTD-ILDs), and therefore, rituximab may be an alternative therapeutic choice in severe CTD-ILDs[14]; yet, the majority of these patients displayed an inflammatory imaging phenotype based on HRCT pattern. In the FOCUSSCED trial, tocilizumab stabilized lung function in a population of patients with early SSc-ILD with diffuse skin involvement, active disease and high inflammatory markers or platelet count[15]. Among anti-fibrotics, only nintedanib has been proved to reduce the annual rate of FVC decline in patients with SSc-ILD. Moreover, a subgroup analysis of SENSCIS trial suggests a possible benefit of nintedanib on top of MMF in SSc, along with a good safety profile[16]. Nintedanib's safety profile and efficacy were also assessed on SENSCIS-ON trial favoring its long-term use[17]. On the other hand, there is a pressing need for further research about pirfenidone, as the unclassifiable ILD and RELIEF trials were limited by their small sample size and the non-significance level of their primary endpoint[18,19]. These results may indicate pitfalls in current clinical practice, where treatment initiation occurs after FVC decline and thus, irreversible lung damage has already been installed.

Ongoing clinical trials could hopefully broaden the therapeutic horizons of ILDs by identifying potential molecular targets and novel effective agents. However, drug development can take years for a single asset, and therefore, acceleration of these processes could be a game-changer. Growing interest has been noted in enhanced methods to bring robust evidence particularly in heterogenous diseases requiring multiple concomitant therapies. A new approach to trial design, which is known as Randomized, Embedded, Multifactorial, Adaptive Platform (REMAP), will favor the assessment of multiple concurrent therapies. A flagship study designed before COVID-19 pandemic for the assessment of community acquired pneumonia (CAP), REMAP-CAP, successfully showed the effectiveness of various treatment options for COVID-19 patients as well. Towards this direction, the aim of REMAP-ILD, detailly presented in this congress, is to create an international platform for clinical trials that can accelerate the assessment of therapies for individuals with ILD[20]. The primary endpoint is the FVC trajectory incorporating data from baseline, 12-month follow-up and any time points in between, indicating it as a better marker due to its easiness and frequency of measurement. The numerous medications that could be assessed simultaneously, the lower risk of individuals receiving ineffective therapy and the spectrum of patients with different types and stages of the disease, including rare forms, highlight a promising global modular adaptive trial.

In the era of personalized medicine, genetic screening could be a strong asset. During the last decades, intense research has elucidated pulmonary fibrosis genetic predisposition by the detection of numerous gene variants related to sporadic or familial fibrotic lung diseases[21]. Fibrogenic variants may reflect disease clinical characteristics, natural history and prognosis and may provide timely therapeutic approaches. Mutations in telomerase reverse transcriptase (TERT) and telomerase RNA(TERC) have been associated with multisystemic clinical syndromes, the telomeropathies, with concurrent hepatic, cutaneous or hematological disorders. Moreover, carriers of TERT and TERC pathogenic variations present pulmonary fibrosis of early onset and rapidly progressive course, with worse prognosis and worse outcomes after lung transplantation compared to non-carriers[22,23]. Interestingly, the prognostic significance of the telomere related gene (TRG) variants is higher than the histopathological and clinical features[24]. Additionally, higher incidence of lung cancer, usually adenocarcinomas, has been noticed in patients carrying pathogenic surfactant-related gene (SRG) variants. In carriers of *SFTPA* mutations, lung cancer is diagnosed more frequently and in younger ages than expected and coexists with pulmonary fibrosis in two-thirds of cases. The possible underlying mechanisms include promotion of necroptosis without apoptosis and deficit surfactant protein-A-associated anti-neoplastic properties[25]. The mucin 5B promoter polymorphism has been associated with UIP pattern and may contribute to the early recognition of subclinical RA-ILD as part of a scoring system[26]. Regarding the therapeutic implications, recent data suggest that antifibrotic agents are beneficial for patients with pathogenic TRG alleles[27]. Clinical trials investigating the potential effect of the synthetic androgen Danazol in telomere related syndromes are currently in process[28]. Gene-based strategies of restoring surfactant function or telomere length are in the development pipeline with growing therapeutic potential, and may present favorable clinical outcomes in the future[29,30].

The recently published European Respiratory Society statement on familial pulmonary fibrosis (FPF), suggests that genetic testing and counselling may be beneficial for: 1) patients with FPF, defined as having more than one relative of first or second degree with pulmonary fibrosis; 2) asymptomatic individuals with a recognized disease-causing allele in their family; 3) patients aged under 50 years with pulmonary fibrosis of unknown cause; and 4) patients with clinical characteristics suggestive of telomeropathy[31]. In the appropriate setting, genetic testing could be an option for patients with interstitial lung abnormalities, pretransplant patients or members of families where pulmonary fibrosis or lung adenocarcinoma appear through generations[32,33]. The routinely analyzed gene panel includes SRGs and TRGs, while screening for single nucleotide polymorphisms is not currently suggested[31]. Considering the current lack of official guidelines, the implementation of genetic testing in clinical practice still presents major challenges. The availability of techniques, the funding requirements and the different legislation rules among countries comprise significant hurdles[33,34]. Expertise in the field, along with a multidisciplinary approach, are prerequisites for the accomplishment and evaluation of the genetic analysis, and therefore, it can only be performed in highly specialized and fully equipped institutions[33,34]. The psychosocial impact of ILD diagnosis or predisposition must be taken into consideration. Therefore, it is necessary that genetic testing be accompanied by genetic counselling and follow-up of the patients and relatives[33]. The discovery of more genetic culprits, the elucidation of possible clinical and therapeutic implications of pathogenic variants in asymptomatic individuals and the demarcation of the role of genetic screening in the personalized management of pulmonary fibrosis, are anticipated future perspectives.

A multidisciplinary team approach will improve the management of the ILD patient. Of note, ongoing efforts to promote personalized medicine will hopefully enrich this effort. The presented findings and proposals for further research may inspire both senior and young investigators to create 'bridges' in order to better understand the upcoming challenges, prolonging survival, and improving patients' quality of life.

CONFLICTS OF INTEREST

The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none was reported.

FUNDING

There was no source of funding for this research.

ETHICAL APPROVAL AND INFORMED CONSENT

Ethical approval and informed consent were not required for this study.

DATA AVAILABILITY

Data sharing is not applicable to this article as no new data were created.

PROVENANCE AND PEER REVIEW

Commissioned; externally peer reviewed.

DISCLAIMER

A. Gogali and A. Tzouvelekis report that they are Editorial Board Members of Pneumon. They had no involvement in the peer-review or acceptance of this article, and had no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to a handling editor of the journal. The views and opinions expressed in this article are those of the authors.

REFERENCES

1. Rajan SK, Cottin V, Dhar R, et al. Progressive pulmonary fibrosis: an expert group consensus statement. Eur Respir J. 2023;61(3):2103187. doi:10.1183/13993003.03187-2021
2. Wells AU, Brown KK, Flaherty KR, Kolb M, Thannickal VJ; IPF Consensus Working Group. What's in a name? That which we call IPF, by any other name would act the same. Eur Respir J. 2018;51(5):1800692. doi:10.1183/13993003.00692-2018
3. Adams TS, Schupp JC, Poli S, et al. Single-cell RNA-seq reveals ectopic and aberrant lung-resident cell populations in idiopathic pulmonary fibrosis. Sci Adv. 2020;6(28):eaba1983. doi:10.1126/sciadv.aba1983
4. Unterman A, Zhao AY, Neumark N, et al. Single-cell profiling reveals immune aberrations in progressive idiopathic pulmonary fibrosis. medRxiv. Preprint posted online April 29, 2023. doi:10.1101/2023.04.29.23289296
5. Raghu G, Remy-Jardin M, Richeldi L, 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(9):e18-e47. doi:10.1164/rccm.202202-0399ST
6. Wongkarnjana A, Scallan C, Kolb MRJ. Progressive fibrosing interstitial lung disease: treatable traits and therapeutic strategies. Curr Opin Pulm Med. 2020;26(5):436-442. doi:10.1097/MCP.0000000000000712
7. Choe J, Chae EJ, Kim YJ, Do KH, Song JS, Song JW. Serial changes of CT findings in patients with chronic hypersensitivity pneumonitis: imaging trajectories and predictors of fibrotic progression and acute exacerbation. Eur Radiol. 2021;31(6):3993-4003. doi:10.1007/s00330-020-07469-2
8. Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Progressive Decline of Lung Function in Rheumatoid Arthritis-Associated Interstitial Lung Disease. Arthritis Rheumatol. 2017;69(3):542-549. doi:10.1002/art.39971
9. Kolb M, Vašáková M. The natural history of progressive fibrosing interstitial lung diseases. Respir Res. 2019;20(1):57. doi:10.1186/s12931-019-1022-1
10. Chen X, Guo J, Yu D, Jie B, Zhou Y. Predictors of Mortality in

Progressive Fibrosing Interstitial Lung Diseases. Front Pharmacol. 2021;12:754851. doi:10.3389/fphar.2021.754851
11. Hoffmann-Vold AM, Allanore Y, Alves M, et al. Progressive interstitial lung disease in patients with systemic sclerosis-associated interstitial lung disease in the EUSTAR database. Ann Rheum Dis. 2021;80(2):219-227. doi:10.1136/annrheumdis-2020-217455
12. Tashkin DP, Roth MD, Clements PJ, et al. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. Lancet Respir Med. 2016;4(9):708-719. doi:10.1016/S2213-2600(16)30152-7
13. Daoussis D, Melissaropoulos K, Sakellaropoulos G, et al. A multicenter, open-label, comparative study of B-cell depletion therapy with Rituximab for systemic sclerosis-associated interstitial lung disease. Semin Arthritis Rheum. 2017;46(5):625-631. doi:10.1016/j.semarthrit.2016.10.003
14. Maher TM, Tudor VA, Saunders P, et al. Rituximab versus intravenous cyclophosphamide in patients with connective tissue disease-associated interstitial lung disease in the UK (RECITAL): a double-blind, double-dummy, randomised, controlled, phase 2b trial. Lancet Respir Med. 2023;11(1):45-54. doi:10.1016/S2213-2600(22)00359-9
15. Khanna D, Lin CJF, Furst DE, et al. Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med. 2020;8(10):963-974. doi:10.1016/S2213-2600(20)30318-0
16. Highland KB, Distler O, Kuwana M, et al. Efficacy and safety of nintedanib in patients with systemic sclerosis-associated interstitial lung disease treated with mycophenolate: a subgroup analysis of the SENSCIS trial. Lancet Respir Med. 2021;9(1):96-106. doi:10.1016/S2213-2600(20)30330-1
17. Allanore Y, Vonk MC, Distler O, et al. Continued treatment with nintedanib in patients with systemic sclerosis-associated interstitial lung disease: data from SENSCIS-ON. Ann Rheum Dis. 2022;81(12):1722-1729. doi:10.1136/ard-2022-222564
18. Behr J, Prasse A, Kreuter M, et al. Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis (RELIEF): a double-blind, randomised, placebo-controlled, phase 2b trial. Lancet Respir Med. 2021;9(5):476-486. doi:10.1016/S2213-2600(20)30554-3
19. Maher TM, Corte TJ, Fischer A, et al. Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: a double-blind, randomised, placebo-controlled, phase 2 trial. Lancet Respir Med. 2020;8(2):147-157. doi:10.1016/S2213-2600(19)30341-8
20. REMAP-ILD: Randomised, embedded, multifactorial, adaptive platform trial for interstitial lung disease. Imperial College London. Accessed February 2, 2024. https://www.imperial.ac.uk/mtw-centre-fibrosing-lung-disease/research/remap-ild/
21. Borie R, Le Guen P, Ghanem M, et al. The genetics of interstitial lung diseases. Eur Respir Rev. 2019;28(153):190053. doi:10.1183/16000617.0053-2019
22. Borie R, Tabèze L, Thabut G, et al. Prevalence and characteristics of TERT and TERC mutations in suspected genetic pulmonary fibrosis. Eur Respir J. 2016;48(6):1721-1731. doi:10.1183/13993003.02115-2015
23. Choi B, Messika J, Courtwright A, et al. Airway complications in lung transplant recipients with telomere-related interstitial lung disease. Clin Transplant. 2022;36(3):e14552. doi:10.1111/ctr.14552
24. Newton CA, Batra K, Torrealba J, et al. Telomere-related lung fibrosis is diagnostically heterogeneous but uniformly progressive. Eur Respir J. 2016;48(6):1710-1720. doi:10.1183/13993003.00308-2016
25. van Moorsel CHM, van der Vis JJ, Grutters JC. Genetic disorders of the surfactant system: focus on adult disease. Eur Respir Rev. 2021;30(159):200085. doi:10.1183/16000617.0085-2020
26. Juge PA, Granger B, Debray MP, et al. A Risk Score to Detect Subclinical Rheumatoid Arthritis-Associated Interstitial Lung Disease. Arthritis Rheumatol. 2022;74(11):1755-1765. doi:10.1002/art.42162
27. Justet A, Klay D, Porcher R, et al. Safety and efficacy of pirfenidone and nintedanib in patients with idiopathic pulmonary fibrosis and carrying a telomere-related gene mutation. Eur Respir J. 2021;57(2):2003198. doi:10.1183/13993003.03198-2020
28. Mackintosh JA, Pietsch M, Lutzky V, et al. TELO-SCOPE study: a randomised, double-blind, placebo-controlled, phase 2 trial of danazol for short telomere related pulmonary fibrosis. BMJ Open Respir Res. 2021;8(1):e001127. doi:10.1136/bmjresp-2021-001127
29. Cooney AL, Wambach JA, Sinn PL, McCray PB. Gene Therapy Potential for Genetic Disorders of Surfactant Dysfunction. Front Genome Ed. 2022;3:785829. doi:10.3389/fgeed.2021.785829
30. Alder JK, Armanios M. Telomere-mediated lung disease. Physiol Rev. 2022;102(4):1703-1720. doi:10.1152/physrev.00046.2021
31. Borie R, Kannengiesser C, Antoniou K, et al. European Respiratory Society statement on familial pulmonary fibrosis. Eur Respir J. 2023;61(3):2201383. doi:10.1183/13993003.01383-2022
32. Newton CA, Oldham JM, Applegate C, et al. The Role of Genetic Testing in Pulmonary Fibrosis: A Perspective From the Pulmonary Fibrosis Foundation Genetic Testing Work Group. Chest. 2022;162(2):394-405. doi:10.1016/j.chest.2022.03.023
33. Papiris SA, Kannengiesser C, Borie R, et al. Genetics in Idiopathic Pulmonary Fibrosis: A Clinical Perspective. Diagnostics (Basel). 2022;12(12):2928. doi:10.3390/diagnostics12122928
34. Borie R, Kannengiesser C, Sicre de Fontbrune F, Gouya L, Nathan N, Crestani B. Management of suspected monogenic lung fibrosis in a specialised centre. Eur Respir Rev. 2017;26(144):160122. doi:10.1183/16000617.0122-2016