ERS International Congress 2023: highlights from the Interstitial Lung Diseases Assembly

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Shareable abstract (@ERSpublications)
This article summarises a selection of scientific highlights in the field of interstitial lung diseases presented at #ERSCongress 2023 https://bit.ly/3FOy10A

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Abstract

This article summarises a selection of scientific highlights in the field of interstitial lung diseases (ILDs) presented at the International Congress of the European Respiratory Society in 2023. Translational and clinical studies focused on the whole spectrum of ILDs, from (ultra)rare ILDs to sarcoidosis, ILDs associated with connective tissue disease and idiopathic pulmonary fibrosis. The main topics of the 2023 Congress presentations were improving the diagnostic process of ILDs, better prediction of disease course and investigation of novel treatment options.

Introduction

During the hybrid European Respiratory Society (ERS) Congress 2023 in Milan, Italy, many sessions were dedicated to interstitial lung diseases (ILDs). Interesting new data were presented in five oral presentation sessions, one ALERT (Abstracts Leading to Evolution in Respiratory Medicine Trials) session and >15 thematic poster sessions. The 2023 symposia and hot topic sessions were focused on progressive pulmonary fibrosis (PPF), symptom burden in ILD, pulmonary hypertension and ILD and the role of novel imaging modalities in sarcoidosis.

Every year, early career members and assembly officers summarise a selection of the scientific highlights presented at the ERS Congress for the different groups of Assembly 12: group 12.01 "Idiopathic interstitial pneumonias (IIPs)", group 12.02 "ILDs/diffuse parenchymal lung diseases (DPLDs) of known origin", group

12.03 “Sarcoidosis and other granulomatous ILDs/DPLDs” and group 12.04 “Rare ILDs/DPLDs” [1, 2]. In this review article, we will focus on key results and take-home messages of translational and clinical research presented in oral presentation or thematic poster sessions.

Group 12.01: Idiopathic interstitial pneumonias

A broad range of novel research findings was presented during the ERS Congress in the field of IIPs. Translational studies focused on unravelling the pathogenesis of pulmonary fibrosis and identifying new treatment targets. Important topics for clinical studies were early and adequate diagnosis, better prediction of disease course and novel disease modifying and symptomatic pharmacological treatment options (figure 1).

Several abstracts highlighted the potential of spatial transcriptomics to unravel disease mechanisms. Justet *et al.* [3] looked for similarities between patients with idiopathic pulmonary fibrosis (IPF) and long COVID. The results showed abnormal cell populations in both disease groups, compared to healthy controls. These preliminary data must be confirmed in larger cohorts but are interesting given the lung parenchymal sequelae that may follow COVID-19 infections. Bell *et al.* [4] also used spatial transcriptomic profiling to characterise fibroblast foci; analysis revealed a distinct gene expression profile with enrichment in complex extracellular matrix productions and bone morphogenesis. They also showed that a 3D spheroids-based culture model most closely recapitulates the transcriptome of fibroblast foci. Another promising *in vitro* model are the organoids used by Khan *et al.* [5]. The group created organoids from IPF-derived alveolar cells able to express similar functional and morphological properties to honeycomb cysts. Bozza *et al.* [6] developed hyaluronic acid decorated liposomes loaded with imatinib (XHALIP), which may represent a tool to deliver drugs with reduced systemic side effects. Promising data for drug development were also presented by Rosas *et al.* [7]. The group showed increased cGAS-STING activity contributes to senescence in IPF; thus, STING inhibitors might be a new alternative with a dual senomorphic/senolytic effect.

A few studies used animal models to investigate the potential of new treatment targets for IPF. Petersen *et al.* [8] studied the therapeutic effects of ALK5i in a mouse model combining bleomycin with high-fat diet. Results were promising and this model could represent a new tool to explore novel therapeutic agents for IPF. Vanegas *et al.* [9] investigated SMAC mimetic treatment (BI891065), targeting the inhibitor of apoptosis protein cIAP1, in a mouse model. SMAC mimetic treatment had anti-fibrotic activity by promoting myofibroblast apoptosis.

Other translational research endeavours focused on characterising various populations affected by pulmonary fibrosis. An interesting Finnish study delved into the genetic landscape of patients with IPF [10]. Through

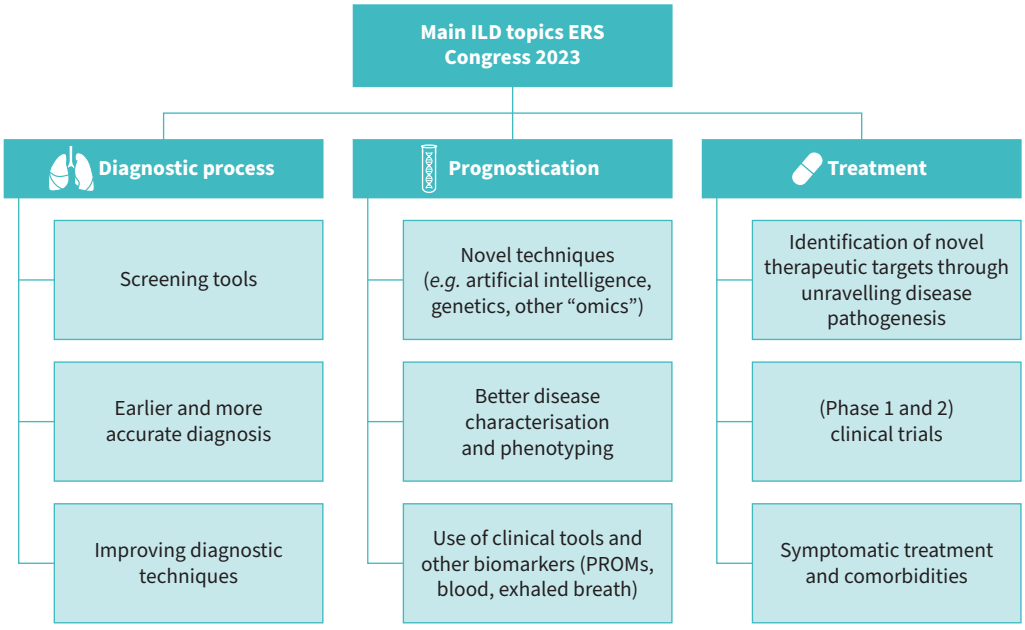

FIGURE 1 Overview of the main topics for interstitial lung disease (ILD) at the European Respiratory Society (ERS) Congress 2023. PROMs: patient reported outcome measures.

genetic mapping they found that a newly identified missense variant in KIF15 was associated with a distinctive worse clinical profile. KIF15 was identified to be enriched in the Finnish population. Patients with this genetic variant had early disease onset and a rapid progression of symptoms, shedding light on the intricate interplay between genetics and disease progression in the context of IPF.

Moving to the diagnostic fields, Furukawa *et al.* [11] presented results of the PROMISE study, the Japanese ILD registry, which included 2741 patients. Interestingly, after a central multidisciplinary discussion ILD diagnosis was changed in 47% of all patients and in 83% of patients that were initially diagnosed as unclassifiable ILD. This highlights the importance of collaboration between community and referral centres. Trushell-Pottinger *et al.* [12] presented data from a UK national pilot lung screening programme. Of 8800 participants, 651 (7.4%) had radiological interstitial lung changes on chest computed tomography (CT). Of these, 85% were successively given a diagnosis of ILD, with no differences between asymptomatic and symptomatic patients. Consequently, lung cancer screening offers an opportunity for early diagnosis and intervention. Van der Sar *et al.* [13] evaluated the potential of exhaled breath analysis using electronic nose (eNose) technology for diagnosis of ILD. The eNose differentiated ILD from other chronic respiratory diseases (asthma, COPD, lung cancer) with an area under the curve (AUC) of 98% (95% CI 96–100). Data should be validated in larger, external cohorts, but hold promise to shorten diagnostic delay, particularly if used as a screening tool in primary care.

Better prediction of disease progression and mortality remains an important field of study in IIPs. The CleanUP-IPF study hypothesised that a less diverse buccal microbiome would be associated with worse survival in IPF, similar to previous findings in the lung microbiome [14]. However, data showed that a greater buccal microbiome diversity was associated with worse survival. Results must be replicated in an independent cohort, but if confirmed, the buccal microbiome could be a predictive tool of survival in IPF. Guler *et al.* [15] analysed the predictive value of the clinical frailty scale, a very simple and widely used tool in clinical practice. Small but significant differences were found in fit *versus* vulnerable patients in mean annual change of forced vital capacity (FVC) and 6-min walking distance. The differences in trajectories remained similar with adjustment for age, sex, body mass index, ever-smoking, ILD diagnosis and drug treatment. If confirmed in other cohorts, the clinical frailty scale might contribute to estimating disease progression in individual patients with pulmonary fibrosis. Finally, Im and Yoo [16] developed a nomogram to predict postoperative pulmonary complications after resection of early-stage lung cancer in IPF. The nomogram is based on six clinical variables and could guide the decision-making process in this patient group. A multicentre cohort from the Netherlands evaluated the real-world use of online home spirometry in patients with different forms of pulmonary fibrosis [17]. Interestingly, lung function course in patients with IPF and other forms of pulmonary fibrosis was similar, with a rapidly progressive disease course in approximately one third of patients. This study emphasised that home spirometry is feasible and reliable as a tool for frequent monitoring in regular care.

More effective treatment for pulmonary fibrosis remains an important unmet need. Encouragingly, many research groups presented results of disease modifying and symptomatic treatment options in this field (table 1). A *post hoc* analysis in patients with IPF investigated the senolitic potential of a combination of dasatinib (100 mg daily) and quercetin (1250 mg daily) [18]. A significant improvement in senolitic markers (increase in alpha-klotho and a decrease in GPNMB/osteoactivin) was found, but no improvement in short-term clinical outcomes. Anti-interleukin (IL)-11 therapies showed promising anti-fibrotic effects in preclinical model of lung fibrosis, reducing collagen deposition and extracellular matrix remodelling. In a phase 1 trial, Arora *et al.* [19] studied the potential of LASN01, a fully monoclonal antibody targeting IL-11. In healthy volunteers, LASN01 inhibited >95% of the IL-11R signalling and was well-tolerated.

Wuyts *et al.* [20] presented the results from the phase 2a INTEGRIS-IPF study on bexotegrast, a dual-selective inhibitor of αvβ6 and αvβ1. Bexotegrast 320 mg was well-tolerated in participants with IPF up to 40 weeks of treatment. Although not powered to assess efficacy, bexotegrast seemed to reduce FVC decline and in a majority of patients Quantitative Lung Fibrosis (QLF) score improved. The follow-up BEACON-IPF study will assess efficacy of bexotegrast. Glaspole *et al.* [21] evaluated ACT001, a drug derived from parthenolide that targets NF-κB and STAT3 signalling pathways, as an interesting therapeutic candidate for pulmonary fibrosis. Results showed that ACT001 reduced FVC decline after 52 weeks in a group of 44 patients. Borie *et al.* [22] presented the results of the ANDROTELO trial, a phase 2 study that evaluated safety and efficacy danazol, a synthetic hormonal drug, in familial pulmonary fibrosis associated with telomere-related gene mutations. While lung function remained stable in a majority of patients, unfortunately, danazol was poorly tolerated, which makes it unlikely to be an option for long-term use in telomeropathy-related pulmonary fibrosis.

TABLE 1 Overview of treatment trials presented at the European Respiratory Society Congress 2023

Study	Treatment	Study population	Study phase	Outcomes
Kellogg *et al.* [18] (NCT02874989)	Dasatinib (100 mg daily) and quercetin (1250 mg daily)	20 patients with IPF	*Post hoc* analysis of a first in human open-label pilot study	A significant improvement in senolitic markers was found, but no improvement in short-term clinical outcomes
Arora *et al.* [19]	LASN01 (a monoclonal antibody targeting IL-11R)	58 healthy volunteers	Phase 1	LASN01 inhibited >95% of the IL-11R signalling and was well-tolerated
Wuyts *et al.* [20] INTEGRIS-IPF (NCT04396756)	Bexotegrast 320 mg (dual-selective inhibitor of αvβ6 and αvβ1)	29 patients with IPF	Phase 2a, multicentre RCT	Well-tolerated in participants with IPF up to 40 weeks of treatment; bexotegrast seemed to reduce FVC decline, and in a majority of patients QLF score improved
Glaspole *et al.* [21] (ACT001-AU-003)	ACT001 (targeting NF-κB and STAT3 signalling pathways)	44 patients, 35 IPF, 9 fILD	Phase 2, multicentre, parallel group	ACT001 reduced FVC decline after 52 weeks
Borie *et al.* [22] ANDROTELO trial (NCT03710356)	Danazol (synthetic hormonal drug)	25 patients with PF with a (likely) pathogenic TRG variant	Phase 2, open-label, multicentre	Danazol was poorly tolerated, only 10 patients completed 12-month treatment
West *et al.* [23] (ACTRN12618001838202)	Nebulised pirfenidone	72 patients with IPF (41 from phase 1b, 31 newly enrolled)	Phase 2 open-label extension, multicentre	Reduction in FVC decline after 48 weeks, −165.5±242.6 mL in patients from 1b, −151.1±358.9 mL in newly enrolled patients
Corte *et al.* [24] (NCT04308681)	30 or 60 mg of BMS-986278 (oral lysophosphatidic acid receptor 1 antagonist)	125 patients with PPF	Phase 2 double-blind placebo-controlled RCT, multicentre	BMS-986278 reduced the rate of FVC decline after 26 weeks and was safe and well-tolerated; rates of FVC decline were 4.3% for placebo, −2.7% for 30 mg and −1.1% for 60 mg
Molyneaux *et al.* [25] PAciFy cough trial (NCT04429516)	Low-dose controlled-release morphine sulphate	44 patients with IPF and chronic cough	Multicentre, double-blind, placebo-controlled, crossover phase 4 RCT	Morphine sulphate reduced objective cough frequency with 39.4% compared to placebo after 14 days; PROMs improved and treatment was well-tolerated
Myall *et al.* [26]	CPAP therapy in managing OSA	44 patients with fILD and OSA, 12 started CPAP	Phase 4 study, non-randomised	Improvement in PROMs (K-BILD and PSQI)
Dhooria *et al.* [27] SARCORT trial (NCT03265405)	Prednisolone	86 patients with pulmonary sarcoidosis	Single-centre, open-label, parallel-group RCT	Daily prednisolone dose of 40 mg is not superior to 20 mg in overall response; the frequency of relapse, treatment failure after 18 months and the mean time to these events were similar
Kinnersley *et al.* [28] (NCT03824392)	Efzofitimod (selective modulator of neuropilin-2)	37 patients with pulmonary sarcoidosis (20 subtherapeutic dose, 17 therapeutic dose)	Phase 1b/2a randomised, double-blind, placebo-controlled, multiple ascending doses	In the therapeutic group a lower percentage of patients relapsed (7.7% *versus* 54.4%), FVC improved over time and health status improved in a significantly higher percentage
Bermudo Peloche *et al.* [29] FIBRO-COVID (NCT04607928)	Pirfenidone	113 patients with post-COVID-19 pulmonary fibrosis	Phase 2, multicentre, placebo-controlled RCT	FVC improved with 12.74% in the pirfenidone group and 4.35% in the placebo group after 6 months, but differences were not statistically significant
Harari *et al.* [30]	Nintedanib	30 patients with LAM	Phase 2, multicentre, open-label	Nintedanib stabilised lung function parameters (FVC, FEV_1, D_{LCO}) and was generally well-tolerated
Trapnell *et al.* [31]	Pulmonary macrophage transplantation	Not informed	Preclinical	Pulmonary macrophage transplantation corrected PAP and normalised disease biomarkers; approved to start a human trial

Continued

TABLE 1 Continued

Study	Treatment	Study population	Study phase	Outcomes
Bonella *et al*. [32] ASCEND trial (NCT02004691)	OAER therapy	36 patients with acid sphingomyelinase deficiency	Phase 2/3, multicentre	Treatment with OAER therapy led to a persistent and progressive improvement of radiological infiltrates, FVC, D_{LCO} and exercise capacity, and was well-tolerated

IPF: idiopathic pulmonary fibrosis; IL-11R: interleukin 11 receptor; RCT: randomised controlled trial; FVC: forced vital capacity; QLF: Quantitative Lung Fibrosis score; fILD: fibrotic interstitial lung disease; PF: pulmonary fibrosis; TRG: telomere-related gene; PPF: progressive pulmonary fibrosis; PROMs: patient reported outcome measures; CPAP: continuous positive airway pressure; OSA: obstructive sleep apnoea; K-BILD: the King's brief interstitial lung disease questionnaire; PSQI: Pittsburgh sleep quality index; LAM: lymphangioleiomyomatosis; FEV_1: forced expiratory volume in 1 s; D_{LCO}: diffusing capacity of the lung for carbon monoxide; PAP: pulmonary alveolar proteinosis; OAER: olipudase alfa enzyme replacement.

West *et al*. [23] presented data of a phase 2 open-label extension study on nebulised pirfenidone in IPF. They found a reduction in FVC decline comparable to previous studies with oral pirfenidone, both in patients that already participated in the phase 1b study and newly treated patients. Results indicate that nebulised pirfenidone may be a well-tolerated and effective treatment for IPF in the future; a placebo-controlled trial is expected. A phase 2 study in patients with PPF evaluated efficacy and safety of BMS-986278, an oral lysophosphatidic acid receptor 1 (LPA1) antagonist in 125 patients [24]. Similar to a previous study in IPF, BMS-986278 reduced the rate of FVC decline after 26 weeks and was safe and well-tolerated. Phase 3 studies for IPF and PPF are currently being set up.

The PAciFy randomised clinical trial investigated the use of low-dose morphine sulphate for treating cough in IPF [25]. After 14 days, morphine sulphate reduced awake cough frequency by 39.4% compared to placebo and was overall well-tolerated, with acceptable side effects. The authors advocate for rapid implementation in clinical practice due to the well-established safety profile and worldwide availability. Finally, Myall *et al*. [26] explored the utility of continuous positive airway pressure therapy in managing obstructive sleep apnoea among patients with PPF. In this small study, quality of life and survival improved, indicating the need for larger studies to validate these findings.

Group 12.02: ILDs/DPLDs of known origin

A major challenge for ILDs of known origin lies in correct prognostication. Currently, clinical characteristics, radiographic patterns and pulmonary function tests are often used for risk stratification. However, this approach is not accurate enough to predict disease progression and prognosis in individual patients.

By using e-Lung, an artificial intelligence (AI)-powered CT tool, multiple new imaging biomarkers have been retrospectively identified. First, the weighted reticulo-vascular score (WRVS), which has previously been validated in IPF, was investigated in a cohort of 352 patients with non-IPF ILD. Baseline WRVS outperformed baseline FVC in predicting survival and was more predictive of a future decline in FVC >10% [33]. Second, the ground glass opacity (GGO) score was investigated as a prognostic marker in non-IPF ILD. Prognosis was worse for patients with a higher WRVS and less GGO, and increase in WRVS and GGO in combination with FVC decline was more predictive than FVC decline alone [33]. The potential of AI in prognosticating ILD was also presented by Guiot *et al*. [34]. They used LungQ to quantify the percentage of interstitial abnormalities and vascular changes in patients with systemic sclerosis (SSc)-ILD (n=68). In this exploratory study, a significant correlation between the change in interstitial lung score and the change in FVC was found. When using an experimental score, combining reticulations and GGOs, a stronger correlation was identified. These studies highlight the potential of radiology AI tools for better prediction of disease outcome in ILD.

Another potential tool to predict the development of lung function impairment in patients with SSc is the non-invasive skin transcriptome [35]. By using publicly available datasets, a weighted gene correlation analysis was performed. Multiple gene networks were associated with skin involvement and lung function evolution. Pathway analysis showed that these pathways were enriched for extracellular matrix interactions, chemokine signalling and cytokine–cytokine receptor interaction. Possibly, these signatures can identify patients at risk for lung involvement and identify targetable pathways for treatment in the future.

Hoffmann-Vold *et al*. [36] examined whether progression in the preceding year could predict progression in the following year among 231 patients with SSc-ILD. Progression was defined based on four different

definitions (FVC >5%, FVC >10%, American Thoracic Society PPF criteria, progressive fibrosing ILD INBUILD criteria). Using multivariable logistic regression adjusted for known risk factors, they found that disease progression in the previous year, no matter the definition, did not predict future progression, even when excluding patients who changed medication due to progression (OR 0.33, p=0.013). These results can have important implications for clinical practice and trial design.

Moving to cellular biomarkers, Moraes *et al*. [37] examined the role of dendritic cells as a predictive tool in airway-centred interstitial fibrosis. 24 patients with a definitive diagnosis of connective tissue disease (CTD), micro-aspiration-induced pneumonitis and hypersensitivity pneumonitis were included after undergoing a surgical lung biopsy. In all groups, patients with more CLEC9a-positive dendritic cells, as well as patients with low CD1c-positive cells, had a worse survival.

Another important challenge is the differentiation of CTD-ILD from other forms of ILD. Moor *et al*. [38] used an electronic nose (eNose) to examine the differences between the breath prints of patients with CTD-ILD and other ILDs. 132 CTD-ILD patients were compared to 122 other ILD patients, using partial least square discriminant analysis in a training and test set. The model could differentiate well between CTD-ILD and other ILDs (test AUC 0.92). Furthermore, an even better separation was seen between interstitial pneumonia with autoimmune features and CTD-ILD (test AUC 0.99). In an exploratory follow-up study, the potential of eNose in the differentiation of SSc without ILD and SSc-ILD was investigated, highlighting the potential future role of eNose as a screening tool for ILD in SSc (test AUC 0.84).

Two studies studied the underlying genetic background of different ILDs. Solomon *et al*. [39] showed that patients with genes associated with the development of seropositive rheumatoid arthritis (RA), had a moderate protective effect on the development of IPF, using Mendelian randomisation. In contrast, patients predisposed to IPF had a significantly higher risk of developing seropositive RA. Upon future validation, this research could help to gain further insights into the pathogenesis of usual interstitial pneumonia (UIP) in patients with RA. Additionally, Novais Bastos *et al*. [40] showed that fibrotic hypersensitivity pneumonitis and IPF seem to share a genetic background as the minor MUC5B allele (rs35705950) was present in nearly 75% of IPF and fibrotic hypersensitivity pneumonitis cases, while 75% of control patients carried the wild type (GG).

Group 12.03: Sarcoidosis and other granulomatous ILDs/DPLDs

One of the main sarcoidosis highlights from the ERS Congress was the presentation of the SARCORT trial results. In a single-centre, open-label, parallel-group randomised controlled trial (n=86) over 26 weeks Dhooria *et al*. [27] reported that an initial daily prednisolone dose of 40 mg was not superior to 20 mg in overall response. The frequency of relapse, treatment failure after 18 months and the mean time to these events were similar. No significant differences in change in FVC at 6 and 18 months, overall response, incidence of adverse effects or changes in health-related quality of life were observed between groups. Overall side effects were frequent in both groups, iterating the need for better tolerated first-line pulmonary sarcoidosis treatments.

A phase 1b/2a randomised, double-blind, placebo-controlled, multiple ascending dose study evaluated the use efzofitimod in chronic pulmonary sarcoidosis [28]. Efzofitimod is a novel immunomodulator binding neuropilin-2, which is upregulated on immune cells in response to lung inflammation. Placebo and 1 $mg \cdot kg^{-1}$ arms were considered subtherapeutic (n=20); 3 $mg \cdot kg^{-1}$ and 5 $mg \cdot kg^{-1}$ arms were deemed therapeutic (n=17). In the therapeutic group a lower percentage of patients relapsed (7.7% *versus* 54.4%). Moreover, FVC improved over time in the therapeutic group and declined in the subtherapeutic group. Finally, health status improved in a significantly higher percentage of patients in the therapeutic group. A phase 3 multicentre, randomised, double-blind study (EFZO-FIT) on efficacy and safety of 3 $mg \cdot kg^{-1}$ and 5 $mg \cdot kg^{-1}$ intravenous efzofitimod is currently enrolling.

Sarcoidosis is associated with various comorbidities and treatment of sarcoidosis often leads to relevant side effects. Cameli *et al*. [41] analysed 252 patients with chronic sarcoidosis from a referral centre in Italy and compared the prevalence of bone fractures with 250 sex- and age-matched healthy controls. Bone mineral density (BMD) was significantly lower in patients with sarcoidosis than healthy controls and prevalence of fragility fractures was higher (30.6% *versus* 12.3%). Interestingly, presence of bone fractures was not associated with use of glucocorticoids. In contrast, Møller *et al.* [42] found that BMD increased over a 12-month interval. There was no difference in BMD between patients with and without glucocorticoid treatment.

Sarcoidosis is a complex disease with a heterogeneous disease course. A German research group evaluated informational needs and resources of patients with sarcoidosis [43]. They found that many patients (40.6%) felt not adequately informed. Patients expressed the need for better information early in their disease course,

especially with regard to future perspectives and symptoms, such as fatigue and pain. In a second study, they analysed whether the internet is a reliable source of information for sarcoidosis. Their conclusion was that the quality of information was moderate (according to standardised criteria) and important aspects of the disease were frequently not addressed. These studies highlight the importance of providing accurate information on sarcoidosis, and collaboration with different medical specialties and patient organisations.

Finally, many studies presented during the congress focused on disease mechanisms and pathogenesis. A few posters from the same group presented results of flow-cytometric analysis of peripheral blood, bronchoalveolar lavage (BAL) and lymph nodes collected from patients with pulmonary sarcoidosis before start of treatment. Fanetti *et al.* [44] demonstrated a relationship between an imbalance of follicular helper $CD4^+$ T-cells (Tfh) in these three anatomical compartments. They found higher percentages of proinflammatory Tfh17 and Tfh2 cells and lower percentages of Tfh1 cells in peripheral blood than in BAL and lymph nodes. These results suggest a link between the imbalance of Tfh subsets and pathogenesis of sarcoidosis. Ventura *et al.* [45] found a higher percentage of natural killer cell concentration in peripheral blood compared to BAL and lymph nodes. Messina *et al.* [46] showed that the highest percentage of T-helper type 1 (Th1) cells was identified in BAL, whereas the highest percentages of Th2 and cytotoxic T-cells were observed in peripheral blood. According to the authors, their findings were similar to what occurs in autoimmune diseases.

The RESPISAM study investigated the role of immune dysregulation in different sarcoidosis phenotypes [47]. They found significantly higher levels of type 1 inflammation biomarkers from bronchial mucosal lining fluid (IFN-γ, IP-10, MCP-4, IL-15, IL12-p40 and IL12-p70) in pulmonary sarcoidosis than in isolated mediastinal lymph node sarcoidosis.

Group 12.04: Rare ILDs/DPLDs

A large variety of studies about rare ILDs were presented at the 2023 ERS Congress. The main focus was on novel treatment options and better characterisation and phenotyping of rare ILDs.

A phase 2 randomised controlled trial from Spain (FIBRO-COVID) evaluated efficacy of pirfenidone compared to placebo for 6 months in 113 patients who had evidence of pulmonary fibrosis (>5% fibrotic abnormalities on chest CT) at least 1 month after hospital discharge for severe COVID-19 and receiving oral glucocorticosteroids [29]. FVC improved with 12.74% in the pirfenidone group and 4.35% in the placebo group, although differences were not statistically significant.

A multicentre, open-label, single-arm study from Italy (MILES) investigated the use of nintedanib in 30 patients with lymphangioleiomyomatosis (LAM) and progressive pulmonary function decline over the last 12 months despite the use of sirolimus, or patients who did not tolerate the treatment [30]. Patients were treated for 12 months and then followed for an additional 12 months. Nintedanib stabilised lung function (FVC, forced expiratory volume in 1 s (FEV_1) and diffusing capacity of the lung for carbon monoxide (D_{LCO})) and was generally well-tolerated.

Results from preclinical studies were presented for hereditary pulmonary alveolar proteinosis (hPAP) [31]. After discovering that lentiviral-mediated CSF2RA gene transfer restores granulocyte–macrophage colony-stimulating factor (GM-CSF) signalling in hPAP patients, the investigators developed and validated Csf2raKO mice as a model of hPAP. The authors found that pulmonary macrophage transplantation corrected hPAP and normalised disease biomarkers. Based on these results, the study was approved to start a human clinical trial.

Bonella *et al.* [32] investigated the use of the olipudase alfa enzyme replacement (OAER) therapy in adult patients with acid sphingomyelinase deficiency (ASCEND trial). They evaluated whether there was a difference in change in pulmonary function, radiology and exercise capacity between the first-year primary analysis of the randomised controlled trial and after 2 years in the open-label extension follow-up. Notably, treatment with OAER therapy led to a significant and sustained improvement in these outcome parameters and was well-tolerated.

A retrospective study proposed a novel radiological method for risk stratification in patients with LAM [48]. Cyst volume index (CVI) was assessed using YACTA (Yet Another Computed Tomography Analyzer) software and correlated with lung function parameters. A significant negative correlation between CVI and FEV_1 and between CVI and D_{LCO} were found. The authors concluded that YACTA software might be useful as a tool for risk stratification and prognosis estimation in patients with LAM.

Krymskaya *et al.* [49] assessed alveolar fibroblast activation and epithelial injury/repair in LAM in a mouse model. Their results suggest that in the late stage of the LAM disease, there is an overall decrease in pulmonary healing that might indicate the exhaustion of alveolar epithelial cell renewal capacity. The results also showed that abnormal epithelial–mesenchymal crosstalk during injury/repair facilitates the fibroblast activation in lung cells of patients with LAM.

A French multicentre retrospective study evaluated 36 participants with mutations in surfactant genes SFTPC and ABCA3 and investigated their clinical, radiological and lung function characteristics [50]. This study shows that patients with these mutations have a heterogeneous phenotype, often classified as unclassifiable ILD on high-resolution CT. Histological pattern was most frequently nonspecific interstitial pneumonia in the ABCA3 group and UIP in the SFTPC group. Multicentre collaborations are needed to gain more insights in these rare causes of ILD.

Ishii *et al.* [51] evaluated 63 patients with myelodysplastic syndrome complicated with secondary pulmonary alveolar proteinosis in the largest case series of this patient group yet studied. The authors found a poor prognosis with a mean survival time of 17 months. There was a high prevalence of trisomy 18 and U2A1F mutations, which may be associated with disease pathogenesis.

Finally, a Greek cohort retrospectively analysed 36 patients with autoimmune pulmonary alveolar proteinosis from 2002 to 2022 [52]. Whole lung lavage was performed in 30.5% of patients, but less frequently in the last 10 years. 58.3% of patients were treated with inhaled GM-CSF which led to an overall improvement in lung function parameters and oxygen saturation regardless of disease severity.

Concluding remarks

In conclusion, the 2023 International Congress of the ERS offered exciting and much needed research endeavours throughout the entire spectrum of ILDs. From innovative therapeutic breakthroughs to comprehensive population studies dissecting the genetic and clinical nuances of this complex and heterogeneous group of diseases, the congress reaffirmed the commitment of the medical community to unravel the mysteries of ILD and its aim to discover new therapeutic targets.

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