ERS International Congress, Madrid, 2019: highlights from the Interstitial Lung Diseases Assembly

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ABSTRACT This article discusses a selection of the scientific presentations in the field of interstitial lung diseases (ILDs) that took place at the 2019 European Respiratory Society International Congress in Madrid, Spain. There were sessions from all four groups within Assembly 12: group 12.01 "Idiopathic interstitial pneumonias", 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". The presented studies brought cutting-edge developments on several aspects of these conditions, including pathogenesis, diagnosis and treatment. As many of the ILDs are individually rare, the sharing of experiences and new data that occur during the Congress are very important for physicians interested in ILDs and ILD patients alike.

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The 2019 #ERSCongress in Madrid provided novel data on interstitial lung diseases
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Introduction

The 2019 European Respiratory Society (ERS) International Congress in Madrid, Spain, was an exciting opportunity for presenting and discussing the most important developments on interstitial lung diseases (ILDs). The scientific programme included sessions on the epidemiology, pathogenesis, new methods for diagnosis and new effective therapies. Importantly, many of the ILDs are individually rare, so the sharing of experiences and data that occurred during the Congress are especially important for the entire ILD community, including patients. This article reports on some of the presentations that took place during the Congress across the four groups within Assembly 12, namely group 12.01 "Idiopathic interstitial pneumonias", 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".

Idiopathic interstitial pneumonias

Most studies aimed to combine cutting-edge developments in basic research with novel clinical aspects of idiopathic interstitial pneumonias (IIPs). The importance of predictors of disease behaviour was highlighted by several studies. The adherence to home spirometry in idiopathic pulmonary fibrosis (IPF) patients has been explored in the INMARK trial [1]. Over 52 weeks, the mean adherence was 86%. It decreased over time but remained at an acceptable level, thus enabling early detection of changes in forced vital capacity (FVC). In the DIVA study, a diurnal variation in FVC in patients with fibrosing ILD was observed using home spirometry twice daily, but there was no relationship with the patients' activity [2]. Importantly, there is still a risk of technical issues with home spirometry, as was found in a pirfenidone trial in patients with progressive fibrosing unclassifiable ILD [3] (see also the later section "ILDs/DPLDs of known origin").

In a *post hoc* analysis of the INPULSIS trials, patients with a body mass index below the median at baseline had a faster FVC decline under placebo and a more pronounced treatment effect of nintedanib [4].

Some presentations focused on advanced imaging technology. Honeycombing independently predicted mortality in patients with unclassifiable ILD, and its inclusion in a prediction model improved the estimation of survival in this patient subset [5]. The PETAL study demonstrated higher levels of αvβ6 integrin in IPF compared to healthy lungs, showing increased uptake in fibrotic areas, as measured by quantitative positron emission tomography [6]. This technique was used to confirm target engagement in IPF lungs following a single dose of a nebulised αvβ6 integrin inhibitor in a randomised, placebo-controlled, phase Ib study [7]. Moreover, an innovative study combining a matrix-assisted laser desorption/ionisation mass spectrometry analysis with transbronchial cryobiopsy showed that inhaled medication can reach the distal regions of the fibrotic lung [8]. Therefore, these techniques may enable the assessment of the regional treatment response in fibrotic ILD.

Several ILD registries were developed worldwide and collaborative efforts led to various observations. The real-life EMPIRE registry showed that patients with usual interstitial pneumonia (UIP) and antineutrophil cytoplasmic antibody (ANCA)-positive ILD without signs of vasculitis had some distinct features but showed a similar survival curve to the ANCA-negative patients with IPF [9]. The INSIGHTS-IPF registry demonstrated that IPF patients, irrespective of antifibrotic therapy, remained relatively stable in terms of FVC and diffusing capacity of the lung for carbon monoxide (D_{LCO}) over a 2-year period, but the risk of death was 37% lower in patients on antifibrotic treatment [10]. The DIAMORFOSIS study, an international survey about the diagnostic and therapeutic management of patients with IPF and lung cancer, showed that there is wide variation in current practice, highlighting the need for a consensus statement on this topic. However, 83% of respondents tend to continue antifibrotics following lung cancer diagnosis [11].

A focus on the development of promising molecular biology tools is emerging. In the INMARK trial, baseline levels of C-reactive protein degraded by matrix metalloproteinase (MMP)-1/8, collagen 3 degraded by MMP-9, C-reactive protein, Krebs von den Lungen 6 (KL-6) and surfactant protein D (SP-D) were predictive of disease progression, with nintedanib reducing collagen synthesis in the early phases of the treatment, as measured by N-terminal propeptide of type VI collagen and SP-D [12, 13]. A phase III trial of pirfenidone in Japanese IPF patients revealed that a decrease in serum concentration of SP-D was predictive of a good response to the drug [14]. The INSTAGE trial showed a reduction of collagen 6 degraded by MMP-2/9 and citrullinated vimentin degraded by MMP-2/8 in patients treated with nintedanib plus sildenafil compared to nintedanib alone [15]. *Post hoc* analyses demonstrated that in patients with brain natriuretic peptide (BNP) levels above the median at baseline, the combination of nintedanib plus sildenafil improved BNP significantly and showed a numerical benefit on FVC [16]. In patients treated with antifibrotics, the rate of leukocyte telomere length (LTL) shortening over time was associated with LTL at baseline [17]. Among genetic studies, TOLLIP gene polymorphisms correlated with disease progression and may potentially be useful to stratify IPF patients [18].

In terms of acute exacerbations (AE) of IIP, an imbalance in the oral bacterial flora was proposed as a risk factor in patients with AE-IPF [19]. Serum high mobility group box 1 (HMGB1) and growth differentiation factor 15 were proposed as promising biomarkers of AE-IPF [19, 20]. Cell senescence and autophagy were proposed as crucial mechanisms in idiopathic or autoimmunity-associated UIP [21]. Along similar lines, a novel bench-to-bedside trial supported the feasibility and safety of dasatinib plus quercetin in IPF patients [22].

Several preclinical studies reported on novel, potentially promising therapies, such as the next-generation lysophosphatidic acid receptor (LPA1) complete antagonist (BMS-986278) or a selective integrin antagonist (ILD-2965) that showed an acceptable safety profile. A clinical study examining ILD-2965 in healthy subjects and IPF patients will start promptly [23, 24].

ILDs/DPLDs of known origin

One of the major ILD highlights from the Congress was the clinical trials session "ALERT: Abstracts Leading to Evolution in Respiratory Medicine Trials: Interstitial lung diseases and pulmonary hypertension". In this session, Maher *et al.* [3] presented the results from a phase II trial of pirfenidone in patients with progressive fibrosing unclassifiable ILD. The primary end-point could not be assessed, due to technical and analysis issues with home spirometry, but key secondary end-points were suggestive of benefits from pirfenidone. Flaherty *et al.* [25] presented the results from the INBUILD trial, on nintedanib in chronic fibrosing ILDs (other than IPF) with a progressive phenotype. Nintedanib reduced the rate of loss of FVC in progressive fibrosis patients, including those with an UIP pattern and those with other fibrotic patterns. Similar results were reported from the RELIEF trial by the German Center for Lung Research, where patients with progressive fibrosing ILD received pirfenidone, demonstrating clinically meaningful effects in this patient cohort as well [26]; however, interpretability of the data were limited by recruiting problems. Denton *et al.* [27] provided data on the FocuSSed trial, which assessed effects of tocilizumab, an anti-interleukin-6 therapy strategy, in patients with early systemic sclerosis (SSc) and a more inflammatory phenotype. This phase III trial, which missed its primary end-point of change in modified Rodnan skin score, demonstrated meaningful effects in a key secondary end-point, change in FVC predicted. Yet, due to the negative primary end-point, effects have to be interpreted with caution. The multicentric COLDICE study assessed the agreement between transbronchial lung cryobiopsy (TBLC) and surgical lung biopsy and found a high level of agreement (weighted κ 0.70, 95% CI 0.55–0.86) [28]. The use of TBLC for ILD diagnosis is thus supported. Table 1 summarises some of the trials presented in this session.

TABLE 1 Summary of some of the presentations from the session "ALERT: Abstracts Leading to Evolution in Respiratory Medicine Trials: Interstitial lung diseases and pulmonary hypertension"

Study name [ref.]	Population	Intervention	Comparison	Primary/secondary outcomes
Exploring efficacy and safety of oral pirfenidone for progressive, non-IPF lung fibrosis (RELIEF) [26]	Progressive fibrosing ILD	Pirfenidone 24 weeks	Placebo	Stopped due to low recruitment; lower FVC decline in treatment arm when applying pre-specified imputation, but not without
Phase II trial of pirfenidone in patients with progressive fibrosing unclassifiable ILD [3]	Progressive fibrosing unclassifiable ILD	Pirfenidone 24 weeks	Placebo	Primary end-point (FVC change by home spirometry) was not assessed due to technical problems; lower FVC decrease in treatment arm in site spirometry
Nintedanib in patients with chronic fibrosing interstitial lung diseases with progressive phenotype: the INBUILD trial [25]	Progressive fibrosing ILD	Nintedanib 52 weeks	Placebo	Lower adjusted annual rate of decline in FVC (mL·year^{-1})
Lung function preservation in a phase 3 trial of tocilizumab (TCZ) in systemic sclerosis (SSc) [27]	Systemic sclerosis	Tocilizumab 48 weeks	Placebo	No difference in change in modified Rodnan skin score; lower proportion of patients losing >10% of FVC on the treatment arm
Transbronchial lung cryobiopsy for interstitial lung disease diagnosis: results of the COLDICE Study [28]	ILD requiring biopsy	Transbronchial lung cryobiopsy	Surgical lung biopsy	High level of agreement between both types of biopsy

IPF: idiopathic pulmonary fibrosis; ILD: interstitial lung disease; FVC: forced vital capacity.

Several presentations focused on ILDs of known origin, particularly hypersensitivity pneumonitis (HP) and connective tissue disease (CTD)-associated ILD.

The search for diagnostic biomarkers for HP was the topic of several presentations. Hernandez-Gonzalez *et al.* [29] highlighted the importance of collecting air and swab samples from the patient's environment when there is positive antibody response but no identified antigen, demonstrating that the most prevalent species are *Penicillium* spp. and *Cladosporium herbarum*. This finding suggested that an indoor environmental study may be crucial to avoid the previously unrecognised exposure to the causative fungal antigen. Similarly, another diagnostic approach exploiting the inhalation challenge test was demonstrated by Okuda *et al.* [30] to be particularly useful for identifying antigens. In this study, the authors demonstrated that sterilised pigeon egg can act as a safe and convenient inhaled antigen for the challenge test for diagnosis of bird-related chronic HP.

With regard to clinical predictors of a diagnosis of HP, Diamanti *et al.* [31] found squeaks in about 40% of patients with HP. Squeaks seem to be more commonly associated with female patients with lower forced expiratory volume in 1 s (FEV_1), lower FVC, and higher residual volume over total lung capacity, suggesting the diagnosis of HP in the appropriate context.

Given the similar behaviour between IPF and chronic HP patients, prognostic factors were also the topic of several presentations. The C–C motif chemokine ligand 15 (CCL15) mRNA, which is highly expressed in the chronic HP lung, was demonstrated to be a useful prognostic biomarker. Increased bronchoalveolar lavage (BAL) fluid level of CCL15 divided by BAL fluid albumin level was independently associated with a poor prognosis in chronic HP patients (hazard ratio 1.1, 95% CI 1.03–1.18, p=0.004) [32]. Similarly, low BAL lymphocyte counts and the presence of honeycombing may predict a worse prognosis and the absence of response to steroid treatment [33]. Moreover, an increase in arterial stiffness assessed by an increase in pulse wave velocity was associated with the extent of lung fibrosis on high-resolution computed tomography (CT), worse diffusion capacity and frequency of exacerbations, representing a possible predictor of worse prognosis [34].

In terms of treatment, one study focused on the effects of antifibrotics in chronic HP. In a retrospective analysis, 18 patients initially diagnosed with IPF received antifibrotics (10 pirfenidone, eight nintedanib) for at least 12 months, which led to stabilisation of FVC [35].

Most of the other presentations on CTD-ILD concerned SSc-associated ILD (SSc-ILD). The prognostic value of several biomarkers was assessed. In a prospective longitudinal study, Gester *et al.* [36] demonstrated that insulin-like growth factor-binding protein (IGFBP)-1 is of potential interest to identify early SSc-ILD whereas IGFBP-2 was predictive of the risk of a rapid evolution of lung fibrosis. From a large retrospective study (European Scleroderma Trials and Research group, EUSTAR database), baseline FVC, baseline extent of skin fibrosis and disease duration were found to be significantly associated with further ILD progression [37]. Similar results emerged from a retrospective study by Vallejos *et al.* [38] including 95 SSc patients. The combination of functional and radiological variables was able to predict functional decline, defined as a loss of ⩾10% of FVC over 2 years.

Several presentations focused on therapy for SSc-ILD. New information came from the SENSCIS trial. Nintedanib reduced ILD progression irrespective of % predicted FVC [39] and extent of lung fibrosis at baseline [40]. The use of dose adjustments for the management of adverse events was reported by Highland *et al.* [41]. Most patients remained on therapy during the 52 weeks (13.9% of patients under nintedanib and 7.3% of patients on placebo discontinued treatment permanently), suggesting that these adjustments were effective at minimising treatment discontinuations.

Similarly to those with IPF, SSc-ILD patients suffer with gastro-oesophageal reflux and thus treatment with anti-acid therapy is frequent. Kreuter *et al.* [42] demonstrated that anti-acid therapy use may be correlated with ILD progression in SSc, suggesting that prospective trials are needed to analyse this. The same authors also shed light on the outcomes for SSc-ILD with respect to immunomodulatory therapies, using a large real-life cohort of SSc patients. Interestingly, the use of immunomodulatory therapies had no significant impact on outcomes in SSc-ILD [43].

Sarcoidosis and other granulomatous ILDs/DPLDs

The presentations on this subject focused mainly on sarcoidosis, specifically on its epidemiological, diagnostic, treatment and prognostic aspects.

Two Swedish population studies were presented. Rossides *et al.* [44] assessed the risk factors for infections resulting in hospitalisation: a diagnosis of sarcoidosis (n=7820) was associated with a higher serious infection risk, independent of treatment status, especially in the first years after diagnosis. Another study, by Köcher *et al.* [45], focused on maternal and fetal outcomes in pregnant women with sarcoidosis. A

total of 259 women with a history of sarcoidosis at time of birth were included and compared to 6633 women with no sarcoidosis. The pregnancies of mothers with sarcoidosis were associated with a higher risk for pre-eclampsia, caesarean delivery and preterm birth, but most had no complications.

Regarding clinical tools for sarcoidosis diagnosis, Jeny *et al.* [46] tested the Sarcoidosis Diagnostic Score (from a team in Cincinnati [47]) in 1341 individuals, showing good discrimination between sarcoidosis and other granulomatous diseases. Savale *et al.* [48] used the Delphi method to reach consensus on recommendations for the screening of sarcoidosis-associated pulmonary hypertension and identified screening tools that help decide on performing an echocardiogram in these patients.

Salman *et al.* [49] evaluated endobronchial ultrasound-guided needle aspiration as a diagnostic tool. The utility of the technique seems to be higher in patients with possible sarcoidosis on chest CT, rather than typical sarcoidosis on chest CT, in which cytology did not influence the final diagnosis.

Biomarkers were the topic of several presentations. Dubaniewicz *et al.* [50] tested monocytic and neutrophilic phagocytic activity by flow cytometry as a differential diagnostic tool between tuberculosis and sarcoidosis. Another group evaluated numerous serum biomarkers (chitotriosidase, angiotensin-converting enzyme (ACE), lysozyme and KL-6) in sarcoidosis patients. KL-6 and chitotriosidase were the most specific and sensitive among them. A possible correlation between KL-6 levels and lung fibrosis was suggested [51].

Regarding prognosis, Calero *et al.* [52] assessed the lymphocyte populations in peripheral blood and BAL. A higher concentration of T-lymphocytes, CD8 and natural killer (NK) cells in the blood was associated with a higher FVC decline; the same correlation was not seen in the BAL.

Familiar sarcoidosis was evaluated by Baranova *et al.* [53], who characterised familiar disease in 26 patients from 12 families, looking at the role of genetic predisposition. Six families achieved remission, three had frequent relapses, and three had advanced pulmonary sarcoidosis. These authors concluded that genetic predisposition does play a role in pulmonary sarcoidosis, as half the families had a favourable course whereas half had a progressive and relapsing course.

The extrapulmonary manifestations of sarcoidosis are a relevant clinical challenge. Ohira *et al.* [54] showed that imaging features on cardiac magnetic resonance, particularly the absence of basal thinning of the interventricular septum, can have a prognostic value regarding recovery from complete heart block in patients with cardiac sarcoidosis.

Other granulomatous lung diseases besides sarcoidosis were the subject of a few presentations. Savard-Heppel and Boursiquot [55] analysed the respiratory profile of common variable immunodeficiency (CVID) patients and, among them, granulomatous-lymphocytic ILD (GLILD) patients. In a series of nine patients already on immunoglobulin replacement, add-on therapy with prednisolone improved lung function with heterogeneous responses [56]. Compared to CVID patients without ILD, GLILD was associated with lower baseline IgA levels, and a nonsmoker status [57]. GLILD was also the subject of a study by Cinetto *et al.* [58], in which it was found in 15 out of 34 patients with CVID.

A retrospective study in paediatric patients, regarding lung involvement in Langerhans cell histiocytosis (LCH), was conducted by Donadieu *et al.* [59]. They analysed 166 cases from between 1983 and 2016. Two different forms of presentation were found: infants with multisystem presentation and risk organ involvement in 50% of cases, and a second form of presentation more similar to adults, found in older children with higher frequency of isolated lung disease and less risk organ involvement.

Finally, there were several basic science presentations: one study on single-cell RNA sequencing of BAL cells showed that this can help in identifying cell subpopulations in sarcoidosis [60]; two presentations analysed genetic polymorphisms, both in the renin–angiotensin system and in inflammatory cytokines [61, 62]; one regarding FcγRIIA, FcγRIII and FcγRIIB expression in sarcoid and foreign body granulomas [63]; and an *in vivo* micro-CT protocol to assess lung fibrosis progression in a mouse model [64].

Rare ILDs/DPLDs

The 2019 ERS International Congress programme encompassed both basic and clinical research on rare ILDs and DPLDs, providing new insights into pathobiological mechanisms as well as new data on treatment and patients' quality of life.

A new therapeutic era has possibly begun in pulmonary alveolar proteinosis (PAP), with the presentation of the much-awaited IMPALA trial results. Inhaled granulocyte–macrophage colony-stimulating factor (GM-CSF) molgramostim was evaluated in a placebo-controlled multicentric 24-week international trial in adult moderate-to-severe PAP patients [65]. Although the primary end-point was not met, as the change in alveolar–arterial oxygen tension difference (P_{A-aO_2}) did not reach statistical significance, GM-CSF

therapy was shown to decrease ground-glass opacities, and improve serum biomarkers, quality of life and D_{LCO}. Therapy was well tolerated and more effective when administered continuously than on alternative weeks. On another note, the Italian registry has been enrolling PAP patients since 1989 and Campo *et al.* [66] presented a series of 126 patients, of whom 93% were of auto-immune aetiology, helping to better understand the natural history of this rare disease.

In a cross-sectional study of 71 LCH patients, Tazi *et al.* [67] showed that psychological abnormalities frequently co-exist, as assessed by self-reported anxiety, depression and addiction questionnaires. These aspects should be considered while making management decisions. Tazi *et al.* [68] also reported on a large French adult series of 83 histologically proven LCH cases, 37% of whom carried the *BRAF*^{V600E} mutation, which leads to activation of the RAS-MEK signalling pathway. No association was identified between the presence of this mutation and disease presentation or outcome, in contrast to what has been reported in paediatric LCH populations who have higher risk of organ involvement. Two large retrospective studies, one from Russia and one from Poland, found a lack of response to corticosteroid therapy in LCH; conversely, cladribine was reported to be associated with 88–100% stabilisation/regression of the disease [69, 70].

Lymphangioleiomyomatosis (LAM) is a rare disease with an almost exclusive female predominance. LAM can be sporadic or associated with tuberous sclerosis complex (TSC-LAM). In an international retrospective survey, Di Marco *et al.* [71] showed that the pulmonary natural history is similar in both forms, underlining that TSC-LAM should not be considered as a milder form of the disease. Alongside being a diagnostic criterion, vascular endothelial growth factor (VEGF)-D may also be a biomarker for faster FEV_1 decline [72]. Mammalian target of rapamycin (mTOR) inhibitors are now the standard of care in LAM, and sirolimus long-term efficacy data were presented in two different communications. Revilla Lopez *et al.* [73] showed that 66% of their patients were considered responders after 5 years of treatment, while a group from Hannover reported a better 10-year transplant-free survival compared to sirolimus-naive patients (97% *versus* 60%) [74]. A novel therapeutic approach may be on the horizon, with the identification of a $K_{Ca}3.1$ channel in LAM nodules and tissue. The selective channel blocker senicapoc inhibits cell activity and may limit progressive lung damage [75]. Clinical studies in this area are eagerly awaited.

Pulmonary alveolar microlithiasis (PAM) is an ultra-rare genetic disorder leading to calcium phosphate deposits in the alveolar spaces. As mutations in type II Na-P-cotransporter NPT2b have been reported in patients with PAM, Saito *et al.* [76] developed an NPT2b$^{-/-}$ mouse model and showed that low phosphate diet prevents and improves microlith accumulation. Theoretically, phosphate binders may reduce phosphate intake as effectively as low phosphate diet and improve pathology of human disease.

Respiratory failure is one of the leading causes of death in Duchenne muscular dystrophy. The long-term effect of idebenone in phase III randomised placebo-controlled studies was presented by Mayer and co-workers [77, 78]. Reduction of annual rate of FVC decline, inspiratory and expiratory respiratory muscle function loss, hospitalisation rates and bronchopulmonary adverse events were seen in patients treated with idebenone (DELOS study) and maintained for up to 6 years (SYROS study).

Other interesting presentations focused on different diseases. Casey *et al.* [79] showed a 4.4% prevalence of shrinking lung syndrome in an Argentinian cohort of systemic lupus erythematosus patients, with a median time to diagnosis of 30 months. In a Portuguese series of patients with organising pneumonia, azithromycin as second-line therapy led to resolution in 69% of cases, reinforcing the potential usefulness of macrolides in this disease [80]. Fibrosing mediastinitis lacks therapeutic options. Rituximab administered with a day 0/day 14 1000 mg regimen improved symptoms in 65% of a 17-patient series and should therefore be considered as a therapeutic option [81]. Ikegami *et al.* [82] compared pathological characteristics of idiopathic and secondary pleuroparenchymal fibroelastosis (PPFE) on explanted lungs. Distribution of intra-alveolar fibrosis and elastosis was similar, but granulomas and peribronchiolar inflammation were more frequently observed in secondary PPFE. Familial pulmonary fibrosis was also the subject of several presentations. Using a linear mixed effect model, Justet *et al.* [83] demonstrated that antifibrotic drugs slowed FVC decline in IPF patients carrying telomere mutations. Therapeutic approaches concerned a great proportion of the assembly presentations, allowing clinicians to get an overview of the most relevant advances on treatment dilemmas in these rare and very rare diseases.

Conclusion

This article reviews only a portion of the many ILD studies that were presented and discussed at the 2019 ERS International Congress. All the abstracts from the Congress can be found at the *European Respiratory Journal* website (https://erj.ersjournals.com/content/54/suppl_63), and most presentations can be accessed at the ERS e-learning resources site (www.ers-education.org/events/international-congress/madrid-2019/).

The 2020 ERS International Congress will be another opportunity for the presentation and discussion of all the new developments in the very active field of ILDs.

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