Research highlights from the 2018 ERS International Congress: interstitial lung diseases

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ABSTRACT This article reviews a selection of the scientific presentations on interstitial lung disease (ILD)/diffuse parenchymal lung disease (DPLD) that were made at the 2018 European Respiratory Society (ERS) International Congress in Paris. A number of advances in the epidemiology, pathogenesis, diagnosis and treatment of these disorders were presented and discussed by clinicians and researchers. The research topics span over all four groups of ERS Assembly 12: Interstitial Lung Diseases (Group 12.01: Idiopathic interstitial pneumonias; Group 12.02: ILD/DPLD of known origin; Group 12.03: Sarcoidosis and other granulomatous ILD/DPLD; Group 12.04: Rare ILD/DPLD).

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Introduction

This article reviews a selection of the scientific presentations on interstitial lung disease (ILD)/diffuse parenchymal lung disease (DPLD) that were made at the 2018 European Respiratory Society (ERS) International Congress in Paris. A number of topics were presented and discussed by clinicians and researchers. They included new developments in epidemiology, pathogenesis, diagnosis and treatment of these disorders. The subjects of the presentations span over all four groups of ERS Assembly 12: Interstitial Lung Diseases (Group 12.01: Idiopathic interstitial pneumonias; Group 12.02: ILD/DPLD of known origin; Group 12.03: Sarcoidosis and other granulomatous ILD/DPLD; Group 12.04: Rare ILD/DPLD).

Group 12.01: Idiopathic interstitial pneumonias

A wide variety of basic, translational and clinical research in idiopathic interstitial pneumonias was presented at the 2018 ERS International Congress. Most studies in Group 12.01 focused on idiopathic pulmonary fibrosis (IPF) or combined the different ILDs.

Several new therapeutic targets for IPF were presented. Chitotriosidase is upregulated in lungs of patients with ILDs, including IPF. The selective chitinase inhibitor OATD-01 reduced lung fibrosis in a mouse model and had an acceptable safety profile in healthy volunteers [1, 2]. Wolffs *et al.* [3] showed that the calcium-sensing receptor (CaSR) is upregulated in IPF lungs and CaSR antagonists reduced fibrotic markers *in vitro*. A phase 1 study demonstrated an acceptable safety profile of aerosolised pirfenidone in healthy volunteers and IPF patients, with higher concentrations of pirfenidone in epithelial lining fluid and lower plasma levels compared with oral pirfenidone [4]. Lee *et al.* [5] showed that molecular markers of telomere dysfunction and senescence are similar in lungs from IPF and non-IPF usual interstitial pneumonia (UIP) patterns, which suggests that treatment for IPF might also be effective in other forms of UIP-associated fibrosis.

A number of studies focused on quality of life (QoL) and symptom relief in ILDs. The INSTAGE trial, combining nintedanib and sildenafil in IPF patients with advanced diffusing capacity of the lung for carbon monoxide (*D*LCO) impairment, showed no significant improvement in health-related QoL [6]. Decline in forced vital capacity (FVC) was numerically lower in patients treated with nintedanib plus sildenafil *versus* nintedanib alone. In the PRAISE trial, progression of dyspnoea was significantly slowed down in a subgroup of IPF patients by pamrevlumab compared with placebo [7]. Another study suggested that a low dose of morphine was safe for the relief of dyspnoea in patients with ILD [8]. Bendstrup *et al.* [9] showed that the majority of IPF patients were fatigued at diagnosis, based on the Fatigue Assessment Scale (FAS). Treatment with antifibrotic drugs did not influence FAS scores after 3 months. A new home monitoring programme including real-time daily home spirometry was presented. This e-health solution was feasible and highly valued by IPF patients, and enabled early detection of changes in FVC and patient-reported outcomes [10].

The importance of identifying more reliable predictors of disease progression and mortality in IPF is underlined by the large number of studies reporting on predictive factors in this field. A nine-gene bronchoalveolar lavage (BAL) signature derived from BAL transcriptome data was predictive of mortality in IPF and had an added value compared with clinical parameters alone [11]. Nolan *et al.* [12] showed that the "4-metre gait speed" independently predicted mortality and hospitalisation after 1 year in newly diagnosed patients with IPF, while self-reported frailty was an independent predictor of hospitalisations in fibrotic ILDs [13]. Innovative imaging studies showed that a deep learning algorithm recognised UIP patterns on high-resolution computed tomography (CT) with the same accuracy as thoracic radiologists, that CT-histogram-derived indexes at diagnosis can predict mortality in IPF and that an automated CT quantification tool was able to detect typical changes in patients with an acute exacerbation of IPF [14–16]. Nonetheless, these tools and predictive factors need to be validated in larger patient cohorts.

In recent years, many prospective ILD registries have been established in different countries worldwide and collaborative efforts have led to the initiation of multicountry registries [17, 18]. Data from the EMPIRE registry confirm that there are significant differences in IPF patient characteristics and treatment access between countries [19]. Moreover, findings from an international survey in 41 countries revealed that only 58% of IPF patients have access to antifibrotic treatment [20]. An international survey of pulmonologists from 66 countries showed that approaches to the diagnosis and treatment of acute exacerbations of IPF also vary widely between countries [21].

Real-life PROOF registry data indicated that pulmonary function remained relatively stable during 24 months in IPF patients treated with pirfenidone [22]. In addition, data from INPULSIS-ON demonstrated that the effects of nintedanib on slowing down FVC decline endured over 192 weeks, with a manageable safety and tolerability profile and without new safety signals [23]. In addition, real-life data showed that the overall bleeding risk in patients with nintedanib was very low [24]. In the European IPF

Registry, a significant survival difference was found between patients treated with antifibrotic drugs and untreated patients; specifically, 50% of patients on antifibrotic drugs survived >100 months from date of diagnosis [17]. However, it is important to note that the long survival after diagnosis is probably accounted for not only by the effect of antifibrotic drugs, but also by earlier diagnosis of IPF. Other real-life data, from a large observational study on cryobiopsy (n=699), showed that overall mortality was low (0.3%) and that the diagnostic yield increased when a higher number of samples was obtained from different lung segments [25]. In two large lung cancer screening studies, 6–7% of patients had ILD features on low-dose CT [26, 27]. In addition, Ezquibela *et al.* [27] demonstrated that ILD was an independent risk factor for lung cancer, which was supported by findings from a large retrospective study showing a lung cancer prevalence of 8.2% among patients with IPF [28].

Group 12.02: ILD/DPLD of known origin

A large number of presentations focused on ILDs of known origin, with many relating to hypersensitivity pneumonitis, connective tissue disease (CTD)-associated ILD and interstitial pneumonia with autoimmune features (IPAF).

Prognostic factors in hypersensitivity pneumonitis were the focus of a number of presentations, highlighting the clinical need for predictive tools in a disease associated with progressive fibrosis and poor prognosis in a subset of patients. BAL lymphocytosis >30% was associated with better survival in a large retrospective study of hypersensitivity pneumonitis patients [29]. Along similar lines, lower BAL lymphocyte counts (<20%) were associated with a poor prognosis [30, 31]. In a small retrospective study, higher lymphocyte counts were associated with response to azathioprine treatment [32]. Comorbidities were also associated with impaired survival [31, 33].

The role of genetic predisposition in hypersensitivity pneumonitis was explored. Roldán *et al.* [34] investigated the association between matrix metalloproteinase (MMP) gene variants (*MMP1*, *MMP2*, *MMP9* and *MMP12*) and susceptibility to the development of hypersensitivity pneumonitis, stratified according to presence (n=34) or absence (n=104) of autoantibodies. The *MMP1* rs7125062 variant was associated with increased risk of hypersensitivity pneumonitis with or without autoantibodies, while the *MMP2* rs11646643 genotype was associated with an increased risk for autoantibody-positive hypersensitivity pneumonitis and a worse prognosis, although these findings will need validation. In an exploratory study of 19 patients with hypersensitivity pneumonitis, Šterclová *et al.* [35] suggested an association between *TOLLIP* gene polymorphisms and disease progression, although replication in a larger group of patients is needed.

A focus on predictors of disease behaviour identifiable at baseline was also evident among studies on CTD-ILD. Stock *et al.* [36] observed that baseline serum KL-6 levels were associated with progression of systemic sclerosis (SSc)-associated ILD in both a retrospective and a prospective validation cohort. In a Spanish cohort, a value of KL-6 >425 $U \cdot mL^{-1}$ was reported as the optimal cut-off to differentiate ILD patients (including CTD-ILD and IPF) from healthy controls [37]. In a cohort of 4131 patients with SSc, Kreuter *et al.* [38] confirmed that ILD is the most frequent type of pulmonary complication, followed by pulmonary hypertension (PH)-ILD and PH alone, with PH-ILD having the worse survival. In patients with rheumatoid arthritis (RA)-associated ILD, a CT staging system based on the presence of UIP pattern, emphysema and a fibrosis score identified patients with a worse prognosis [39].

In terms of treatment effects, a retrospective analysis of patients with RA-ILD treated (n=26) or not (n=18) with rituximab for joint involvement reported a trend bordering on statistical significance towards a slower rate of lung function decline in the rituximab-treated group [40]. Preliminary data on the effect of nintedanib on fibroblasts from patients with SSc-ILD and control lungs suggest that nintedanib inhibits myofibroblast differentiation and contractility [41].

The significance of autoimmunity features/autoantibodies in ILD was also explored [42, 43]. In a retrospective study of 102 patients with high-resolution CT-defined nonspecific interstitial pneumonia (NSIP) pattern, no differences in clinical characteristics or 3-year survival were observed between patients with IPAF and idiopathic NSIP. However, within the IPAF group, the presence of antisynthetase antibodies was associated with a more frequent acute onset [43]. In a large cohort of 82 anti-MDA5-positive patients, the prevalence of ILD was high (63%), with NSIP being the most frequent pattern. Acute onset and rapidly progressive ILD was frequent in this subgroup of patients [44]. Finally, in a Japanese study comparing histological findings between anti-neutrophil cytoplasmic antibody myeloperoxidase-positive (MPO^+) ILD patients (n=28; 20 with a histology pattern of UIP) and IPF, a greater degree of peri-bronchiolar inflammation was seen surrounding cystic lesions in MPO^+ ILD, suggesting that the pathogenesis of the cystic changes seen in a UIP pattern associated with MPO^+ may differ from the honeycomb lesions of IPF [45].

The importance of symptom management and improvement of healthcare quality in patients with non-IPF ILD was highlighted by a systematic review on pharmacological and nonpharmacological interventions [46]. In particular, patients with non-IPF progressive fibrosing ILD had higher healthcare utilisation and costs compared with other ILD patients, underlining the need to focus resources in this group [47]. In a large review of the Swedish respiratory failure registry, comprising 1603 ILD patients, the use of low-dose benzodiazepines and the use of either low or high doses of opioids for symptom management of patients with oxygen-dependent ILD appeared safe, since no increased hospital admissions or mortality were reported, whereas an association between high-dose benzodiazepines and mortality was observed [48]. Finally, the inclusion of a specialist pharmacist in the ILD multidisciplinary team is likely to improve the management of drug interactions and adverse effects, optimising treatment adherence and reducing medical costs [49].

A few innovative presentations focused on imaging biomarkers as a tool for detection and quantification of ILD. Magnetic resonance imaging (MRI) findings in animal models of drug-induced ILD were correlated with extent of inflammation and fibrosis [50, 51]. The use of *in vivo* confocal laser endomicroscopy during bronchoscopy in nine patients with ground-glass changes on CT provided additional information and appeared to allow differentiation between inflammatory *versus* fibrotic changes as the underlying cause of ground-glass opacities (partially filled alveoli by cellular infiltrates *versus* fine fibrosis) [52].

Group 12.03: Sarcoidosis and other granulomatous ILD/DPLD

The presentations in these sessions almost always concerned the field of sarcoidosis, and provided a rich array of information regarding phenotype, QoL, dangerous sarcoidosis and translational research for understanding disease pathogenesis.

Regarding phenotyping sarcoidosis, Lhote *et al.* [53] analysed 1237 patients with at least one extrapulmonary localisation. The authors performed a cluster analysis to identify clinical phenotypes. Five clusters were finally identified, in line with those previously reported [54], but in a multiethnic population. In this analysis, phenotypes could be explained, at least partially, by sex, geographical origin and professional environmental exposure.

Schupp *et al.* [55] presented results from the GenPhenResa study. In this large European cohort including more than 2100 Caucasian sarcoidosis patients, genetic profiles associated to specific phenotypes were studied. Some genetic variants (*e.g.* polymorphisms) were associated with specific clinical features, such as *TNFA* rs1800629 with acute sarcoidosis, but links between genetics and phenotype often varied according to the regional origin of patients.

The prognostic value of pulmonary function tests in patients with hypersensitivity pneumonitis has been explored in two large retrospective studies from the Royal Brompton Hospital (London, UK), with decline in FVC $\geqslant$10% and in *D*LCO $\geqslant$15% within the first year both being predictive of mortality after adjusting for age, sex, smoking and exposure history [56]. In pulmonary sarcoidosis, Kouranos *et al.* [57] analysed the prevalence of mixed ventilatory defect in 1110 patients. Depending upon definition criteria, 25–35% of sarcoidosis patients with airflow obstruction had a mixed pattern, which was associated with further *D*LCO reduction compared with patients with only airflow obstruction, and higher prevalence of chest radiographic stage IV than other ventilatory defects (63.5% for mixed *versus* 38.3% for obstructive *versus* 38.5% for restrictive defects). Mortality was higher in patients with mixed and restrictive pattern than those with obstruction alone, but this difference was more linked to the level of *D*LCO than to the type of ventilatory defect *per se*.

Evaluation and management of QoL impairment are essential in sarcoidosis. An international survey including 1842 patients was undertaken in order to gather views about which treatment outcomes matter most to sarcoidosis patients [58]. QoL and functionality were the highest priority for outcomes of sarcoidosis patients. Blood tests and pulmonary function testing were not viewed as important. In a double-blind, randomised, placebo-controlled trial, the effect of low-dose oral dexamethasone (1 mg) on QoL was studied [59]. A total of 16 patients were randomised and followed-up for 1 year. Low-dose dexamethasone resulted in a reduction of the inflammatory profile, and improved QoL parameters and fatigue, but with higher weight gain than control patients [59].

Cardiac sarcoidosis was the subject of three presentations. Ohira *et al.* [60] showed that the prevalence of cardiac sarcoidosis diagnosed according to the revised Japanese guidelines [61] exceeds 20% in biopsy-proven extracardiac sarcoidosis patients with no cardiac symptoms, and normal ECG and echocardiogram. This raises the question of systematic screening with MRI and positron emission tomography in this particular population. In a study from Poland, lower left ventricular ejection fraction was associated with decreased value of forced expiratory volume in 1 s (FEV_1) (r=0.31, p=0.003) in cardiac sarcoidosis [62]. The main hypothesis is that heart failure may cause bronchial wall oedema [63]. An

alternative hypothesis is the existence of a phenotype associating obstruction and cardiac sarcoidosis. Nevertheless, a decrease of FEV1 should warn of the possibility of heart failure in sarcoidosis. The Royal Brompton Hospital [64] reported its large experience of 644 patients referred for suspected cardiac sarcoidosis. Cardiac sarcoidosis diagnosis was based on Heart Rhythm Society consensus statement criteria [65] *via* multidisciplinary team discussion. Two groups were identified: one with known extracardiac sarcoidosis (n=461) and one with cardiac manifestation as first presentation (n=183). The diagnosis of cardiac sarcoidosis was done in 36.9% and 76.5%, respectively, of the two groups. Active myocardial inflammation was present in 41.8% and 60.7%, respectively. Mortality in the first group was 15% at 10 years and was predicted by late gadolinium enhancement on MRI only in univariate analysis, whereas only age was predictive of mortality in multivariate analysis.

A number of presentations reported on basic research in sarcoidosis. Schott *et al.* [66] studied the role of the immune paradox (*i.e.* diminished peripheral responses) on peripheral blood mononuclear cells from sarcoidosis patients with a gene network analysis. There was an association between peripheral lymphopenia and worse lung function. Decreased expression of lymphocyte activity genes was observed and associated with a more severe phenotype in sarcoidosis, but also in other ILDs. The importance of T-helper 17 subsets in the pathogenicity and chronicity of sarcoidosis was once again observed [67]. Lepzien *et al.* [68] analysed the distribution of mononuclear phagocytes in different anatomical compartments in patients with Löfgren syndrome and non-Löfgren syndrome sarcoidosis. Cytometry analysis identified different populations of monocytes and dendritic cells among these compartments, but in different proportions. Löfgren syndrome patients had a decreased frequency of dendritic cells in bronchial tissue and lymph nodes, which may translate to differences in T-cell responses associated with disease progression. Mononuclear phagocytes in the bronchial tissue and BAL were more activated than in blood and lung lymph nodes, indicating local inflammation.

Two studies concerning microbiota did not identify a specific profile or pathogen in the lungs of sarcoidosis patients [69, 70]. Several other lines of research on sarcoidosis were presented: analysis of ubiquitin and PU-1 (a transcriptional activator involved in the differentiation and activation of macrophages) [71], analysis of vascular endothelial growth factor (VEGF) [72], the possible involvement of autoimmune factors, owing to the detection of elevated levels of autoantibodies against modified citrullinated vimentin [73], and metabolomics study on plasma [74].

Group 12.04: Rare ILD/DPLD

Rare diseases are challenging for both treating physicians and researchers, as they tend to be exposed to a limited number of cases. Most of these conditions are orphan, as they are ultrarare, not widely researched and no effective treatment strategies or approved drugs exist [75]. The 2018 ERS International Congress included several educational and scientific sessions on rare lung diseases, where clinicians and scientists from all around the world shared and discussed new data on the pathogenesis, diagnosis and treatment of these neglected disorders.

Pleuroparenchymal fibroelastosis (PPFE) is a distinctive ILD that may be primary or secondary. Its prognosis is unpredictable, with some cases showing inexorable progression [76]. In a study of 62 lung transplanted patients, 15 had PPFE in pre-transplant imaging studies. Five cases were idiopathic, eight were associated with hypersensitivity pneumonitis and two with IPF [77]. In 72 asymptomatic PPFE subjects, the presence and severity of traction bronchiectasis in PPFE areas was correlated with the extent and severity of the disease ($p<0.05$). Plathythorax, with deepened suprasternal notch on CT, correlated with progression ($p<0.01$) and death ($p<0.05$) [78].

Lymphangioleiomyomatosis (LAM) is a rare cystic lung disease affecting almost exclusively females [79]. Terraneo *et al.* [80] assessed the levels of serum VEGF-C, VEGF-D, MMP-2 and MMP-7 in 27 LAM patients and 16 healthy volunteers. Higher levels of VEGF-D (area under the curve (AUC) 0.833), MMP-2 (AUC 0.756) and MMP-7 (AUC 0.820) were predictive of LAM diagnosis. Novikova *et al.* [81] reported on the use of mammalian target of rapamycin (mTOR) inhibitors in 15 patients with progressive LAM and showed a decrease of abdominal leiomyomas in three patients, with no cases of pneumo-, chylo- or haemothorax, suggesting treatment efficacy.

Pulmonary Langerhans cell histiocytosis (PLCH) is a cystic disorder that is typically associated with smoking [82]. Le Guen *et al.* [83] reported on 43 patients with pneumothorax complicating PLCH and found a high risk (53%) for recurrence that was not changed by surgery ($p=0.96$). Thoracotomy, however, was more effective than video-assisted thoracoscopic surgery in preventing recurrences ($p=0.03$) and was recommended by the authors [83]. A detailed genotyping analysis of the mitogen-activated protein kinase (MAPK) pathway in 50 PLCH patients found genetic alterations in 44 (88%). Some of these gene alterations lead to variable sensitivity to MAPK targeting drugs and the authors proposed this strategy for refractory cases [84]. Radzikowska *et al.* [85] reported on the effects of cladribine for the treatment of

PLCH in 12 patients. There was improvement in lung function in five patients and stabilisation in seven patients. None of the patients progressed.

Pulmonary alveolar proteinosis is characterised by alveolar accumulation of surfactant lipids and proteins. INOUE *et al.* [86] reported on 34 fatal cases from a nationwide Japanese cohort. Deceased patients had a similar age and sex distribution to survivors, but were more symptomatic (p=0.035) and had more frequent secondary disease (p<0.001). The median survival time for nonsurvivors was 16.5 years post-diagnosis, and major causes of death were malignancy (26.5%), infection (20.6%) and respiratory failure (11.8%).

In addition to the classical rare DPLDs, there were several reports on ultrarare diseases affecting adults and children. ALIMI *et al.* [87] reported that nine out of 34 patients with pulmonary haemosiderosis had Down syndrome, and this group had more severe disease with increased dyspnoea (p=0.03) and pulmonary arterial hypertension (p=0.01). Additionally, all the three reported deaths occurred in the Down syndrome group.

MARANGU *et al.* [88], from Cape Town, South Africa, reported on 12 Zimbabwean children with exogenous lipoid pneumonia caused by repeated oil administration for cultural reasons. Children were between 2.1 and 10.8 months of age, and all displayed cough and alveolar infiltrates on chest radiography. The authors argued for health education for the caregivers and community in order to prevent the disease.

NASSER *et al.* [89] studied 71 patients with unclassifiable ILD from a national French reference centre and found progressive disease in 46 (64%). Progressors had higher mortality (p=0.004), but the only predictor of disease progression was lower baseline FVC (mean±SD 70±20% *versus* 84±27%; p=0.049).

Pulmonary lymphangiomatosis is an extremely rare disease characterised by lung, pleural and mediastinal infiltration by abnormal lymphatics. SARMAND *et al.* [90] reported on six cases from a tertiary German centre. Most were young adults (mean age 35 years) and five were female. Only one had pulmonary interstitial changes. Three were treated with sirolimus with good response. A 24-month survival of 83% was found.

YOUNG *et al.* [91] reported on a US national registry for childhood ILDs. A total of 254 subjects had been enrolled, of which 23% were subjected to genetic studies. There was substantial morbidity with failure to thrive in 53% and use of oxygen at some point in 66%. The most frequent disease was diffuse idiopathic pulmonary neuroendocrine cell hyperplasia. Childhood ILD registries are fundamental for the advancement of research on rare diseases.

TAKEUCHI *et al.* [92] studied the predictive factors for relapse in 56 consecutive patients with chronic eosinophilic pneumonia. On multivariate analysis, centrilobular infiltrates, but not blood or BAL markers, predicted relapses (p=0.032). The authors proposed that this finding relates with eosinophilic bronchiolitis.

Concluding remarks

This article summarises only some of the many and exciting developments on ILD/DPLD that were presented at the 2018 ERS International Congress. We encourage readers to follow-up on their personal topics of interest and aim to spark further interest for participation in the 2019 ERS International Congress in Madrid (https://erscongress.org).

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