Editorial

Highlights from the 2018 European Respiratory Society Congress presentations on interstitial lung diseases

Tiago M. Alfaro[1], Margarida Afonso[1], Sebastiano Emanuele Torrisi[2]

[1]Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal; [2]Regional Referral Centre for Rare Lung Diseases, A.O.U. Policlinico-Vittorio Emanuele, Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy

Correspondence to: Tiago M. Alfaro. Centro Hospitalar e Universitário de Coimbra, Serviço de Pneumologia, 3000-075 Coimbra, Portugal. Email: alfarotm@gmail.com.

Submitted Aug 10, 2018. Accepted for publication Aug 16, 2018.
doi: 10.21037/jtd.2018.08.101
View this article at: http://dx.doi.org/10.21037/jtd.2018.08.101

Interstitial lung diseases (ILDs) are a large and heterogeneous group of lung disorders characterized by primary involvement of the lung interstitium. Several studies point out their increasing incidence and global burden leading to a growing interest and massive literature production in the last few years.

In 2017, the European Respiratory Society (ERS) created a new assembly dedicated to ILDs and elected this topic as one of the eight key educational fields for the Annual Congress. This paper highlights some of the outstanding abstracts on this area that were selected for presentation at the 2018 Congress. It is also remarkable that ILDs resulted one of the most popular topics among the submitted abstracts, thus giving light to this particular group of impacting diseases.

We hope that this short summary of some of the best abstracts may capture the interest of readers towards ERS ILDs-related activities.

Idiopathic pulmonary fibrosis (IPF)

IPF is a progressive and fatal lung disease, with a median survival of 3 to 5 years from diagnosis. Two drugs have been demonstrated to slow the progression of the disease highlighting the importance of an early diagnosis. However, despite the efforts to facilitate diagnostic work-up, an early identification of the disease remains an unmet goal (1).

Backer *et al.* from Belgium (2) tested whether an analysis of the chest movements could easily differentiate patients with IPF from healthy controls. In a previous study it was demonstrated that in IPF patients most of the inhaled air is usually directed to the upper lobes (3). Using HRCT scans as a proof-of-concept study, the authors showed that the lower chest region demonstrated a larger displacement in the healthy subjects than in IPF patients. This could pave the way for the development of an early disease screening tool using non-invasive sensor systems (such as displacement sensors). Of course, definitive diagnosis would be subsequently confirmed through conventional methods.

Estimation of survival in IPF is a real challenge for clinicians (1). Currently, validated composite indexes such as GAP, allow an estimation of mortality through the evaluation of common demographic and functional variables. However, the assessment of new variables may further increase our ability to estimate prognosis. Nolan *et al.* from UK (4) performed a reliable and robust test, the four metre gait speed (4MGS), in 130 IPF patients. They demonstrated how this test may predict all-cause mortality at one year (AUC 0.81) after adjusting for age, FVC and hospitalization. The 4MGS also predicted one-year risk of hospitalization (AUC 0.84), after adjusting for sex, DLCO and number of chest infections, constituting an independent predicting factor. The 4MGS has been validated in other chronic lung disorders and may be promising for the assessment and monitoring of IPF patients (5).

Comorbidities and extra-pulmonary complications of IPF such as depression and neurocognitive dysfunction, are frequent in IPF patients and may greatly impact the quality of life, functional status and survival (6). Elhefny *et al.* from Egypt (7) studied this association analysing 100 IPF patients and 50 controls. They confirmed that both these complications are frequent in IPF patients. Moreover,

they also showed some interesting associations between depression and hypoxia as well as between neurocognitive dysfunction and pulmonary arterial hypertension that could partially explain their genesis in IPF. These results underline once again the importance of an early detection and treatment of comorbidities and extra-pulmonary complications in IPF patients.

IPF acute-exacerbations (AE-IPF) are a deadly complication of the disease. Up to 46% of IPF deaths are preceded by an AE-IPF, but no definite international guidelines for their management exist (8). Kreuter *et al.* (9) performed a very large survey to investigate common management of these events. A total of 469 pulmonologists (64% experts) from 66 countries participated to this survey. While HRCT, BNP and d-dimer were broadly used, some diagnostic differences emerged on the use of KL-6 and viral testing. Regarding treatment, the majority (92% of respondents) usually used high dose steroids, while the administration of immunosuppression was quite variable. The major finding of this survey was the high variability in international approaches for the prevention, diagnosis and treatment of AE-IPF. Therefore, the authors, an extended group of international ILD experts, call for the development of global international guidelines and trials to evaluate these approaches.

Hypersensitivity pneumonitis

Hypersensitivity pneumonitis (HP) is caused by the repeated and/or intense inhalation and subsequent sensitization to organic dusts or occupational agents in predisposed subjects. Although the prognosis in chronic-HP (cHP) is usually better compared to IPF, a certain amount of progression was also demonstrated in these patients and the mortality risk is not negligible. Currently, widely accepted methods for estimating prognosis in cHP patients are lacking (10).

Bronchoalveolar lavage (BAL) is usually helpful for diagnosing HP, but according to Wälscher *et al.*, (11) it can also inform on the prognosis. The authors studied a cohort of 211 patients with cHP (194 with BAL results) showing a significant association between the proportion of lymphocytes in the BAL and survival. In particular, BAL lymphocytes >30% (P=0.009) and >40% (P=0.020) were associated with improved survival compared to patients without BAL lymphocytosis (P=0.037). According to these results, BAL lymphocytosis should be considered in the work-up of cHP not only for diagnostic but also for prognostic reasons.

Another promising prognostic marker for cHP patients comes from the study of Boccabella *et al.* (12) from UK. They retrospectively analysed 205 subjects with cHP and demonstrated that a 15% or higher reduction of DLCO or 10% or higher reduction of FVC within the first year of follow-up were predictive of a higher mortality (HR 2.4, P<0.0001 and HR 2.28, P=0.001 respectively). Importantly, both associations remained significant after adjusting for age, gender, smoking history and ILD severity. Based on these findings, the authors suggest that FVC and DLCO could be used as prognostic variables in future clinical trials dedicated to cHP patients.

Auto-immunity

Rheumatoid arthritis (RA) affects about 1% of the global adult population and is frequently associated with ILD. Lung involvement in the course of RA (RA-ILD) is a clinical challenge both for the unpredictable clinical course and for the lack of an easy and widely accepted survival prediction tool (13). Woo Song *et al.* from Republic of Korea performed a retrospective analysis of 158 RA-ILD patients, developing a prediction staging system based on CT features. A multivariate cox analysis was used for analysing predictors of mortality. Finally, three variables were included in the model (UIP pattern, fibrosis score ≥20% and emphysema) and three different stages were identified that demonstrated a 1-year mortality of 1.6%, 6.9% and 33.3%, respectively.

Meloni *et al.* (14) from Italy retrospectively analysed 82 patients with positive anti-MDA5 (melanoma differentiation-associated gene 5) antibodies, a rare antibody subtype associated with clinically amyopathic dermatomyositis and rapidly progressive ILD (15). They reported ILD in 53 patients (63%), 15 of which with acute onset and 9 with acute flares leading to ICU admission in a total of 16 cases. A high rate of mortality was also registered (12 patients), 6 of which occurred in ICU. Other important findings were muscle involvement that was reported in 49 patients (only 39 symptomatic) and arthritis, reported in 42 cases. Therefore, the authors demonstrated that ILD with acute onset or flares is frequent in patients with anti-MDA5, and muscle and/or joint involvement may suggest seeking the presence of these antibodies.

Other interstitial lung diseases

Sarcoidosis multiorgan involvement is well described. However, few data are currently available on the associations

among the various organ disorders. More information in this field may help in clinical management and therapeutic choice (16). In their abstract, Lhote *et al.* (17) from France reported on the results of the Episarc study. They analysed 1,237 patients with sarcoidosis recruited through the French Medical Information Systems Program databases and performed a cluster analysis to identify clinical phenotypes. Five clusters were finally identified, which differed for subject's origin (European versus non-European), organ involvement, gender distribution, occupation and need for treatment. This large study brings new and important information on the different presenting patterns of sarcoidosis, thus being helpful for the clinical assessment of patients. Phenotyping is also important for the standardization of cohorts for research purposes (18).

Autoimmune pulmonary alveolar proteinosis (APAP) is caused by neutralizing autoantibodies against GM-CSF (19). Yamaguchi *et al.* (20) from Japan analysed possible correlations between the activity of these antibodies and the clinical course of a cohort of 52 patients with APAP. Neutralizing capacity of each serum was assessed by measuring 50% inhibitory concentration. They described that the 50% inhibitory concentration of anti GM-CSF antibodies was positively correlated with DLCO and negatively correlated with a total semi-quantitative score of lung shadows on CT. Therefore, the authors argue that the neutralizing capacity of serum antibodies may affect lung physiology and radiological features in patients with APAP.

Genes and ILDs

Most ILDs are currently of unknown origin. Gene expression may differently contribute to disease onset, progression and response to therapy. Consequently, genetic background could be evaluated in every patient to increase diagnostic accuracy and management. However, despite first discoveries, this field remains largely unexplored (21).

In their study, Nathan *et al.* (22) from France reported on a prospective assessment of surfactant genes mutations in 477 patients (190 children and 287 adults) with idiopathic interstitial pneumonia (IIP) that were included in the French network of rare lung diseases centres. All SFTPA1, SFTPA2, SFTPB, SFTPC, ABCA3, NKX2-1 exons and flanking intronic sequences were analysed. Interestingly, the disease was familial in 22% of cases while 15% had a personal or family history of lung cancer. The authors identified mutations in 45 patients (9.4%), including 22 children and 23 adults. Based on this, they suggest these molecular tests as part of the diagnosis process of IIP regardless of age, especially when there is a family history of IIP and/or lung cancer.

Šterclová *et al.* (23) from the Czech Republic explored a panel of polymorphisms (SNPs) in 19 patients with HP. They selected different SNPs based on candidate loci for HP susceptibility using MALDI-TOF MS based MassARRAY (Agena Bioscience) or TaqMan (Life Technologies) assays. They subsequently looked for possible associations between SNPs and disease progression defined by >10% absolute decrease in FVC, >15% absolute decrease in DLCO, exacerbation or death every 6 months of follow-up. No significant associations between SNPs and progression were observed within the first 12 months of follow-up. However, after 18 months since diagnosis, an effect of TOLLIP SNP (rs111521887) and TOLLIP (rs5743890) on patient's outcome was observed and a relative risk of progression was also found in patients TOLLIP SNP (rs5743894) with CG genotype (allele CC was found to be protective), OR 16.0 (95 % CI, 1.1-234.3, P=0,04). These results demonstrated how genetic factors may play an important role for both the development and the progression of the disease.

The mitogen-activated protein kinase (MAPK) pathway is constantly activated in patients with Langerhans cell histiocytosis (LCH) (24). However, despite MAPK alterations having been well described in LCH, they have not been accurately evaluated in pulmonary-LCH (PLCH) lesions. Jouenne *et al.* (25) from France performed a detailed analysis to evaluate MAPK pathway genes alterations from surgical lung biopsies of PLCH patients. Interestingly, they described a variable number of genes alterations that were present in 88% of cases. These genetic changes are associated with different sensitivity to MAPK targeting drugs, therefore a wide genomic evaluation should be pursued in patients with refractory progressive disease.

Frailty and quality of life

Frailty is common in elderly populations and is characterized by the accumulation of multiple deficits that lead to increased mortality (26). Guler *et al.* (27) from Switzerland assessed 540 patients with fibrotic ILD, including 100 with IPF, using a 42-item patient reported frailty index (FI). They probed for associations between frailty and non-elective hospitalizations. Interestingly, half of the subjects were classified as frail (median FI was 0.21). Moreover, frailty was associated with a higher number and

length of all cause and respiratory related hospitalizations. This study highlights how frailty impacts the natural history of ILD patients representing an independent predictor of number and length of all cause and respiratory related hospitalizations.

ILDs frequently cause bothersome and difficult to manage symptoms, such as dyspnoea. This leads to a wide use of benzodiazepines (BZDs) and opioids for symptomatic control, even if data on their safety are still lacking (28). For this reason, Bajwah *et al.* (29) from Sweden decided to analyse the impact of these drugs on mortality in a cohort of subjects with severe ILDs. Data come from a large longitudinal study (Swedevox) of patients that underwent long term oxygen therapy (LTOT). Out of a total of 1603 patients with ILD under LTOT, BZDs were used by 196 subjects (12%), opioids by 254 subjects (15%) and both drugs by 60 subjects (4%). Treatment with opioids, both with low or higher doses, and also low doses of BZDs were generally not associated with increased mortality while higher doses of BZDs were demonstrated to impact on mortality (HR 1.46; 95% CI, 1.08 to 1.98). This study brings important and new information pointing to the general safety on the use of opioids and lower doses of BZDs for symptomatic control in patients with interstitial lung diseases.

Conclusions

The posters and oral presentations being presented at the 2018 ERS Congress bring exciting updates on risk factors, pathogenesis, diagnosis and management of some of the most challenging diseases. IPF remains the undisputed protagonist of ILDs even if much interest moves also towards chronic HP, sarcoidosis, autoimmune-related and other fibrotic ILDs. Importantly, genetic analysis is increasingly taking hold, also in ILDs, radically changing our approach to diagnosis and management. Several other important aspects as comorbidities, frailty and quality of life will be discussed during the 2018 ERS Congress.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Martinez FJ, Collard HR, Pardo A, et al. Idiopathic pulmonary fibrosis. Nat Rev Dis Primers 2017;3:17074.
2. Backer JD, Holsbeke CV, Vos W, et al. Proof of concept of a non-invasive screening tool to detect idiopathic pulmonary fibrosis (IPF) in an early stage. Eur Respir J 2018;52. [Epub ahead of print].
3. Wu X, Kim GH, Salisbury ML, et al. Computed Tomographic Biomarkers in Idiopathic Pulmonary Fibrosis: The Future of Quantitative Analysis. Am J Respir Crit Care Med 2018. [Epub ahead of print].
4. Nolan CM, Maddocks M, Maher TM, et al. Four metre gait speed (4MGS) predicts mortality and hospitalisation in IPF. Eur Respir J 2018;52. [Epub ahead of print].
5. Kon SS, Patel MS, Canavan JL, et al. Reliability and validity of 4-metre gait speed in COPD. Eur Respir J 2013;42:333-40.
6. Kreuter M, Ehlers-Tenenbaum S, Palmowski K, et al. Impact of Comorbidities on Mortality in Patients with Idiopathic Pulmonary Fibrosis. PLoS One 2016;11:e0151425.
7. Elhefny R, Elessawy A, Shaheen H, et al. Cognitive impairment and depression in patients with Idiopathic Pulmonary Fibrosis. Eur Respir J 2018;52. [Epub ahead of print].
8. Collard HR, Ryerson CJ, Corte TJ, et al. Acute Exacerbation of Idiopathic Pulmonary Fibrosis. An International Working Group Report. Am J Respir Crit Care Med 2016;194:265-75.
9. Kreuter M, Polke M, Walsh S, et al. A global perspective on acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF): results from an international survey. Eur Respir J 2018;52. [Epub ahead of print].
10. Salisbury ML, Myers JL, Belloli EA, et al. Diagnosis and Treatment of Fibrotic Hypersensitivity Pneumonia. Where We Stand and Where We Need to Go. Am J Respir Crit Care Med 2017;196:690-9.
11. Wälscher J, Gross B, Bruhwyler J, et al. Prognostic impact of bronchoalveolar lavage lymphocytosis in patients with chronic Hypersensitivity Pneumonitis. Eur Respir J 2018;52. [Epub ahead of print].
12. Boccabella C, Macaluso C, Kokosi M, et al. Pulmonary function trends predict mortality in patients with hypersensitivity pneumonitis. Eur Respir J 2018;52. [Epub ahead of print].
13. Solomon JJ, Chung JH, Cosgrove GP, et al. Predictors of mortality in rheumatoid arthritis-associated interstitial

lung disease. Eur Respir J 2016;47:588-96.
14. Meloni F, Cifrian JM, Pesci A, et al. Lung involvement and clinical characteristics in anti-MDA5 positive connective tissue diseases. Eur Respir J 2018;52. [Epub ahead of print].
15. Kurtzman DJB, Vleugels RA. Anti-melanoma differentiation-associated gene 5 (MDA5) dermatomyositis: A concise review with an emphasis on distinctive clinical features. J Am Acad Dermatol 2018;78:776-85.
16. Judson MA. The Clinical Features of Sarcoidosis: A Comprehensive Review. Clin Rev Allergy Immunol 2015;49:63-78.
17. Lhote R, Cohen-Aubart F, Nunes H, et al. Clinical phenotypes of extra-pulmonary sarcoidosis. The EpiSarc study. Eur Respir J 2018;52. [Epub ahead of print].
18. Schupp JC, Freitag-Wolf S, Bargagli E, et al. Phenotypes of organ involvement in sarcoidosis. Eur Respir J 2018;51. pii: 1700991.
19. Kumar A, Abdelmalak B, Inoue Y, et al. Pulmonary alveolar proteinosis in adults: pathophysiology and clinical approach. Lancet Respir Med 2018;6:554-65.
20. Yamaguchi E, Kosaka K, Yonezawa T, et al. Neutralizing capacity of autoantibody against GM-CSF in patients with autoimmune pulmonary alveolar proteinosis. Eur Respir J 2018;52. [Epub ahead of print].
21. Furukawa H, Oka S, Shimada K, et al. Genetics of Interstitial Lung Disease: Vol de Nuit (Night Flight). Clin Med Insights Circ Respir Pulm Med 2015;9:1-7.
22. Nathan N, Legendre M, Filhol-Blin E, et al. Contribution of mutations in genes of the surfactant system to idiopathic interstitial pneumonia (IIP). Eur Respir J 2018;52. [Epub ahead of print].
23. Šterclová M, Ek MP, Kishore A, et al. Effect of genotype on hypersensitivity pneumonitis despite treatment. Eur Respir J 2018;52. [Epub ahead of print].
24. Vassallo R, Harari S, Tazi A. Current understanding and management of pulmonary Langerhans cell histiocytosis. Thorax 2017;72:937-45.
25. Jouenne F, Lorillon G, Laurent-Issartel C, et al. Genetic landscape of pulmonary Langerhans cell histiocytosis. Eur Respir J 2018;52. [Epub ahead of print].
26. Milne KM, Kwan JM, Guler S, et al. Frailty is common and strongly associated with dyspnoea severity in fibrotic interstitial lung disease. Respirology 2017;22:728-34.
27. Guler S, Kwan J, Wilcox P, et al. Frailty is an independent predictor of number and length of hospitalizations in patients with fibrotic ILD. Eur Respir J 2018;52. [Epub ahead of print].
28. Ferrara G, Luppi F, Birring SS, et al. Best supportive care for idiopathic pulmonary fibrosis: current gaps and future directions. Eur Respir Rev 2018;27.
29. Bajwah S, Davies J, Tanash H, et al. Safety of benzodiazepines and opioids in interstitial lung disease: national prospective study. Eur Respir J 2018;52. [Epub ahead of print].

Cite this article as: Alfaro TM, Afonso M, Torrisi SE. Highlights from the 2018 European Respiratory Society Congress presentations on interstitial lung diseases. J Thorac Dis 2018;10(Suppl 25):S3024-S3028. doi: 10.21037/jtd.2018.08.101

