

Course report

Interstitial lung disease: course report

Faculty

A. Bush, V. Cottin, B. Crestani, F.J.F. Herth, C.P. Heussel, M. Kreuter, T. Maher, M. Molina-Molina, V. Poletti, M. Vasakova, A. Wells, M. Wijsenbeek, H. Winter

Overview

According to the most recent update of the global burden of disease study [1], a rising number of years of lives lost and deaths due to interstitial lung diseases (ILDs) is to be expected in the coming years. This highlights the need for better tools to defeat these diseases worldwide. Nelson Mandela stated that “Education is the most powerful weapon which you can use to change the world.” The European Respiratory Society (ERS) realised over 5 years ago that there was a requirement to improve education in the field of rare lung disease, especially in ILDs.

Since then, five ERS courses on ILDs have been held in Heidelberg, Germany, and provided a broad and current overview on the diagnosis and treatment of ILDs. The most recent ERS course on ILD was held in Heidelberg from 4–6 November 2019 with 80 participants from 23 different countries attending (figure 1). Following successful introduction during the fourth course earlier that year, the course was again live streamed to over 80 participants from 34 countries. Given the current COVID-19 pandemic, this was a wise decision as

it may allow future education to go ahead even in difficult times when travelling and direct exchange might not be possible and to communicate within the society on important topics.

Over the years, the organisers’ and ERS’s ambition has been to improve the interactivity and interdisciplinary aspects of this course. To address this, the participants studied the diagnostic approach to ILDs and the difficulties that may arise in ILD diagnosis, a topic discussed based on real-life cases. Special emphasis was given to practical workshops including high-resolution computed tomography (CT) evaluation and sessions on ILD pathology and cryobiopsy.

As therapy remains a challenging aspect in the management of ILDs, this course provided participants with insights into the newest developments, and the advantages and disadvantages of specific ILD treatments. In addition, further important therapeutic aspects such as end-of-life strategies, acute complications such as acute exacerbation and lung transplantation were approached. Multidisciplinary team discussions were held between specialists and course participants. Moreover, course attendees had the opportunity to present their own challenging cases and discuss them with leading experts. There was a dedicated session on the pathogenesis and future trends in ILDs as well as specific conditions and treatments for ILDs, especially the new concept of progressive phenotypes of non-idiopathic pulmonary fibrosis (IPF) fibrosing interstitial lung diseases.

One of the main challenges during these courses is the different levels of knowledge of

Cite as: Kreuter M, Poberezhets V. Interstitial lung disease: course report. *Breathe* 2020; 16: 200075.



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Figure 1 Faculty and participants at the venue in Heidelberg.

the participants. While most had an advanced, sometimes excellent comprehension of ILDs, for others, this course was their first step into the world of ILDs. This also reflected the different challenges identified during the course; for many, the complex diagnostic approach to ILDs, its sophisticated treatment approach and its complications like acute exacerbations or comorbid conditions. For more advanced colleagues, difficulties in end-of-life strategies and the more individualised management of chronic diseases were challenging, especially when it comes to progression despite conventional therapies and the complex approach to the diverse forms of connective tissue disease (CTD)-associated ILDs. Participants of the course were again very passionate, and people were eager to learn about all aspects of ILD highlighted by exciting discussions outside of the direct course schedule. This also includes the opportunity to meet people from all over the world and make new friends in the society.

Finally, we thank all the faculty members for their outstanding contribution to the success of this course.

Vitalii Poberezhets, Ukraine, a participant

The ERS course on ILDs highlighted a great number of issues in the management and treatment of these respiratory diseases.

The session dedicated to rare ILDs, covering Langerhans cell histiocytosis, lymphangioleiomyomatosis (LAM), pulmonary alveolar proteinosis, eosinophilic pneumonias and familial ILDs, was extremely informative. The discussion provided me with the latest diagnostic criteria for these diseases, examples of lung involvement and described updates in pharmacological treatment using mTOR1C inhibitors, including indications for its initiation and the most common adverse effects, the role of tobacco cessation, glucocorticoids, cytotoxic agents (vinblastine, methotrexate) in systemic forms, 2-chlorodeoxyadenosine (2CDA, cladribine)

and surgical treatment. According to TAVEIRA-DASILVA and Moss [2] indications for mTOR1C inhibitor initiation are progressive disease (forced expiratory volume in 1 s decline), chylous effusions, lymphangioleiomyomas and large angiomyolipomas >4 cm. The most common adverse effects due to mTOR1C inhibition using sirolimus over several years include infections (respiratory and non-respiratory), stomatitis, hypercholesterolaemia, hypertriglyceridaemia, peripheral oedema, acne, rash, delayed wound healing, hypertension, headache, thrombocytopenia, neutropenia and proteinuria [3]. The adverse event profile of everolimus is similar to sirolimus and includes gastrointestinal pathology, pain, dermatological problems and pulmonary events [4]. Surgical treatment of LAM in case of the first episode of pneumothorax consists of pleurodesis using chest tube or appropriate surgical interventions. Among these patients the usual rate of pneumothorax relapse despite surgery is one third. Moreover, it is desirable to avoid talc because of increased risk of perioperative pleural bleeding during lung transplantation in future [5]. Lung transplantation should be performed according to the established procedure, recurrence of LAM is possible and may be treated with sirolimus, but at the same time, sirolimus is contraindicated at the early phase of transplantation [6, 7]. During the discussion about pulmonary Langerhans cell histiocytosis the speaker highlighted the mandatory role of an aggressive smoking cessation programme in its treatment, which influences prognosis because this disease is related to tobacco smoking: 90–100% of patients are smokers (usually >20 cigarettes per day). Treatment may include glucocorticoids in nodular forms with constitutive symptoms (that may accelerate resolution of the symptoms and radiological abnormalities), and cytotoxic agents (vinblastine, methotrexate) in systemic forms of Langerhans cell histiocytosis. 2-chlorodeoxyadenosine (2CDA, cladribine) has not been demonstrated improvement in lung function among patients with pulmonary Langerhans cell histiocytosis [8].

Another important session for my daily practice was the session dedicated to occupational ILDs. It focused not only on special considerations in diagnosis and treatment of asbestosis, but also, presented practical guidelines on how to perform differential diagnosis for asbestosis with IPF. I received information on how to evaluate cumulative exposure for asbestosis, mesothelioma and other occupational diseases. Cumulative exposure is an estimation of the mean concentration of asbestos dust at the workplace multiplied by the duration of exposure (in years), usually expressed as fibres·mL⁻¹·year⁻¹. According to MOSSMAN *et al.* [9] asbestosis is unlikely if exposure is below 25 fibres·mL⁻¹·year⁻¹. However, some research showed that lower exposure to asbestos fibres (2–5 fibres·mL⁻¹·year⁻¹) may also increase the risk

of asbestosis. However, there was a strong critic of this research concerning study design and coexisting other interstitial diseases [10]. Mesothelioma is much more sensitive to cumulative exposure and its risk increases if exposure is higher than 0.5 fibres·mL⁻¹ [11].

Practical workshops, where participants were divided into four groups, gave the opportunity to get familiar with the most common radiological patterns of increased and decreased density and with transbronchial lung cryobiopsy. A practical workshop on lung cryobiopsy provided opportunity not only to discuss the bioptic strategy, the volume of activity, the role of bronchoalveolar lavage as a contributor to the diagnosis and safety issues, but also to hone skills in this diagnostic procedure using all the necessary equipment and lung models. A practical workshop on radiology presented the role of chest radiography in diagnostics of ILDs, adequate technique and typical radiological patterns of ILDs based on the latest American Thoracic Society (ATS)/ERS Statement and Fleischner Society white paper. The latest ATS/ERS Statement on the idiopathic interstitial pneumonias highlighted that the typical usual interstitial pneumonia (UIP)-pattern includes reticular findings with subpleural and basal predominance, traction-bronchiectasis and honeycombing. Possible UIP-pattern refers to presence of the same reticular findings with subpleural and basal predominance, traction-bronchiectasis and no honeycombing. Inconsistent with UIP pattern includes any of the seven features: upper or mid-lung predominance, peribronchovascular predominance, extensive ground-glass abnormality (reticular abnormality), profuse micronodules, discrete cysts, diffuse mosaic attenuation/air-trapping, and consolidation in bronchopulmonary segment(s)/lobe(s) [12, 13]. According to the recent Fleischner Society white paper the typical UIP CT pattern includes basal (occasionally diffuse) subpleural predominant, distribution often heterogeneous reticular pattern, peripheral traction bronchiectasis and honeycombing. Probable UIP CT pattern refers to the same features but without honeycombing, CT pattern indeterminate for UIP variable or diffuse fibrosis, distribution of non-UIP pattern an inconsistent pattern including upper or mid-lung peribronchovascular, subpleural sparing consolidation, ground-glass opacity mosaic, air trapping nodules, cysts [14].

There was a lot of attention to the issue of CTD and rheumatoid arthritis-associated ILD. It raised the importance of developing the discussion

between rheumatologists and pulmonologists because ILD is a significant complication in most of the CTDs that should be differentiated from drug-related ILD, indirect pulmonary impairment, and immunosuppressant-related infection. This session provided me with the EULAR (European League Against Rheumatism) recommendations for treatment of systemic sclerosis (SSc), discussed if antifibrotics are a potential treatment in CTD-ILD and provided an overview of current trials with anti-fibrotics in non-IPF-ILD. According to latest EULAR recommendations treatment of SSc with skin and lung involvement includes methotrexate (for treatment of skin manifestations of early diffuse SSc), cyclophosphamide (treatment of SSc-ILD, for patients with SSc with progressive ILD) and haematopoietic stem cell transplantation (HSCT) (for patients with rapidly progressive SSc at risk of organ failure) [15]. According to ROJAS-SERRANO *et al.* [16] use of methotrexate in rheumatoid arthritis-associated ILD significantly improved survival. Use of cyclophosphamide in patients with scleroderma-related ILD improves lung function, reduces dyspnoea, cutaneous sclerosis and quality of life [17, 18]. HSCT improves event-free and overall survival in patients with scleroderma, but with increased expected toxicity compared with cyclophosphamide [19]. According to KHANNA *et al.* [20] pirfenidone presented a good tolerability profile in patients with SSc-ILD. Also, a combination of mycophenolate mofetil with pirfenidone did not affect tolerability. Following KREUTER *et al.* [21], for ILDs with a primarily inflammatory component the treatment should be based on steroids and/or other immunosuppressive agents, while preliminary evidence suggests that pirfenidone and nintedanib may be effective in treating fibrosing ILDs other than IPF.

The final session was a case-based discussion. This session brought together all the knowledge I had gained during the course and helped to structure it into the defined diagnostic and treatment algorithms. It was helpful to involve in the discussion specialists from different fields such as radiologists, pathologists and clinicians. Interaction with the audience in the form of onsite and online questions helped to build real clinical discussion, where everyone could defend his or her opinion.

The ERS course on ILDs in Heidelberg not only fulfilled my expectations but also exceeded them. I have received extremely important information for my practice, met many colleagues engaged in the field of ILDs from many countries all over the world and had a great time walking through the old town of Heidelberg.

Affiliations

Michael Kreuter^{1,2}, Vitalii Poberezhets³

¹Center for Interstitial and Rare Lung Diseases, Thoraxklinik, University Clinic of Heidelberg, Heidelberg, Germany.

²German Center for Lung Research, Heidelberg, Germany. ³National Pirogov Memorial Medical University, Vinnytsya, Ukraine.

Conflict of interest

None declared.

References

1. Foreman KJ, Marquez N, Dolgert A, *et al.* Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016-40 for 195 countries and territories. *Lancet* 2018; 392: 2052-2090.
2. Taveira-DaSilva AM, Moss J. Clinical features, epidemiology, and therapy of lymphangioleiomyomatosis. *Clin Epidemiol* 2015; 7: 249-257.
3. Yao J, Taveira-DaSilva AM, Jones AM, *et al.* Sustained effects of sirolimus on lung function and cystic lung lesions in lymphangioleiomyomatosis. *Am J Respir Crit Care Med* 2014; 190: 1273-1282.
4. Goldberg HJ, Harari S, Cottin V, *et al.* Everolimus for the treatment of lymphangioleiomyomatosis: a phase II study. *Eur Respir J* 2015; 46: 783-794.
5. Johnson SR, Cordier JF, Lazor R, *et al.* European Respiratory Society guidelines for the diagnosis and management of lymphangioleiomyomatosis. *Eur Respir J* 2010; 35: 14-26.
6. Reynaud-Gaubert M, Mornex JF, Mal H, *et al.* Lung transplantation for lymphangioleiomyomatosis: the French experience. *Transplantation* 2008; 86: 515-520.
7. Kpodonu J, Massad MG, Chaer RA, *et al.* The US experience with lung transplantation for pulmonary lymphangioleiomyomatosis. *J Heart Lung Transplant* 2005; 24: 1247-1253.
8. Tazi A. Adult pulmonary Langerhans' cell histiocytosis. *Eur Respir J* 2006; 27: 1272-1285.
9. Mossman BT, Churg A. Mechanisms in the pathogenesis of asbestosis and silicosis. *Am J Respir Crit Care Med* 1998; 157: 5, 1666-1680.
10. Roggli VL, Gibbs AR, Attanoos R, *et al.* Pathology of asbestosis- An update of the diagnostic criteria: Report of the asbestosis committee of the college of american pathologists and pulmonary pathology society. *Arch Pathol Lab Med* 2010; 134: 462-480.
11. Iwatsubo Y, Pairon JC, Boutin C, *et al.* Pleural mesothelioma: dose-response relation at low levels of asbestos exposure in a French population-based case-control study. *Am J Epidemiol* 1998; 148: 133-142.
12. Raghu G, Collard HR, Egan JJ, *et al.* An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011; 183: 788-824.
13. Travis WD, Costabel U, Hansell DM, *et al.* An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2013; 188: 733-748.
14. Lynch DA, Sverzellati N, Travis WD, *et al.* Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society White Paper. *Lancet Respir Med* 2018; 6: 138-153.
15. Kowal-Bielecka O, Fransen J, Avouac J, *et al.* Update of EULAR recommendations for the treatment of systemic sclerosis. *Ann Rheum Dis* 2017; 76: 1327-1339.
16. Rojas-Serrano J, Herrera-Bringas D, Pérez-Román DI, *et al.* Rheumatoid arthritis-related interstitial lung disease (RA-ILD): methotrexate and the severity of lung disease are associated to prognosis. *Clin Rheumatol* 2017; 36: 1493-1500.
17. Tashkin DP, Elashoff R, Clements PJ, *et al.* Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med* 2006; 354: 2655-2666.
18. Tashkin DP, Roth MD, Clements PJ, *et al.* Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. *Lancet Respir Med* 2016; 4: 708-719.
19. Sullivan KM, Goldmuntz EA, Keyes-Elstein L, *et al.* Myeloablative autologous stem-cell transplantation for severe scleroderma. *N Engl J Med* 2018; 378: 35-47.
20. Khanna D, Albera C, Fischer A, *et al.* An open-label, phase ii study of the safety and tolerability of pirfenidone in patients with scleroderma-associated interstitial lung disease: the LOTUSS trial. *J Rheumatol* 2016; 43: 1672-1679.
21. Kreuter M, Wälscher J, Behr J. Antifibrotic drugs as treatment of nonidiopathic pulmonary fibrosis interstitial pneumonias: the time is now (?). *Curr Opin Pulm Med* 2017; 23: 418-425.