Editorial

Reference centers for interstitial lung diseases

Vasilios Tzilas, MD,
Demosthenes Bouros, MD, PhD, FERS, FCCP, FAPSR

Academic Department of Pneumonology, Interstitial Lung Diseases Unit, Medical School, National and Kapodistrian University of Athens; Hospital for Diseases of the Chest "Sotiria", Greece

Facing a patient with interstitial lung disease (ILD) is one of the most challenging tasks of respiratory medicine both in terms of diagnosis and management. We should remember that interstitial lung diseases constitute a huge pool of over 500 clinical entities (ILD of known cause e.g. drugs or association e.g. collagen vascular disease, Idiopathic Interstitial Pneumonias (IIPs), granulomatous ILD, e.g. Sarcoidosis, other ILDs, e.g. Lymphangioleiomyomatosis, Pulmonary Langerhans' Cell Histiocytosis etc). Vast improvements have been accomplished in understanding the pathogenesis of these diseases in order to categorize them in a clinically meaningful way[1,2]. Idiopathic Pulmonary Fibrosis is the commonest of the IIPs. It is characterized by a variable but relentlessly progressive course, leading to a median survival of 3 to 4 years which is worst comparing to many types of cancer[3,4]. The incidence and prevalence of IPF seems to be on the rise during the last decade[4,5]. 2014 signaled the dawn of a new era[6] with the publication of two positive studies that led to the approval of pirfenidone[7,8] and nintedanib[9] for the management of IPF. After many years of disappointment, negative results and even administrating potentially harmful therapies[10,11] we now have in our arsenal two antifibrotic agents. This in turn increases the responsibility for both early and accurate diagnosis. Diagnosing IPF is now important not only because it is of prognostic value[12] but also because it actually influences therapeutic choices. This emphasizes the importance of having operational referral centers.

There are guidelines for the diagnosis of IPF but actual implementation in every day clinical practice poses significant challenges (Table 1). In the appropriate clinical setting HRCT is considered diagnostic (obviating the need for surgical lung biopsy) when it demonstrates a definite UIP pattern (i.e. peripheral and basilar predominant irregular reticular pattern, presence of honeycombing and absence of features suggestive of alternative diagnoses). However, the majority of patients do not present with a definite UIP pattern on HRCT. Furthermore, although the identification of honeycombing seems pretty straightforward it is actually characterized by poor interobserver agreement even among experienced radiologists[13-15]. In these cases there is the false impression that obtaining lung tissue secures a diagnosis. This is not the case. Pathologists must have expert skills in interstitial lung disease pathology. Even then, interobserver agreement between pathologists can be poor especially regarding the distinction between UIP and fibrotic NSIP[16]. It is also important to keep in mind that

Correspondence to
Prof. Demosthenes Bouros, MD, PhD, FERS, FCCP, FAPSR
Medical School, University of Athens,
Academic Department of Pneumonology,
Hospital for Diseases of the Chest "Sotiria",
152 Messogion Ave. , Athens 11527, Greece,
Tel.: +30-210-7763500, +30-210-7763559
e-mail: dbouros@med.uoa.gr.

TABLE 1. Diagnostic approach of idiopathic Pulmonary Fibrosis (from reference 1).

Radiologic Pattern	Histopathologic Pattern: UIP	Probable UIP	Possible UIP	Not UIP	Not performed
UIP	IPF	IPF	IPF	Not IPF	IPF
Possible UIP	IPF	IPF	+/- IPF	Not IPF	Not IPF
Inconsistent with UIP	+/- IPF	Not IPF	Not IPF	Not IPF	Not IPF

subjecting a patient with lung fibrosis to surgical lung biopsy is not a decision to be taken lightly as it can be potentially harmful and even life threatening[17,18]. Thus, it is important to refer patients to specialty centers where there is the appropriate experience, standardization of assessment, evaluation in accordance to the concept of multidisciplinary approach and avoidance of aggressive and potentially harmful diagnostic procedures. After establishing a diagnosis, the proper follow up of patients is equally important as it includes serial evaluation of the response to therapy, recognition, recording and reporting of adverse events, diagnosing and management of comorbidities and complications.

The lack of accurate diagnosis is depicted on the generic and often erroneous use of the ICD-10 code for IPF (J84.1)[19,20]. Patients classified as J84.1 in fact represent a heterogeneous population with IPF corresponding to just a fraction of cases. Without a thorough re-evaluation, this population cannot provide reliable epidemiological data. The operation of referral centers can prove pivotal for the creation of reliable registries. Accurate registries are essential in understanding the incidence, prevalence, natural history, complications of diseases and to evaluate the response to therapy in real life clinical practice. Also, delayed access to a specialty center is associated with a decreased survival in IPF patients[21]. Although lead time bias could represent a possible explanation, the results did not change substantially after adjustment for age and FVC.

Referral of patients to specialty centers gives them the opportunity of enrollment into clinical trials and early access to novel therapies. Also, the interconnection of specialty centers internationally, gives them the opportunity to establish cooperative actions. The lack of lung transplantation in Greece represents a characteristic example. Referral to a specialty center increases the possibility of a timely referral for lung transplantation abroad.

Finally, referring patients to specialty centers helps in identifying and grouping patients with rare diseases, evaluating and treating them taking advantage of existing experience and eventually increasing our knowledge leading to better management.

We need strategic planning and will on a national level in order to officially create such specialty centers. Having specialty centers operating at the highest level is of clear value for the patients for the aforementioned reasons that are summarized in Table 2. These centers must be subjected to periodic evaluation (auditing) in order to ensure that they continue to function according to prespecified requirements/criteria as the number of examined patients, the ability to provide multidisciplinary assessment according to current guidelines, to create and sustain reliable registries, to provide consultation to other hospitals to interact with other foreign and domestic centers, to interact with patients groups, to provide disease education and support group information to patients, to

TABLE 2. Gains from the operation of referral centers

1. Accurate diagnosis within the context of multidisciplinary approach
2. Enrollment in clinical trials
3. Early access to novel therapies
4. Timely referral for lung transplantation
5. Take advantage of existing experience and know-how to manage other rare diseases
6. Avoidance of erroneous detrimental treatments
7. Experts networking

TABLE 3. Suggested criteria for the establishment of referral centers

1. Total number of patients under surveillance
2. Number of new patients each year
3. Number of referred patients (domestic and abroad)
4. Ability to provide multidisciplinary assessment
5. Ability to create and sustain reliable registries
6. Consultation to other hospitals
7. Interaction with other foreign and domestic centers
8. Interaction with patients groups (provide disease education, support group information)
9. Educational, Clinical and Research activities
10. Involvement in clinical trials

maintain a high level of educational, clinical and research work, to be involved in clinical trials (Table 3).

We have no conflict of interest to declare.

REFERENCES

1. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. Am J RespirCrit Care Med 2002;165:277-304.
2. Travis WD, Costabel U, Hansell DM, et al; ATS/ERS Committee on Idiopathic Interstitial Pneumonias. 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; 188:733–48.
3. Raghu G, Collard RH, 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.
4. Raghu G, Chen SY, Yeh WS et al. Idiopathic pulmonary fibrosis in US Medicare beneficiaries aged 65 years and older: incidence, prevalence, and survival, 2001-11. Lancet Respir Med 2014;2:566-72.
5. Hutchinson J, Fogarty A, Hubbard R, et al. Global incidence and mortality of idiopathic pulmonary fibrosis: a systematic review. Eur Respir J 2015;46:795-806.
6. Bouros D. Idiopathic Pulmonary Fibrosis: The dawn of a new era. Pneumon 2014;27:117.
7. Bouros D. Pirfenidone for idiopathic pulmonary fibrosis. Lancet 2011; 377:1727-9.
8. King TE, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med 2014; 370:2083–92.
9. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med 2014; 370:2071–82.
10. Idiopathic Pulmonary Fibrosis Clinical Research Network; Raghu G, Anstrom KJ, King TE Jr, et al. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. N Engl J Med 2012;366:1968-77.
11. Bouros D. Current therapy of idiopathic pulmonary fibrosis: primum non noccere! Pneumon 2012;25:256-8.
12. Bjoraker JA, Ryu JH, Edwin MK, et al. Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1998;157:199–203.
13. Lynch DA, Godwin JD, Safrin S, et al; Idiopathic Pulmonary Fibrosis Study Group. High-resolution computed tomography in idiopathic pulmonary fibrosis: diagnosis and prognosis. Am J RespirCrit Care Med 2005; 172:488–93.
14. Watadani T, Sakai F, Johkoh T, et al. Interobserver variability in the CT assessment of honeycombing in the lungs. Radiology 2013;266:936-44.
15. Walsh SL, Calandriello L, Sverzellati N, et al. Interobserver agreement for the ATS/ERS/JRS/ALAT criteria for a UIP pattern on CT. Thorax 2016;71:45-51.
16. Nicholson AG, Addis BJ, Bharucha H, et al. Inter-observer variation between pathologists in diffuse parenchymal lung disease. Thorax 2004;59:500-5.
17. Kreider ME, Hansen-Flaschen J, Ahmad NN, et al. Complications of video-assisted thoracoscopic lung biopsy in patients with interstitial lung disease. Ann Thorac Surg 2007;83:1140–44.
18. Chida M, Ono S, Hoshikawa Y, Kondo T. Subclinical idiopathic pulmonary fibrosis is also a risk factor of postoperative acute respiratory distress syndrome following thoracic surgery. Eur J Cardiothorac Surg 2008;34:878–81.
19. Tzilas V, Bouros D. Inherent weaknesses of the current ICD coding system regarding idiopathic pulmonary fibrosis. Eur Respir J 2015;45:1194-6.
20. Kaunisto J, Kelloniemi K, Sutinen E, et al. Re-evaluation of diagnostic parameters is crucial for obtaining accurate data on idiopathic pulmonary fibrosis. BMC Pulm Med 2015;15:92.
21. Lamas DJ, Kawut SM, Bagiella E, et al. Delayed access and survival in idiopathic pulmonary fibrosis: a cohort study. Am J Respir Crit Care Med 2011;184:842–7.