Eur Respir J, 1993, 6, 770–771
Printed in UK - all rights reserved

European Respiratory Journal
ISSN 0903 - 1936

EDITORIAL

Management of idiopathic pulmonary fibrosis: academic postulate and clinical practice

U. Costabel*

Idiopathic pulmonary fibrosis (IPF), or cryptogenic fibrosing alveolitis (CFA) as the British say, is a slowly progressive interstitial lung disease, which carries a grave prognosis. Current textbook knowledge informs us that, after exclusion of other causes of diffuse lung disease by careful analysis of history, physical examination, chest radiography, clinical and laboratory tests [1], the diagnosis of IPF should be confirmed by open lung biopsy, which is the gold standard [2]. This is the academic postulate. But what is today's clinical practice?

A surprising answer is given by JOHNSTON *et al.* [3] in this issue of the Journal. They reviewed the case notes of 200 patients with CFA from three regions in the UK, and found that the diagnosis of CFA was based solely on clinical grounds, in the majority of cases. Transbronchial biopsy was attempted in 33% of patients. In 40% of these, it was believed to be diagnostic. Open lung biopsy was performed in only 7.5% of patients. Which peer-reviewed journal would accept a paper on IPF with this low percentage of cases being confirmed by biopsy?

The current practice in the USA for establishing the diagnosis of IPF seems to be somewhat different, as assessed by postal survey among 219 members of the Californian Thoracic Society, with a response rate of 67% [4]. The majority of physicians in this survey try to obtain tissue by transbronchial biopsy (8% always, 66% usually), but mainly to exclude other aetiologies of interstitial lung disease, not to establish the diagnosis of IPF. When a nonspecific transbronchial biopsy is obtained, 42% of the responders proceed to open lung biopsy.

It would be of interest to know what the usual practice is in European countries other than the UK.

Why do practicing physicians hesitate to perform open lung biopsy in patients with suspected IPF? The reasons are discussed, in part, by JOHNSTON *et al.* [3]. Physicians may feel that the results obtained by open lung biopsy would not change the further management of a given patient, when clinical and laboratory findings are characteristic enough for IPF. In particular, they may know that treatment of IPF poses significant problems, and is not successful in many cases.

It is often argued that open lung biopsy, in addition to being the gold standard for diagnosis, is also helpful in this regard, being of value for the assessment of disease activity and, thus, for the indication of treatment [2]. Patients with the histological features of a predominant cellular alveolitis, with little fibrosis, are thought to respond better to treatment, and to survive longer, than those with extensive fibrosis on biopsy [5, 6]. This may be true for groups of patients, but not for individual cases. I have seen patients with widespread fibrosis on biopsy, who have responded well to treatment, and, conversely, have also observed patients with cellular histology who have steadily declined despite therapy. Also in my opinion, a patient with less cellular histology should at least receive an empirical, short-term trial of treatment.

In this regard, another surprising result of the British study was that only 66% of CFA patients are treated, and that there is a wide variation in doses of drugs and duration of therapy [3]. Similarly, in a USA survey on treatment of IPF, 81% of physicians stated that there are patients they would never start on drug therapy; reporting of severe symptoms by the patients was the most common criterion to initiate treatment [7]. However, once severe symptoms have developed in IPF, the disease is usually in an advanced stage. Thus, treatment is obviously often begun when severe disease is already present and when response to immunosuppressants is less likely. It would be more logical, and more academic, to start treatment in the very early cellular stage, in an attempt to prevent progression to irreversible extensive fibrosis, but as we can see from the above-mentioned studies, today's clinical practice is different. We can thus easily recognize that uncertainty remains about the critical questions: which IPF patient should be treated, when should therapy start, and what drug should be used?

A potential answer to the first question is given by WELLS *et al.* [8] in this issue of the Journal. In a carefully selected study population of 82 nonsmoking patients with CFA, 29 of them with lone CFA, 53 associated with scleroderma, they found that the speed of ^{99m}Tc-diethylenetriamine-pentacetate (DTPA) clearance from the lung was predicitive for disease progression, as judged by pulmonary function tests. In this study, the disease was confirmed by open lung biopsy in about 70% of cases; in the remainder, typical features of CFA were seen on computed tomography (CT). Indeed, CT studies have shown that CFA has a usually pathognomic pattern with crescentic subpleural distribution of reticular opacities, with or without patchy areas of airspace opacification, concentrated in the posterobasal segments of the lower lobes [9–11].

*Abt. Pneumologie/Allergologie, Ruhrlandklinik, Tüschener Weg 40, D-4300 Essen 16, Germany.

WELLS *et al.* [8] found at the initial measurement, in 23 patients with a normal ^{99m}Tc-DTPA clearance, that none had deteriorated in pulmonary function tests after a mean follow-up of 27 months. In contrast, a decline in lung function tests was seen in 25 out of 59 patients who initially had a rapid clearance. Thus, a normal clearance at initial measurement was found to be a strong predictor of a subsequent favourable course without decline in lung function. Whereas, a rapid clearance was less precise as a prognostic indicator, since only half of this subgroup later deteriorated, and a quarter improved.

As a consequence of the results of their study, WELLS *et al.* [8] report that they now adopt a less aggressive therapeutic approach and reduce the frequency of follow-up visits in those patients with a normal clearance at first measurement. Since abnormal clearance was not associated with subsequent deterioration in all patients, further studies should investigate whether other techniques, such as CT or bronchoalveolar lavage (BAL), when applied in combination with ^{99m}Tc-DTPA clearance, might improve the predictive value in this subgroup. CT-pathological correlation studies have shown that areas of disease activity on open lung biopsy may be visualized by CT as patchy areas of airspace opacification [12, 13]. These studies were retrospective, however, and did not prospectively examine the predicitive power of CT abnormalities on the subsequent course of disease. BAL has also been advocated to be of potential value for the assessment of disease activity and prognosis. In IPF, a marked increase in neutrophils and/or eosinophils was reported to adversely affect prognosis, whereas elevated lymphocytes were more likely to be associated with a good response to corticosteroid treatment [14]. Overlap between the subgroups is large, however, and in a given patient these BAL parameters are not precise enough to indicate prognosis reliably. Further studies are necessary, and they should analyse carefully which of the above modalities, either alone or in combination, are able to identify the individual patient with IPF who will take a down-hill course and, therefore, requires immediate and aggressive treatment.

Let us hope that continuous academic research interest in interstitial lung disease will finally provide solid data for pulmonary physicians on which to base optimal management of their IPF patients, so that the gap between academic postulate and clinical practice can one day be closed.

References

1. DeRemee RA. – Diffuse interstitial pulmonary disease from the perspective of the clinician. *Chest* 1987; 92: 1068–1073.
2. Raghu G. – Idiopathic pulmonary fibrosis: a rational clinical approach. *Chest* 1987; 92: 148–154.
3. Johnston IDA, Gomm SA, Kalra A, Woodcock AA, Evans CC, Hind CRK. – The management of cryptogenic fibrosing alveolitis in three regions in the United Kingdom. *Eur Respir J* 1993; 6: 891–893.
4. Smith CM, Holbrook T. – Utilization of the transbronchial biopsy and open lung biopsy for tissue to establish the diagnosis of idiopathic pulmonary fibrosis: survey of the California Thoracic Society membership. *Am Rev Respir Dis* 1990; 141: A62.
5. Carrington CB, Gaensler EA, Coutu RE, Fitzgerald MX, Gupta RG. – Natural history and treated course of usual and desquamative interstitial pneumonia. *N Engl J Med* 1978; 298: 801–809.
6. Turner-Warwick M, Burrows B, Johnson A. – Cryptogenic fibrosing alveolitis: response to corticosteroid treatment and its effect on survival. *Thorax* 1980; 35: 593–599.
7. Smith CM, Holbrook T, Picchi M. – Survey of pulmonologists: criteria used to initiate drug therapy in patients with idiopathic pulmonary fibrosis. *Am Rev Respir Dis* 1991; 143: A58.
8. Wells AU, Hansell DM, Harrison NK, Lawrence R, Black CM, du Bois RM. – Clearance of inhaled ^{99m}Tc-DTPA predicts the clinical course of fibrosing alveolitis. *Eur Respir J* 1993; 6: 797–802.
9. Müller NL, Miller RR, Webb WR, Evans KG, Ostrow DN. – Fibrosing alveolitis: CT-pathologic correlation. *Radiology* 1986; 160: 585–588.
10. Müller NL, Miller RR. – Computed tomography of chronic diffuse infiltrative lung disease. *Am Rev Respir Dis* 1990; 142: 1206–1215 and 1440–1448.
11. Hansell DM, Kerr IH. – The role of high resolution computed tomography in the diagnosis of interstitial lung disease. *Thorax* 1991; 46: 77–84.
12. Müller NL, Staples CA, Miller RR, Vedal S, Thurlbeck WM, Ostrow DN. – Disease activity in idiopathic pulmonary fibrosis: computed tomographic-pathologic correlation. *Radiology* 1987; 165: 731–734.
13. Wells AU, Hansell DM, Corrin B, *et al.* – High resolution computed tomography as a predictor of lung histology in systemic sclerosis. *Thorax* 1992; 47: 508–512.
14. Haslam PL, Bauer W, de Rose V, *et al.* – The clinical role of BAL in idiopathic pulmonary fibrosis. *Eur Respir Rev* 1992; 2: 58–63.