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Recognition and Treatment of Idiopathic Pulmonary Fibrosis

Laurent P. Nicod

Pulmonary Division, Cantonal Hospital, Geneva, Switzerland

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Summary

The diagnosis of idiopathic pulmonary fibrosis can be made only after exclusion of other entities such as neoplasm, toxic treatments, collagen vascular diseases, occupational exposure or granulomatous diseases, such as sarcoidosis. The repercussions on gas exchanges are the most reliable indications of the severity of the disease, the measure of lung volume or chest x-rays alone often being misleading. Biopsies obtained during transbronchial procedures by thoracoscopies or thoracotomy are of great help, but mainly to rule out other diseases. In many cases, only a high resolution computerised tomography (CT) scan and bronchoalveolar lavage are performed to rule out infection or tumour and to assess the inflammatory state of the disease.

Due to the fact that barely a quarter of patients respond to corticosteroids alone, cytostatics (in particular azathioprine) are often prescribed simultaneously with low dose corticosteroids, either initially or after an unsuccessful trial of corticosteroids. Cyclosporin has been useful for only a limited number of patients. Colchicine has been shown useful in an open trial but its role still needs to be assessed. Anticytokine therapy and the role of substances such as relaxin are still at the experimental stage. Lung transplantation is now a therapeutic option for selected patients.

The evaluation of patients with dyspnoea is a complex diagnostic challenge. Dyspnoea may arise from pulmonary, cardiac, muscular or neuropsychiatric abnormalities. In order to diagnose the presence of pulmonary parenchymal abnormalities, several techniques have been used, including

pulmonary function testing (PFT), cardiopulmonary exercise testing (CPET,) various radiological imaging studies and a number of biopsy techniques. Recently, high resolution computerised tomography (HRCT) has been shown to predict the histology of the lungs more accurately than conventional CT.[1] Several interstitial lung processes can evoke the diagnosis of pulmonary fibrosis. In the presence of such infiltrates, the possibility of a neoplasia, the consequences of chemotherapy or radiotherapy, or a collagen disease, must be looked for on the basis of the anamnesis and of clinical findings.

A careful professional anamnesis will need to be conducted to rule out an occupational or environmental disease. The inhalation of organic antigens known to be responsible for hypersensitivity pneumonitis or the use of drugs known to elicit lung disorders must be carefully investigated. The various tests mentioned above will help to diagnose other specific entities that should not be confused with idiopathic pulmonary fibrosis (IPF) such as histiocytosis x, lymphangioleiomyomatosis or cryptogenic organising pneumonia.[2] Figure 1 shows the main differential diagnoses that should be kept in mind, excluding neoplasia and its treatments, in the presence of interstitial lung disease in a nonimmunosuppressed patient.

1. Clinical Evaluation of Idiopathic Pulmonary Fibrosis

Dyspnoea is the usual symptom present when patients are referred for IPF. Cough is also reported by more than 80% of individuals. Several symptoms such as flu-like syndrome, fatigue, bodyweight loss or arthralgia are noticed by more than 50% of patients.[3] More than two-thirds of them have digital clubbing and fine but loud rales on auscultation. Clinical findings and the chest x-ray correlate poorly with the pathological score. Chest x-ray is even considered normal in up to 16% of patients despite biopsy-proven IPF.[4] The forced vital capacity (FVC), the alveolar-arterial oxygen difference at rest and an increased physiological dead space or desaturation during exercise, correlate best with the pathological scores.[5] The forced expiratory volume in 1 second (FEV_1) is usually normal, although small airways disease has been described in up to 70% of patients. HRCT is a very useful tool as it can image up to the anatomy of the secondary pulmonary lobule.

The criteria for a positive interpretation in diagnosing IPF can include one or more of the following: irregular interlobular septal thickening, intralobular interstitial thickening or irregular interfaces, visible intralobular bronchioles, honeycombing, traction bronchiectases or ground-glass opacity. With these criteria, HRCT had a sensitivity

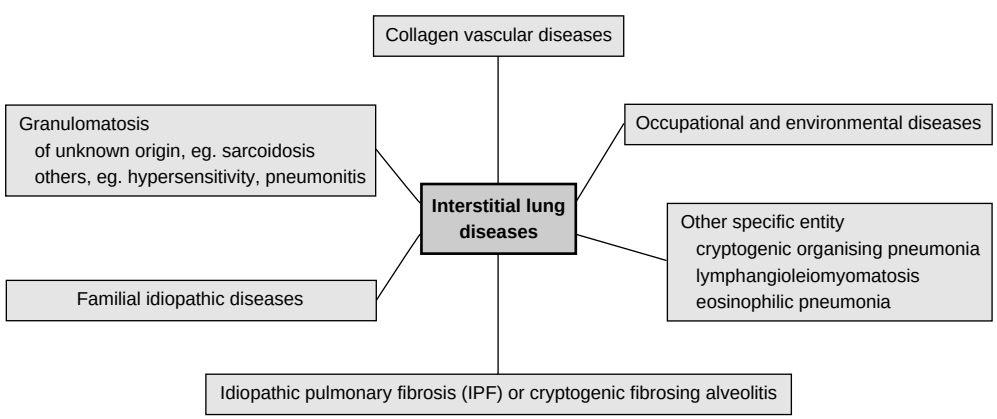

Fig. 1. Interstitial lung diseases in immunocompetent patients, excluding neoplasia.

of 88%, being described as normal in 12% of patients presenting with dyspnoea and having a biopsy-proven IPF in a referral centre.[4] In this group of patients, the most common PFT abnormality was a reduced diffusion capacity for carbon monoxide.

2. Pathophysiologies of IPF

Morphologically, IPF shows zones of pulmonary parenchyma with various extents of inflammation due to mononuclear cells in the interstitium and in the alveoli where type II pneumocytes, fibroblasts, macrophages and neutrophils can be seen. The inflammation will lead to endothelial changes and parenchymal remodelling with the following alterations:[6]

- Disappearance of type I epithelial cells and re-epithelialisation by type II cells.
- Cytoplasmic changes of endothelial cells which might lead in some places to necrosis.
- Thickening, fragmentation and often duplication of basal membranes.
- Layering of fibrin, fibronectin and proteaglycans in the interstitium and in the airways.
- Budding of fibroblasts into the alveoli and occasionally obliteration of distal airways. The fibroblasts can be incorporated into the various walls and re-epithelialisation can occur. The amount of mesenchymal cells in the interstitium can double.
- Type I collagen fibres are increased compared with type III collagen which predominates early on. This collagen accumulation will also impair gas exchanges.

It is likely that not one but several aetiologies are responsible for the IPF. The presence of immune complexes in the alveoli is in favour of an active participation of T and B lymphocytes against endogenous or exogenous antigens. Immune complexes could activate alveolar macrophages which can liberate chemotactic factors for neutrophils, such as leukotrienes B4, or chemokines, such as interleukin (IL)-8 or GRO-α.[7] A cascade of injuries and repairs could follow.[8] Some of the mechanisms leading to injury are:

- Oxidants are released during inflammatory processes of IPF. High concentrations of oxidised methionine residues secondary to the release of reactive oxygen metabolites have been found in the alveoli.[9] Myeloperoxidase, released by neutrophils, transforms hydrogen peroxide into toxic radicals. Glutathione, an antioxidant found in significant amounts in healthy individuals, is decreased in IPF, increasing the risk of injuries by oxidants.[10]
- Overexpression of tumour necrosis factor α (TNF)-α has been shown to induce pulmonary fibrosis in transgenic mice. This has confirmed *in vitro* results showing that TNF-α can not only induce injury but can promote fibroblast replication and collagen synthesis.
- Collagenases have been found in the epithelial lining fluid of patients with IPF. The exact origin and activity of these proteases have not yet been clearly elucidated. Several metalloproteases could be released by macrophages, neutrophils and fibroblasts under the influence of inflammatory cytokines such as IL-1 and TNF-α. To the extent that when activated they are not inhibited locally, they could degrade not only collagens but also elastic fibres. This could explain some of the alterations found in IPF. Corticosteroids could control the expression of several metalloprotease genes while enhancing the production of their inhibitors, thus preventing further injury to lung parenchyma.
- Eosinophils and mast cells are thought to play a role in IPF: mediators such as eosinophil cationic protein (ECP) or histamine have indeed been detected. These findings suggest that a cytotoxic substance such as ECP, and maybe others also contained in eosinophils, may contribute to the lung injury and the secondary development of fibrosis.[11]

Repair mechanisms following injuries which lead to fibrosis are currently better understood.[12] Not only macrophages but other parenchymal cells can produce factors enhancing lung fibrosis. The increase in total collagen mass resulting from the production of the following mediators appear to be

of major importance in idiopathic pulmonary fibrosis:[13]

- 'Platelet derived growth factor' (PDGF) is a 30 kDa dimer, one of the most powerful chemoattractants for fibroblasts, inducing them to enter phase G of the cell cycle. It is released in large part by activated macrophages. Great interest has focused on various forms of 'transforming growth factor-β' (TGF-β). TGF-β can be released by macrophages, epithelial cells and type II pneumocytes.[14-15] It increases the proliferation of fibroblasts and collagen deposition.
- Fibronectin too is a dimer, a component of the extracellular matrix, and also a growth factor for fibroblasts. It is also clear that macrophages are a major source of this factor.
- Somatomedin-1 (somatomedin-C) or insulin growth factor (IGF-1) are macrophage-derived progression factors for the proliferation cycle of fibroblasts.
- In IPF, epithelial cells in the airways and pneumocytes type II also produce another potent mitogen for fibroblasts and smooth muscle cells, known as endothelin-1 (ET-1).
- Thrombin has been shown to be also a potent mitogen for fibroblasts, which must be taken into account.[13]

In addition to these profibrotic agents, it has been suggested recently that a lack of natural inhibitors of collagen synthesis such as prostaglandin E_2[16] or interferon-γ could favour the appearance of IPF. [13]

3. Treatment of IPF

3.1 Corticosteroids

Corticosteroids inhibit the synthesis of many inflammatory cytokines, some of which favour the proliferation of fibroblasts. They reduce the synthesis of proteases including the metalloproteases. At high doses, they induce the death of lymphocytes and markedly reduce the functioning of neutrophils. Thus, there are many reasons why corticosteroids should prevent the development of fibrosis.

The first trials with corticosteroids were performed, however, on an empirical basis. Unfortunately, a beneficial role has been demonstrated for only 15 to 30% of patients with IPF. An IPF evolving for less than 1 year, with more cellular reaction with less fibrosis on open lung biopsy specimen, and a bronchoalveolar lavage (BAL) cell population with increased proportions of lymphocytes, have each been correlated with a better response to treatment.[17-19] Usual dosages are prednisone 1 to 1.5 mg/kg/day given for 2 to 3 months before a patient can be classified as a responder or a nonresponder (fig. 2). These patients responding to corticosteroids have a survival rate of more than 70% at 3 years, whereas for nonresponders the 3-year survival rate is only 35%, if another treatment is not tried.[18]

The effect of intermittent high dose parenteral corticosteroids in IPF (methylprednisolone 2g/week) has been studied in patients over a period of 6 months. This has led to a decrease only in neutrophil count in the BAL, but no significant changes in lung function tests were noticed in the high dose–treated group compared with the low dose group. Thus, these corticosteroid pulses are not recognised as an effective treatment in IPF.[20]

3.2 Cytotoxic Drugs

In view of the poor prognosis of IPF and the often poor results obtained with corticosteroids, several studies have tried the use of cytostatics. The first randomised and controlled study comparing prednisone alone against cyclophosphamide plus low dose prednisone was published in 1989.[21] After 3 years, 10 of 22 patients receiving corticosteroids alone had died, compared with only 3 of 22 receiving cyclophosphamide 100 to 120 mg/day plus prednisone 20mg every other day. The follow-up was not much changed if total lung capacity was already below 60% of the predicted value before the start of treatment. Neutropenia or thrombocytopenia occurred with cyclophosphamide in the follow-up of 6 patients during the first 18 months, and 1 patient presented with haematuria. Cyclophos-

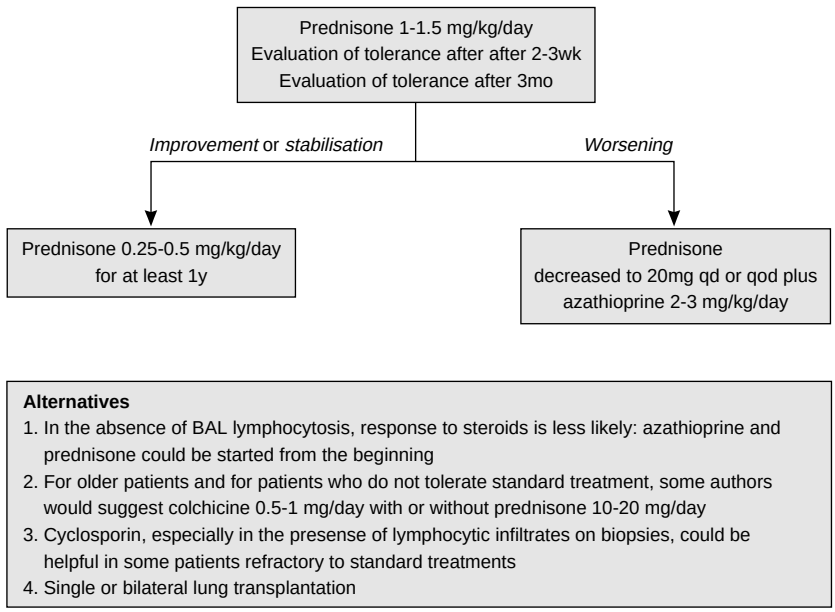

Fig. 2. Treatment of idiopathic pulmonary fibrosis. *Abbreviations:* BAL = bronchoalveolar lavage; qd = once daily; qod = every other day.

phamide had to be discontinued in 6 of these 7 patients due to these reasons.

If significant improvements are already noticed after a month of prednisone therapy, the response to cytotoxic treatment is much slower, typically taking 3 months to be detected and 6 to 9 months for maximum benefit.[22] Monthly cyclophosphamide pulses (500 to 1500mg) were tried by Dayton et al.[23] for nonresponders to corticosteroids. None of the monitored physiological parameters were improved for the 12 patients; in addition, 6 died in the following 6 months. Thus, this type of treatment appears to be of limited value in IPF.

A prospective, randomised, controlled, double-blind study with azathioprine was conducted by Raghu et al.[24] One group received azathioprine and prednisone while the other was given a placebo and prednisone. No major toxicity occurred in the azathioprine group and only 43% of the patients died in the 9-year follow-up, whereas 77% died in the group receiving placebo. The good tolerance of azathioprine compared with cyclophosphamide, and the long term benefit observed with the former, led many groups to consider azathioprine as the cytostatic drug of choice for treating IPF.

3.3 Colchicine

The Mayo Clinic[25] has reported the evolution of 23 patients with IPF treated with colchicine, with a mean follow-up of 22 months. An 'initial treatment' of prednisone had been given to 18 of the 23 patients and 5 patients received colchicine alone (0.5 to 1 mg/day). The retrospective study showed an objective improvement of FVC and in carbon monoxide diffusion (DCO) for 5 patients and a stabilisation of functional parameters for 9 others.[25] This study was sufficiently encouraging to have led to a new prospective trial, and to the recommended use by some authors of colchicine for patients not responding to conventional treatments or who experienced severe adverse effects.[26]

3.4 Cyclosporin

Only a few studies have addressed the role of cyclosporin in IPF. The first report was made on 7 patients who had no response to usual treatments; these patients were compared with 7 patients with similarly severe disease who did not receive cyclosporin, but did receive prednisone and cyclophosphamide. The mean survival of the cyclosporin-treated patients was 5 months, compared with 2.5 months for the control group.[27] These authors suggested that cyclosporin be used for patients on a waiting list for lung transplantation, as a 'bridge to transplantation'. Another study noticed a significant improvement of FVC after 6 months of cyclosporin therapy for 5 patients with a lymphocytic interstitial pneumonitis of unknown origin and for 3 of 5 with IPF without lymphocytosis.[28] Three of the 10 patients died from an infection and another died as a result of renal failure.

Such adverse effects require that blood concentrations be well monitored in order to obtain an acceptable cost-benefit ratio in the treatment of IPF. Data are still insufficient but we have obtained good results in patients thought to have IPF with a BAL rich in CD8 lymphocytes secondary to anti–Jo-1 (antisynthethases) antibodies, in the absence of mixed connective tissue disease at the time of diagnosis.[29] Other such entities may be described in the future.

3.5 Lung Transplantation

Lung transplantation has been a real therapeutic option for some years, providing a 60% survival rate at 2 years in the St Louis international registry, which as at January 1997 had recorded more than 969 patients with IPF. These results are being improved in most centres by using new immunosuppression protocols and anti-infectious prophylaxis. Lung transplantation should be considered for hypoxic subjects or for those having a total lung capacity lower than 60% of the predicted values. The survival of these latter individuals if not operated on is less than 20% at 1 year.[21] The age limit for performing a graft in such patients is between 60 and 70 years old.

3.6 New Prospects for Treatment

The anticytokine approaches should be mentioned, in particular those using natural inhibitors, receptor antagonists or the more sophisticated antisense approach. The cytokines that are currently the best target candidates are TNF-α or TGF-β.[30] Indeed, soluble TNF-α receptors have been shown to attenuate fibrosis in murine models of lung fibrosis, and anti-TGF-β antibodies have been able to reduce lung fibrosis following bleomycin-induced injury.[31] A natural inhibitor of TGF-β, decorin, is a proteoglycan which could also be investigated in the near future. Among the antifibrotic agents, some need to be mentioned, such as niacin, pirfenidone or relaxin. To simply diet with niacin would facilitate the generation of adenosine triphosphate (ATP) and taurine, which then would inhibit reactive oxygen species, but this approach remains very theoretical.

Pirfenidone is currently in phase II in human trials: its mode of action is still unknown, but preliminary results in animals are promising.[32] Relaxin is a human protein, able to block extracellular matrix deposition by human lung fibroblasts *in vitro* and to inhibit lung fibrosis in a bleomycin-induced murine model.[33] Further studies are being performed with this molecule. The use of *cis*-4-hydroxy-L-proline has also been envisaged for its ability to inhibit triple helix formation of collagen in animal models of pulmonary hypertension.[34] These agents which prevent the formation of stable collagen molecules are too nonspecific for clinical use unless they can be targeted to the affected tissues without preventing wound healing in other tissues.

Recently, antioxidative treatment with high doses of N-acetylcysteine during 12 weeks has been shown to be able to slightly improve the carbon monoxide diffusion capacity in IPF.[35]

4. Conclusions

IPF is still an exclusion diagnosis, and several aetiologies could still be revealed in the future. However, after an injury of unknown origin, the ensuing cascades of events are being better known. Some cytokines seem to be initially involved, including TNF-α. Other important cytokines responsible for the fibrosing process itself include TGF-β or PDGF.

Treatment of IPF has been successful with corticosteroids in only a small proportion of cases. Survival has been improved by combining either cyclophosphamide or azathioprine with low doses of corticosteroids in some additional patients. The use of colchicine or cyclosporin has been explored in only small series. New approaches are very promising using either cytokine inhibitors or agents able to prevent collagen deposition such as pirfenidone or relaxin.

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Correspondence and reprints: Dr *Laurent P. Nicod*, Pulmonary Division, Cantonal Hospital, 1211 Geneva 14, Switzerland.
E-mail: LaurentNicod@hcuge.dh