Respirology (2005) **10**, 284–289

REVIEW ARTICLE

Treatment of idiopathic pulmonary fibrosis: Is there anything new?

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Treatment of idiopathic pulmonary fibrosis: Is there anything new?
ABDELAZIZ MM, SAMMAN YS, WALI SO, HAMED MMA. *Respirology* 2005; **10**: 284–289

Abstract: Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic fibrosing interstitial pneumonia of unknown aetiology and is associated with the histological picture of usual interstitial pneumonia. Treatment in most cases is unsatisfactory and the prognosis remains poor. There is insufficient evidence to suggest that any treatment, apart from lung transplantation, improves survival or halts disease progression for IPF patients. Data on treatment response are limited by the paucity of clinical trails, the lack of homogenous clinical features, the small number of patients, and the absence of histological and radiological documentation in many cases. Anti-inflammatory medications such as corticosteroids, azathioprine and cyclophosphamide remain the commonly used medications. More recently, it has been proposed that IPF is a primary fibrotic disease rather than an inflammatory condition. Antifibrotic agents such as colchicine, pirfenidone and interferon-gamma (IFN-γ) have been tried. However, a recent placebo-controlled trial has failed to demonstrate a significant effect of IFN-γ on disease progression, lung function or quality of life in IPF patients, though a clinically significant survival benefit of the drug could not be ruled out.

Key words: azathioprine, corticosteroids, idiopathic pulmonary fibrosis, interferon-gamma, treatment, usual interstitial pneumonia.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF), also known as cryptogenic fibrosing alveolitis, belongs to a group of interstitial lung diseases known as idiopathic interstitial pneumonias, which comprise four histologically distinct forms: usual interstitial pneumonia (UIP), desquamative interstitial pneumonia (DIP), non-specific interstitial pneumonia (NSIP), and acute interstitial pneumonia (AIP).[1,2] Respiratory bronchiolitis-associated interstitial lung disease (RB-ILD) is a clinical syndrome characterized by the presence of pigmented macrophages within the lumen of respiratory bronchioles with peribronchiolar infiltrate of lymphocytes and histiocytes. This condition occurs in smokers and seems to be related to DIP.[2] In addition, some experts have regarded cryptogenic-organizing pneumonia (COP) as belonging to idiopathic interstitial pneumonia, however, this condition has been treated as a different entity because the pathology is mainly intraluminal rather than interstitial.[2]

Accurate epidemiological data regarding the prevalence of IPF are limited, however, various reports estimate the prevalence to be 3–6 per 100 000.[3,4] The differential diagnosis of this condition is quite large and includes a heterogeneous group of interstitial lung disorders and pneumonias.[1,2,4,5] Diagnosis of IPF is based on clinical grounds and specific radiological features. However, differentiating IPF from other interstitial lung disorders can be difficult and may necessitate surgical lung biopsy.[4–7]

PATHOLOGY

Traditionally, the term IPF was used loosely to include other idiopathic interstitial pneumonias, such as DIP, NSIP and AIP.[4,8,9] However, it is now recognized that this condition has different clinical, radiological and pathological features from other types of interstitial pneumonias and the term IPF should be confined to the histological picture of UIP

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Received 18 June 2004; revised 28 August 2004; accepted for publication 29 November 2004.

for prognostic and therapeutic reasons.[2,3,10] Pathologically, it is characterized by a triad of temporal heterogeneity, fibroblastic foci and minimal interstitial inflammation.[2,10] Temporal heterogeneity implies the presence of alternating areas of normal lung, inflammatory infiltrate, fibroblastic foci, fibrotic changes and honeycombing.[2,10] Fibroblastic foci are discrete aggregates of actively proliferating fibroblasts and myofibroblasts representing areas of aberrant wound healing following alveolar damage.[2,11,12] In fact, many believe that fibroblastic foci are the hallmark of IPF pathology and that understanding the pathogenesis of these spots hold the clue to the effective treatment. In contrast to DIP, which is characterized by filling of the alveolar space with abundant macrophages, minimal inflammatory infiltrate is seen in UIP.[2] This may explain the poor response of UIP to anti-inflammatory medications compared to DIP.

PATHOGENESIS

Although the cause of IPF is not known, risk factors that have been implicated include cigarette smoking,[13] infections[14] and environmental factors.[15] Previously, IPF was regarded as an inflammatory condition with alveolitis following alveolar epithelium injury leading to progressive interstitial fibrosis.[16,17] This concept may be valid for DIP, which was thought to represent the early stages of UIP. However it is now considered that UIP is a different entity from DIP, and has distinct pathological features characterized by minimal inflammation and prominent fibroproliferative foci.[12,18,19] Consequently, IPF is currently conceived as a primary fibrotic condition characterized by aberrant wound healing.[12] This is believed to be due to defective re-epithelization and increased fibroproliferative activity. Basement membrane disruption, increased pro-coagulant activity and increased epithelial cell apoptosis contribute to the defective re-epithelization. In contrast, decreased fibroblast apoptosis with increased activity of fibrogenic cytokines such as transforming growth factor β_1 (TGF-β_1), tumour necrosis factor-α (TNF-α), platelet growth factor and insulin growth factor lead to increased fibroblast and myofibroblast migration and proliferation.[12]

CLINICAL FEATURES

IPF is a progressive disease that usually presents with dry cough and dyspnoea.[4,10,18,20] Clubbing is present in 25–50% of patients.[4] Chest auscultation characteristically reveals end inspiratory crackles (Velcro crackles).[4,20] CXRs show a symmetrical interstitial reticulonodular pattern in both lungs, predominantly present in the bases and the lung periphery.[4,19,20] As the disease advances, honeycombing predominates the picture. High resolution CT (HRCT) demonstrates subpleural reticular or linear bands, honeycombing with absent or limited ground glass opacification.[4,19] Five-year survival can be as low as 20%.[21]

PHARMACOLOGICAL THERAPY FOR IPF

Currently there are two main types of therapeutic agents used to treat IPF: anti-inflammatory medications and antifibrotic agents. However, there is insufficient clinical evidence to suggest that any one treatment improves survival or disease progression for patients with IPF.[4,20,22]

ANTI-INFLAMMATORY TREATMENT

Anti-inflammatory therapies continue to be used despite there being little evidence of inflammation in the pathogenesis of IPF.[4,20,23] However, given the bleak prognosis of the condition and the lack of readily available alternative and efficacious treatment, a therapeutic trial with anti-inflammatory medications is still justified.[4]

Corticosteroids

Despite the fact that the impact of prednisolone on survival or quality of life has not been studied in randomized, double blind placebo-controlled trials, corticosteroids continue to be the mainstay of IPF treatment.[4,19,20] Most of the corticosteroid studies have been retrospective and suffer from many limitations, including heterogenous patient groups with no consistent clinical and histological criteria, small number of patients; different doses and variable follow-up duration.[4,20] Nevertheless, it has been suggested that some patients with IPF seem to respond to corticosteroids either subjectively (40%) or objectively (10–30%).[4,20] However, these statistics were based on studies that did not differentiate UIP from other forms of interstitial pneumonia. Studies that have defined the different histopathological subgroups have shown a very poor response rate to corticosteroids in UIP ranging between 8 and 17%.[9,24–26] Recently, Gay *et al.*, using a scoring system based on symptoms, HRCT and pulmonary function tests (PFT), conducted a prospective study on 38 patients with biopsy-proven IPF and analyzed which patients were more likely to respond to corticosteroid treatment.[27] A better response to corticosteroids was noticed in those who were younger, had worse PFT and gas exchange and had extensive ground glass changes in HRCT as well as an extensive cellular infiltrate on biopsy. However, in this study UIP and NSIP were not well differentiated and as such the patients with extensive ground glass on HRCT were unlikely to have UIP, and a better response to treatment is not surprising. Although there is no clinical trial to indicate the dose and duration of corticosteroids to be used in IPF, the American Thoracic Society (ATS) and the British Thoracic Society (BTS) recommended starting dose of prednisolone of 0.5 mg/kg bodyweight with gradual tapering.[4,12]

Cyclophosphamide

Most of the studies on cyclophosphamide were either uncontrolled or case reports. There is only one trial

comparing cyclophosphamide used in conjunction with low dose prednisolone (21 patients) against high dose prednisolone (22 patients).[28] Although there was an apparent initial survival improvement in the first 3 years among those receiving cyclophosphamide plus low dose prednisolone compared with patients given high dose prednisolone, at 5 years there was no significant difference in the outcome between the two groups. Side-effects of cyclophosphamide were common and sometimes required discontinuation of the treatment. More recently, Zisman *et al.* studied the role of cyclophosphamide alone on the treatment of 19 corticosteroid-resistant patients.[29] Cyclophosphamide failed to produce clear benefits on IPF and there were significant toxic effects due to the drug.

Azathioprin

The effect of azathioprine as a single agent on the management of IPF is not known, as no study has tested the drug as a sole treatment. However, one small prospective controlled trial (27 patients) compared azathioprine plus prednisolone against high dose prednisolone and demonstrated a statistically significant improved long-term survival among patients given the azathioprine regimen.[30] There was also a non-significant trend of improved lung function test among the azathioprine group. Azathioprine was well tolerated and the side-effects were reported to be similar in the two groups.[30] Therefore, azathioprine plus corticosteroid is a plausible regimen to be used in the treatment of IPF, though this recommendation is based on the results of a small trial. The dose recommended by ATS and BTS is 2–3 mg/kg bodyweight per day.[4,20]

ANTI-FIBROTIC MEDICATIONS

Recently, there was a paradigm shift in the treatment of IPF, with more of a trend towards using antifibrotic treatment, based on the concept that the disease is a fibrotic condition with a notable lack of significant inflammatory component.[12,19,23] Many antifibrotic agents have been used in the treatment of IPF, including penicillamine, colchicine, pirfenidone, and interferon-gamma (IFN-γ).

Colchicine and penicillamine

Colchicine has been shown to inhibit collagen formation and increase collagen degradation *in vitro*.[31,32] Similarly, penicillamine inhibits collagen synthesis by interfering with collagen cross-linking.[33] However, both drugs failed to influence survival of patients with IPF.[33,34] Douglas *et al.*, in a small prospective, open, randomized trial, demonstrated no significant difference in survival between patients given colchicine (14 patients) and those given prednisolone (12 patients).[25] Similarly, Selman *et al.*, in a prospective, open and non-randomized four-limb study, showed no significant difference in survival between patients receiving colchicine/prednisolone (19 patients), penicillamine/prednisolone (11 patients), colchicine/penicillamine/prednisolone (11 patients), and prednisolone alone (15 patients).[34]

Pirfenidone

Pirfenidone has been demonstrated to inhibit TGF-β_1-induced collagen synthesis *in vitro*[35] and ameliorate bleomycin-induced pulmonary fibrosis in a hamster model.[36] Raghu *et al.* examined the effect of pirfenidone on the treatment of 54 patients with advanced IPF, who were either resistant or refused conventional treatment, in an open uncontrolled study.[37] One and 2-year survival was 78% and 63%, respectively. In addition, patients whose lung function deteriorated before enrolment appeared to stabilize after treatment. However, there was no control group for comparison.[37] Similarly Nagai *et al.* in an open study examined the effect of 1-year treatment of pirfenidone on eight patients with advanced IPF and noticed no deterioration in terms of CXR scores and arterial oxygen pressure.[38] Recently, the results of a double-blind randomized, placebo-controlled trial were presented at the ATS 100th International Conference 2004.[39] The Data Safety Monitoring Board aborted the study as increased acute exacerbations occurred in the placebo group. Five of the 35 patients in this arm suffered an acute exacerbation with one death compared with no acute exacerbations or deaths among the 72 patients given pirfenidone. The primary end point of this study was based on the 6-min walking test at room air (the lowest saturation and the area under the saturation curve were analysed). There was a significant difference in the minimal exercise saturation between the two groups at 6 months ($P = 0.0069$) and 9 months ($P = 0.0305$). In addition, there was a smaller decline in the FVC at 9 months in the pirfenidone group compared with the placebo group. Another controlled trial is anticipated.

Interferon-gamma

IFN-γ has been shown to inhibit collagen formation by fibroblasts *in vitro*.[40] It also down-regulates the gene transcription for pro-fibrogenic mediators such as TGF-β_1 and connective tissue growth factor (CTGF).[41,42] Furthermore, studies suggest that IFN-γ production is impaired in patients with IPF.[42,43] Ziesche *et al.*, in a small prospective open trial, randomized patients with corticosteroid-resistant IPF to receive either IFN-γ-1b 200 units subcutaneously three time weekly plus prednisolone 7.5 mg (nine patients) or prednisolone 7.5 mg alone (nine patients) for 12 months.[42] This study demonstrated that both total lung capacity and gas transfer significantly improved after 12 months in patients who were given IFN-γ-1b plus prednisolone. The same study showed an increased level of gene transcription of TGF-β_1 and CTGF in patients with IPF prior to treatment. Twelve months later the level of these

mediators had decreased significantly in patients who received IFN-γ.[42] A recent multicentre placebo-controlled double-blind trial of IFN-γ in patients with IPF recruited 330 patients to receive either IFN-γ-1b 200 units subcutaneously three time weekly (162 patients) or placebo (168 patients) for 12 months.[22] There was no significant difference noted in disease progression, lung function, gas exchange or quality of life between IFN-γ-1b and placebo groups. However, a non-significant trend towards an enhanced survival in the IFN-γ-1b group was noted. The trend towards enhanced survival reached significance in treatment-adherent patients and in those with less severely impaired lung function (FVC above 62%), though the study was not powered for this analysis.[22] Therefore, a clinically significant survival benefit could not be excluded because of the size and duration of the trial. It also seems likely that there is a specific group of IPF patients with relatively better lung function who can benefit from IFN treatment, but this is yet to be proven. Accordingly, a longer and larger randomized double-blind, placebo-controlled trial has started (INSPIRE trial) in December 2003, aimed at recruiting 600 patients to address these issues.

LUNG TRANSPLANT

Lung transplant remains the only option for end-stage pulmonary fibrosis and for patients who fail to respond to medical treatment.[4,20] Early referral is recommended as many patients with IP die while waiting for the transplant.[44] It is generally recommended that the patient be referred for transplantation when progressive symptoms have a vital capacity less than 60–70% and a corrected diffusion capacity below 50–60% of predicted.[45] Five-year survival following transplant is estimated to be 50–60%.[4] In a recent study by Thabut and co-workers, survival from lung transplantation was found to be 79.4% at 1 year, 63.5% at 2 years, and 39% at 5 years. Statistical multivariable analysis of the results from the same study suggested that lung transplantation reduced the risk of death by 75% after adjustment for potential confounding variables.[46]

NEW DIRECTION

As has been highlighted, IPF is now believed to be the result of aberrant wound healing following epithelial injury. Consequently, new therapeutic agents have been developed to target either defective re-epithelization or exaggerated fibro-proliferation. This includes N-acetylcysteine (prevents epithelial injury),[47] captopril (abrogates epithelial apoptosis and inhibits fibroblast proliferation),[48,49] relaxin (inhibits TGF-β_1 mediated collagen and fibronectin formation),[50] lovastatin (induces fibroblast apoptosis)[51] and beractant (induces fibroblast apoptosis).[52] Some of these medications are currently being investigated in clinical trials. In particular, N-acetylcysteine has been evaluated in a phase 3 multicentre study in Europe. The results of that trial were presented at the 14th European Thoracic Society Congress 2004.[53] This trial enrolled 184 patients (155 qualified for the final analysis), and both the treatment arm and the control group were well matched with respect to baseline mean FVC 65% of predicted and the mean DLCO was 44% of predicted. All patients received prednisone and azathioprine, but in addition, those in the treatment group received N-acetylcysteine at a dose of 600 mg three times daily. The primary end points were a change in the FVC and DLCO. Although both FVC and DLCO continued to worsen in both groups, there was a significant difference in the rate of decline in both parameters in favour of the N-acetylcysteine group. The difference in FVC was 8% ($P < 0.05$) and in DLCO was 24% ($P < 0.005$). There was no difference in mortality between the two groups, though the study was not powered to detect a mortality difference.

CONCLUSION

It is now clear that IPF (UIP) should be distinguished from other subgroups of idiopathic interstitial pneumonia for therapeutic and prognostic reasons. It is currently believed that lung fibrosis in IPF is the primary pathology rather than a consequence of inflammation. Accordingly, there is a paradigm shift in the treatment of IPF with a trend towards using antifibrotic agents. In particular, IFN-γ has received much attention in the last few years, although a recent controlled trial failed to show a significant beneficial effect on disease progression, lung function, and quality of life. However, a trend towards improved survival was noticed in the IFN-γ group. In addition, there may be a subgroup of IPF patients with relatively better lung function who may benefit from IFN-γ, but this is yet to be proven. In contrast, N-acetylcysteine did not produce significant survival benefit, but significantly decreased the deterioration in pulmonary function. Obviously, more studies are required in order to address the many issues regarding both drugs, such as confirming the possible beneficial effect of IFN-γ-1b on survival and whether the diminished physiological deterioration produced by N-acetylcysteine will translate into a survival benefit. Therefore, despite the current availability of several novel therapeutic agents and the development of additional agents, treatment of IPF remains largely unsatisfactory. To date, there is no strong evidence to suggest that any form of medical treatment would substantially influence the disease progression or survival. Anti-inflammatory medications continue to be the mainstay of the treatment. Azathioprine plus prednisolone is probably the most plausible regimen available for the time being.

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