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EVIDENCE-BASED REVIEW

Corticosteroid and immunomodulatory agents in idiopathic pulmonary fibrosis ☆

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Summary Idiopathic pulmonary fibrosis (IPF) is a progressive pulmonary disease leading to death within a few years of diagnosis despite medical therapy. On the basis of methodologies of the Cochrane collaboration, this overview discusses the evidence for IPF therapy. Good-quality studies on oral corticosteroids, the most common medical therapy in use for IPF, are lacking. A few small studies have been carried out on the efficacy of many non-steroid immunosuppressive agents, and the results have been generally disappointing. The most extensively studied medical therapy, gamma interferon, showed a significant effect in a small randomized study, but its efficacy was not confirmed in a larger randomized-controlled trial. The long-awaited good news for patients affected by this deadly disease, and for their physicians, could come in the near future from large randomized-controlled trials with gamma interferon or other immunomodulatory agents.

Aim of the overview

The aim of this overview is to describe the level of evidence available on the efficacy of corticosteroids and immunosuppressive, antifibrotic or immunomodulatory therapies in the treatment of idiopathic pulmonary fibrosis (IPF). Such a systematic approach is needed, as many studies on the treatment of IPF are weakened by the fact that the diagnostic criteria used to define the study populations are not those currently agreed upon in consensus guidelines. Therefore, to consolidate

☆The following Cochrane reviews are cited in this evidence-based review: Richeldi L, Davies HR, Ferrara G, Franco F. Corticosteroids for idiopathic pulmonary fibrosis. The Cochrane Library, Issue 3, 2004. Davies HR, Richeldi L, Walters EH. Immunomodulatory agents for idiopathic fibrosis: In: the Cochrane Library, Issue 3, 2004. *Copyright Cochrane Library, reproduced with permission.*

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the evidence derived from single studies at levels that would provide a guide to the clinical management of IPF patients, studies need also to be evaluated for both patients' characteristics and study design. Cochrane reviews summarize the highest quality evidence for efficacy of interventions, by incorporating results from randomized-controlled trials.[1] The Airways Group of the Cochrane Collaboration has recently published two systematic reviews on the treatment of IPF,[2,3] in which only studies of adult patients with a diagnosis of IPF based upon adequate clinical and radiological criteria in accordance with current guidelines[4] were included. The present review is largely based on the results of these two Cochrane reviews.

The pathogenesis of idiopathic pulmonary fibrosis

IPF is a clinical and pathological entity, for which precise diagnostic criteria have been recently defined[4] and significant advances in the understanding of underlying mechanisms have been made. As the basis for a therapeutic approach to any disease mainly resides in understanding the mechanisms leading to the disease, a brief summary of our current knowledge about IPF pathogenesis follows.

Many studies have questioned the role of chronic lung inflammation in IPF pathogenesis.[5–7] According to the ''inflammatory'' hypothesis, IPF is a disease in which pulmonary fibrosis is directly caused by chronic inflammation; therefore, if in theory the inflammation cascade could be interrupted before irreversible tissue injury occurs, fibrosis might be avoided. However, chronic inflammation is not required for the development of a fibrotic response, and IPF is instead the result of a process similar to abnormal wound healing, in which altered signalling mechanisms originate from activated epithelial and mesenchymal cells.[8] The distinctive feature of IPF is not lung inflammation but, rather, the predominance of fibroblastic foci. They are the hallmark histopathologic feature of IPF, and their number directly correlates with prognosis, whereas the level of interstitial inflammation is less predictive.[9] After injury, the alveolar epithelium initiates a wound healing process to restore its barrier integrity. In IPF, this process seems slow and inadequate, leading to a marked disruption in the integrity of the alveolar epithelium. This process differs from the normal wound healing model mainly in the lack of adequate re-epithelialization.[5] In IPF, epithelial cells express several cytokines and growth factors, such as platelet-derived growth factor, transforming growth factor β (TGF-β), and tumour necrosis factor alpha, all of which are central mediators in the development of pulmonary fibrosis.[10] Recent findings suggest that alveolar epithelial cells are the primary source of cytokines and growth factors involved in fibroblasts migration and proliferation, and myofibroblasts differentiation, which are found to be the primary source of heightened type I procollagen gene expression in animal model of lung injury and fibrosis.[11] One of the current hypotheses for the causation of IPF suggests that a still unidentified stimulus produces repeated episodes of acute lung injury; wound healing at the sites of injury ultimately leads to fibrosis, with loss of lung function. If this hypothesis is proved to be true, then an effective therapeutic strategy should point to modulation of epithelial cell activation, fibroblast replication and matrix deposition more than to suppression of the inflammatory process.

The diagnosis of idiopathic pulmonary fibrosis

IPF is the most clinically relevant entity of the heterogeneous group of pulmonary disorders of unknown aetiology known as idiopathic interstitial pneumonias. Idiopathic interstitial pneumonias comprise a number of clinical and pathological entities that are sufficiently different from one another to be considered separate disease entities. These lung diseases have been described by lung pathologists by means of various classifications, in which the main entity is always reported as ''usual interstitial pneumonia'' (UIP).[12–14] However, various terms have been used to identify the clinical entity associated with the different histological patterns (e.g. diffuse interstitial fibrosis, diffuse fibrosing alveolitis, cryptogenic fibrosis alveolitis, classical interstitial pneumonitis-fibrosis, diffuse interstitial pneumonitis and IPF).[15] Therefore, for some time, patients with histologically different forms of interstitial pneumonias have been grouped together. With the demonstration of different survival and responses to steroids associated with different histological patterns, the term IPF is restricted to those patients with a histological appearance of UIP on a surgical lung biopsy.[4] The most relevant differential diagnosis is between IPF, and UIP and the entity known as non-specific interstitial pneumonia (NSIP).[16] NSIP occurs a

decade or more earlier than IPF[17] and, unlike IPF, may occur in children.[16] There is neither sexual predominance nor association with cigarette smoking. The NSIP histological pattern encompasses a broad spectrum of histological features with varying degrees of alveolar wall inflammation or fibrosis.[16] At the fibrosing end of the spectrum of NSIP, the pattern is of dense or loose interstitial fibrosis in varying degrees, and the connective tissue is temporally homogeneous.[16] Fibroblast foci, the key lesion that gives the UIP pattern the appearance of temporal heterogeneity, are absent or inconspicuous. The computed tomography (CT) features show that ground glass attenuation is the predominant finding in most cases. It is most commonly bilateral and symmetrical, with subpleural predominance. However, in a study of 50 patients, CT pattern was found to be indistinguishable from UIP in 32% of patients.[18] The prognosis of NSIP is more variable than in IPF, and seems to depend on the extent of fibrosis.[19,20] Some patients experience almost complete recovery. Unlike IPF, most of the remainder stabilize, improve spontaneously or remain on corticosteroid treatment (Fig. 1).[21] Relapse may occur; only a few patients progress and die compared with IPF.

In IPF, the onset of symptoms is usually gradual, with dyspnoea the most prominent and disabling symptom. These patients are usually aged between 50 and 70 years. Cigarette smoking has been identified as a potential risk factor for the disease. IPF is characterized by spatial and temporal heterogeneity, with areas of mature fibrosis juxtaposed to active fibroblastic foci and normal lung. Chest radiography in IPF is almost always abnormal, and reveals diminished lung volumes and symmetric, bibasilar and peripheral reticulations. With high-resolution CT (HRCT), typical features of IPF are honeycomb cysts, distorted intralobular reticulations and traction bronchiolectasis, with a striking predilection for the lung periphery and bases. Ground-glass attenuation is typically admixed with fibrosis, and is rarely the dominant pattern.[22]

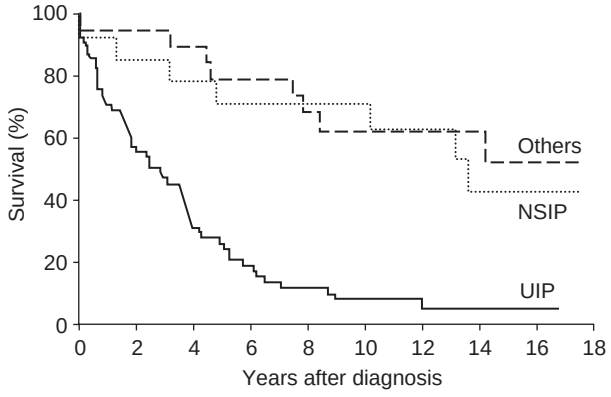


Figure 1 Patients with usual interstitial pneumonia (UIP)/idiopathic pulmonary fibrosis (IPF) had a significantly worse survival compared with patients with nonspecific interstitial pneumonia (NSIP) and patients with a heterogeneous group of interstitial lung diseases. (Reproduced with permission from Bjoraker et al.[21]).

Transbronchial lung biopsy is not an adequate tool to identify the pathological pattern of UIP, but, together with bronchoalveolar lavage, can be helpful to exclude alternative diagnoses, in particular, sarcoidosis.[23] Definitive histological diagnosis of IPF requires a surgical lung biopsy. In the presence of a surgical biopsy showing a UIP pattern, the diagnosis of IPF requires (1) exclusion of other known causes of interstitial lung disease; (2) characteristic abnormalities on conventional chest X-ray or HRCT; and (3) abnormal pulmonary function tests, showing restriction, impaired gas exchange (or both), decreased P_aO_2 with rest or exercise or decreased DL_{CO}.[22–24]

In conclusion, the definite diagnosis of IPF requires a compatible clinical history, the exclusion of other known causes of other interstitial lung diseases (such as drug injuries, environmental exposures or collagen vascular disease) and a surgical biopsy showing the pattern of UIP. However, surgical biopsy cannot be carried out in all patients with a clinical and radiological suspect of IPF. Exclusion of other known causes of interstitial lung diseases and abnormal pulmonary function tests, which include evidence of restriction and characteristic radiological abnormalities, particularly HRCT, increases the likelihood of a correct clinical diagnosis of IPF. Together with the recognition that IPF is characterized by a distinct pathology, many studies have focused on the extremely poor prognosis of patients with IPF, as defined above; sadly, these patients usually die within 5 years of diagnosis,[25] as do most patients with lung cancer. As in lung cancer, a clinical response to the current therapeutic agents is unusual, and treatment is unlikely to alter outcome in most patients. Current guidelines, based upon consensus, indicate prednisone, azathioprine and cyclophosphamide as the basis for IPF treatment;[4] however, it is common for chest physicians to observe that these drugs are ineffective in most patients with IPF. Therefore, on the basis of methodologies of the Cochrane collaboration, this review discusses the evidence for IPF therapy, drawing on the findings of two systematic reviews on the treatment of IPF.[2,3] Drugs have been divided into two main groups: those included in current guidelines and those not (yet) included in such documents.

Drugs recommended by current guidelines

Corticosteroids

On the basis of early observations demonstrating inflammatory cells in the distal air space, numerous studies have investigated the use of corticosteroids in IPF. Some early studies suggested that corticosteroids reduced the so-called ''ground-glass opacities'' of HRCT in people with interstitial pneumonia, and that this reduction paralleled improvement in pulmonary function.[26] Interestingly, although HRCT ground-glass attenuation is reduced after steroid treatment, the progression to irreversible honeycomb fibrosis is not altered.[27] Clearly, in these studies, lung diseases other than IPF were included. A recent Cochrane review[2] explored the efficacy of corticosteroids in the treatment of adults with IPF. Of 15 studies potentially eligible for meta-analysis, no eligible studies were found after review because of inadequate methodologies; therefore, no data were available for inclusion in a meta-analysis. At present, no evidence for an effect of corticosteroids in IPF is available. Considering the enormous empirical clinical experience and recent developments in the understanding of the pathogenesis of IPF, it is reasonable to assume that appropriate trials to investigate the efficacy of steroids in IPF will never be carried out. Alternatively, a trial of steroids should be considered for those patients with idiopathic interstitial pneumonia but without a definite diagnosis of IPF, when another diagnosis cannot be ruled out. In such cases, a trial of prednisone should be limited to 3–6 months, and objective improvement in physiological measures, radiographical findings and clinical symptoms should be rigorously assessed. Longer trials of prednisone and the prolonged use of cytotoxic agents remain controversial. In the absence of measurable improvement, steroid therapy should, in most instances, be discontinued.

Azathioprine

Azathioprine is an antimetabolite. Usually taken orally, it is well absorbed by the gastrointestinal tract. It is primarily metabolized in the liver, where its side chain is removed. Through these actions, azathioprine blocks most T-cell functions, inhibits primary antibody synthesis and decreases the number of circulating monocytes and granulocytes.[28]

Only three randomized-controlled trials have studied the effect of this cytotoxic agent in the management of IPF. The first reported trial Fulmer et al.[29] was published only as an abstract. This study was a 12-month, randomized, double-blind, placebo-controlled trial, in which 26 patients with IPF were randomly assigned to receive either prednisone and placebo or prednisone and azathioprine (2.5 mg/kg/day). Five patients developed drug toxicity: two in the placebo group and three in the azathioprine group. No significant differences in outcome were reported.

The trial by Winterbauer[30] was a prospective, randomized, double-blind, placebo-controlled trial, which included 27 patients with IPF, 13 of whom received prednisone and placebo, and 14 of whom received prednisone and azathioprine. Patients were given prednisone at an initial dose of 1.5 mg/kg/day for 2 weeks, with a bi-weekly taper until a maintenance dose of 20 mg/day was reached. Azathioprine was given at 3 mg/kg/day to a maximum of 200 mg/day. The number of patients who showed a decrease in alveolar–arterial difference in resting partial pressure of oxygen was greater in the azathioprine group (seven out of 14) than in the placebo group (two out of 13), a difference that just achieved statistical significance. A trend toward clinical improvement in the azathioprine group was noticed, but no significant difference was observed in changes in forced vital capacity (FVC) or diffusing capacity for carbon monoxide. Mean survival time for the azathioprine group was 43 months, with eight survivors (57%). Mean survival time in the placebo group was 34 months, with four survivors (31%). The total number of adverse effects was similar in the two groups.

The trial by Raghu et al.[31] reported results of 27 newly diagnosed patients with IPF, previously untreated, who were enrolled in a prospective, double-blind, randomized, placebo-controlled study to compare the therapeutic effect of combined prednisone/azathioprine with that of prednisone/placebo. All patients underwent open lung biopsy. Prednisone was started at 1.5 mg/kg/day (not to exceed 100 mg/day) for the first 2 weeks, followed by a bi-weekly taper to a maintenance dose of 20 mg/day. Azathioprine was given as a daily dose of 3 mg/kg (not to exceed 200 mg/day). Changes in lung function after 1 year, as measured by alveolar–arterial difference in resting partial pressure of oxygen, FVC, and single-breath diffusing capacity for carbon monoxide, were all somewhat better in the azathioprine/prednisone group than in the prednisone/placebo group, although none of these comparisons was statistically

significant. Six of 14 (43%) patients randomized to azathioprine/prednisone died during the 9-year follow-up period, compared with 10 out of 13 (77%) patients randomized to prednisone/placebo. A Cox model survival analysis showed a non-significant, but potentially large, survival advantage for azathioprine/prednisone. When adjusted for age as a continuous variable, there was a significant difference favouring the combination of azathioprine/prednisone ($P = 0.02$). There were a large number of adverse events, mostly related to prednisone, but with no significant differences between groups. Using evidence-based criteria, this study is the only one that could be considered to be of high quality (Table 1). This is probably the reason that current guidelines recommend the use of azathioprine in IPF patients not responding to steroids.

In conclusion, the addition of azathioprine to oral corticosteroid therapy seems to provide little or no benefit in the treatment of patients with IPF, although the drug seemed to be well tolerated in these studies.

Cyclophosphamide

Cyclophosphamide is an alkylating agent primarily used for the treatment of autoimmune disease and cancer. In a randomized-controlled study, Johnson et al.[32] compared the effects of prednisolone plus cyclophosphamide with those of alternate-day, low-dose prednisolone in 43 patients with previously untreated fibrosing alveolitis, diagnosed mainly on clinical grounds. Patients received either alternate-day, high-dose prednisolone or the minimum dose to maintain early improvement. Patients in the cyclophosphamide/prednisolone series received 100, 110, or 120 mg of cyclophosphamide daily (depending on body weight) plus 20 mg of prednisolone on alternate days. Treatment was continued indefinitely, or changed to the alternative regimen if the patient deteriorated, failed to improve, or developed drug toxicity. For response to treatment (as judged by change in breathlessness score, radiographic appearance and lung function), patients were classified as improved, stable or deteriorating. Improvement occurred at one or more assessments in seven out of the 22 patients in the prednisolone series and in five of the 21 patients in the cyclophosphamide/prednisolone series. After 3 years, only two of the 22 patients in the prednisolone series were still improved, and three were stable; in comparison, one out of the 21 patients in the cyclophosphamide/prednisolone series was still improved, and seven were stable. Life table analysis suggested that there was better survival of patients in the cyclophosphamide/prednisolone series, but it was not significant. After 3 years, 10 out of 22 patients in the prednisolone series had died, compared with three out of 21 patients in the cyclophosphamide/prednisolone series. With death or failure of first-treatment regimen as outcome, there was a significant advantage to the patients receiving cyclophosphamide/prednisolone. This advantage was explained in part by the better lung volumes in this group on admission. Analyses of subgroups according to total lung capacity (TLC) on admission showed that patients with a TLC below 60% predicted did badly and those with a TLC of 80% or more predicted did well with both regimens. Therefore, the combination of low-dose prednisolone and cyclophosphamide was as effective as high-dose prednisolone and was well tolerated. However, patients in the cyclophosphamide/prednisolone group received a significant dose of prednisolone that may have been responsible for the apparent benefit; alternatively, cyclophosphamide may have had a corticosteroid-sparing effect, boosting the effective dose. Methodologically, the trial was inadequate, with no blinding and poor procedures that may have broken down, as there was a trend toward lower baseline TLC and FVC in the prednisolone group. Finally, there was significant disease heterogeneity in the study population; five patients in each group had connective tissue disorders, and it is highly likely that patients with histological patterns other than UIP were included.

Drugs not included among those recommended by current guidelines, but with a rationale for use in idiopathic pulmonary fibrosis

Gamma interferon-1beta

Gamma interferon (IFN-γ) is the main Th1 cytokine, and recent advances have pointed to a lack of Th1 response as a key element in IPF. Therefore, its use in IPF treatment has been the subject of well-designed and large studies. IFN-γ is an endogenously produced cytokine with various effects, including antifibrotic, anti-infective, antiproliferative and immunomodulatory. Its dose-dependent inhibition of fibroblast proliferation, collagen-matrix deposition and collagen synthesis has been demonstrated *in vitro* and in rodent models. Studies of lung tissue and blood from patients with IPF have found absolute and relative deficits in

Table 1 Published studies on medical therapy for IPF.

Reference	Year	Study design	Study population (*n*)	Diagnostic criteria	Study treatments	Level of evidence*
Winterbauer[30]	1991	Randomized, double-blind, placebo-controlled, prospective study	27	Not specified	Prednisone + placebo ($n = 13$) vs. prednisone + azathioprine ($n = 14$)	B
Raghu et al.[31]	1991	Randomized, double-blind, placebo-controlled, prospective study	27	Open lung biopsy	Prednisone + placebo ($n = 13$) vs. prednisone + azathioprine ($n = 14$)	A
Johnson et al.[32]	1989	Randomized-controlled study	43	Open lung biopsy in 33 out of 43 patients	Prednisone high dose ($n = 22$) vs. cyclophosphamide + prednisone low dose ($n = 21$)	D
Douglas et al.[44]	1998	Randomized, prospective study	26	HRCT findings and/or open lung biopsy		D
Ziesche et al.[38]	1999	Randomized, prospective study	18	Open lung biopsy	Prednisolone ($n = 9$) vs. prednisolone + IFN-γ-1b ($n = 9$)	A
Raghu et al.[39]	2004	Randomized, double-blind, placebo-controlled, prospective study	330	Open lung biopsy, HRCT findings, or both		A

HRCT, high-resolution computed tomography.

*Assessed on the basis of criteria used in the Cochrane reviews.[2,3]

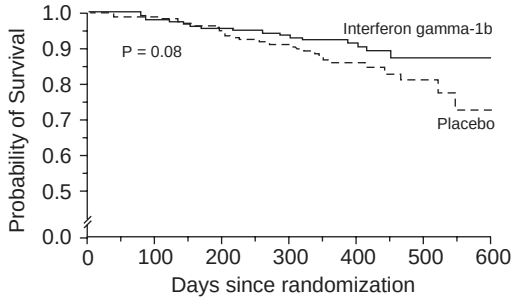
IFN-γ compared with Th2 cytokines.[33,34] Furthermore, in a bleomycin-induced model of lung fibrosis, exogenous IFN-γ downregulated the transcription of the gene for TGF-β1.[35]

The three major classes of interferons are alpha, beta, and gamma. As IFN-α and IFN-β share components of the same receptor, they have been referred to as type I interferons. IFN-γ uses a separate receptor system, and has been referred to as type II interferon. IFN-α and IFN-β are secreted by virus-infected cells, whereas IFN-γ is secreted mainly by T cells, natural killer cells and macrophages.[36] Compared with IFN-α and IFN-β, the gene for IFN-γ is located on a different chromosome, it binds to a different receptor, its structure is different and it is the only interferon that is considered to be capable of activating macrophages and inducing HLA class II antigens.[37] Interferons do not normally circulate, are formed constitutively by most cells and function physiologically by autocrine or paracrine mechanisms.[36]

IFN-γ converts macrophages from a resting to an active state, and induces the synthesis of an array of receptors for binding to pathogens and endothelia, degradative enzymes, transcription factors and cytokines involved in host defense. These broad immunoregulatory activities allow IFN-γ to play an important role in controlling diseases caused by intracellular bacteria (e.g. *Listeria* and *Mycobacterium*), parasites (e.g. *Leishmania* and *Toxoplasma*) and fungi (e.g. *Cryptococcus*). The broad activity of IFN-γ is still only partially understood. However, several key immunoregulatory roles of IFN-γ are known: (1) improved antigen presentation; (2) enhanced killing of intracellular pathogens, which induces the synthesis of enzymes in phagocytes that are involved in the generation of reactive oxidants (e.g. superoxide, hydrogen peroxide, and nitric oxide); these reactive species are involved in the killing of intracellular and some extracellular infections; (3) heightened capacity for microbial killing; and (4) enhanced recruitment of leukocyte-enhanced macrophage activity and increased intracellular concentration of antimicrobials.

Ziesche et al.[38] reported the findings of a small, non-placebo-controlled, randomized trial of long-term treatment with IFN-γ-1b and low-dose prednisolone in patients with IPF. They found striking improvement in lung function in the nine patients treated with IFN-γ-1b in addition to prednisolone, compared with those who received only prednisolone, over the course of 1 year. All nine patients treated with IFN-γ-1b showed statistically significant improvement in TLC and resting partial pressure of arterial oxygen, and eight of them showed improvement in partial pressure of arterial oxygen on maximal exertion. In contrast, eight of the nine patients in the control group, who received prednisolone alone, had a decline in all three measurements over the same period. Using the reverse transcription-polymerase chain reaction, Ziesche et al.[38] showed that therapy with IFN-γ-1b decreased the levels of mRNA for TGF-β1 and connective tissue growth factor, the main growth factor product of TGF-β stimulation, as assessed in transbronchial biopsy specimens obtained before and after treatment in a sample of the study group. This study, even though small and not placebo controlled, heralded a new concept in IPF therapy, namely, a treatment based more on modification of the immune response (by using a Th1 cytokine) than on suppression of inflammation (using corticosteroids). It also had the considerable merit of stimulating a larger, randomized, multicentre study on IPF therapy, discussed next.

This phase III randomized, double-blind, placebo-controlled, multinational trial of 330 patients with a definite diagnosis of IPF/UIP, was based on the findings of a lung biopsy for most patients or the consensus diagnostic criteria.[4] The study aimed at evaluating the safety and efficacy of IFN-γ-1b in IPF. Progression-free survival, defined as the time to disease progression or death, was the primary efficacy end point.[39] Over a median of 58 weeks, IFN-γ therapy did not significantly affect the primary end point of survival, and no significant effects on measures of lung function, gas exchange, or quality of life were observed. Ten percent of patients in the IFN-γ group died, compared with 17% of patients in the placebo group ($P = 0.08$) (Fig. 2). Treatment with IFN-γ was also associated with more frequent constitutional symptoms and the occurrence of pneumonia, but the incidence of severe life-threatening respiratory tract infections



Number at Risk

Interferon gamma-1b	162	158	154	144	83	29	4
Placebo	168	165	159	142	80	27	4

Figure 2 Survival curves (Kaplan–Meier estimates) for patients affected by idiopathic pulmonary fibrosis and treatred with IFN-gamma or placebo in a large randomized, placebo-controlled trial. (Reproduced with permission from Raghu et al.[39]).

was similar in the two groups.[39] These findings differed from those of the previous study;[38] a possible explanation for the discrepancy is a potential selection bias due to the lack of expression for IFN-γ in the transbronchial biopsy specimens of all patients in the 1999 study. Nevertheless, a statistical trend favouring the IFN-γ group was detected (relative risk reduction of 41%) in the 1-year study.[39] Further analysis of this cohort of IPF patients after a follow-up period of 3 years suggested that those patients with less severe disease (FVC $>$ 60%) potentially derive a greater benefit from therapy with IFN-γ. These results are concordant with the finding of a more pronounced toxicity of IFN-γ in patients with advanced IPF,[40] many of whom also developed irreversible acute respiratory failure shortly after initiation of IFN-γ therapy.[41]

Colchicine

Among its biological effects, colchicine reduces procollagen synthesis by impairing its cellular secretion.[42] Collagenolytic activity is also enhanced, with increased collagenase production. Colchicine induces mitotic arrest and inhibits DNA synthesis. Finally, colchicine inhibits cell-mediated immune responses by inhibiting immunoglobulin secretion, interleukin-1 production, histamine release, HLA-DR expression,[42] and alveolar macrophage release of two mediators that are associated with the development of fibrosis: fibronectin and alveolar macrophage-derived growth factor, which stimulate fibroblast proliferation.[43] For this reason, colchicine has been hypothesized to have a role in IPF treatment.

Douglas et al.[44] carried out a multicentre, unblinded, randomized, prospective, parallel study of 26 symptomatic people with clinical evidence plus either HRCT ($n = 25$) or open-lung biopsy ($n = 1$) patterns typical of IPF, to evaluate and compare the efficacy of colchicine vs. prednisone as single-drug therapy. Twelve patients received high-dose prednisone, and 14 patients received colchicine. The minimum dose of prednisone used was 60 mg/day for 1 month, tapering to 40 mg/day over the second month and 40 mg on alternate days during the third month, with subsequent doses adjusted as clinically indicated. The dose of colchicine was 0.6–1.2 mg/day, as tolerated. Participants treated with high-dose prednisone experienced a higher incidence of serious side-effects and exhibited a trend (though not statistically significant) to more rapid decline of pulmonary function and shortened survival compared with people treated with colchicine. In most participants with typical clinical and HRCT features of IPF, neither prednisone nor colchicine resulted in objective improvement, and the disease continued to progress in most people. In conclusion, there is no evidence to suggest that colchicine is any more effective in the treatment of IPF than is prednisone alone. Colchicine did seem to be better tolerated than oral corticosteroids in the trial.

Other drugs

Cyclosporine, penicillamine and pirfenidone have been used alone or as an adjunct in the management of IPF. No randomized-controlled trials have been carried out for these drugs. Therefore, at the moment, there is no good evidence that they are of benefit in IPF treatment. However, a number of trials are ongoing. For other treatments, studies with the endothelin 1 antagonist bosentan, the antioxidant *N*-acetylcysteine and the anti-TNF-α etanercept are ongoing. Trials with statins (which induces fibroblast apoptosis) and ACE-inhibitors (which mainly inhibits fibroblast procollagen synthesis) are ongoing or planned in the future.

Conclusions

Although the current consensus statements recommend a combination of anti-inflammatory and immunosuppressive therapy for patients with IPF, there is little high-quality evidence that these drugs are better than no treatment at all. Therefore, there is little rationale for treating IPF patients with steroids, unless the diagnosis is uncertain or the characteristics of the particular patient are atypical. As some other forms of interstitial pneumonia (in particular NSIP) may respond better to immunosuppressive agents and steroids, it remains crucial to obtain an accurate diagnosis of IPF/UIP, possibly in the early stages of the disease, before the end-stage fibrotic disease becomes predominant and makes any intervention less effective, if not harmful. Even though IPF/UIP has a very poor prognosis, and there is a lack of evidence for drug therapy, a small number of patients with IPF may benefit from lung transplantation. The option of lung transplantation for IPF is, however, a result of failure to find a therapy for this disease, and its usefulness in this group is obviously limited by patient eligibility, morbidity and mortality of the procedure and the supply of donor organs.

As for which therapy to choose for our patients, any recommendation must now be made on an individual basis. Advancement of the basic knowl-

edge of the pathogenetic mechanisms causing IPF should eventually result in a larger number of effective therapeutic options. Even if the goal of cure for IPF remains elusive,[45] the good news for patients affected by this deadly disease, and for their physicians, resides in the forthcoming well-designed, randomized, large controlled trials with IFN-γ and other immunomodulatory agents.

Research directions

- High-quality trials are lacking for the most commonly used agents, and the results of interventions have been greatly disappointing.
- The most pressing need is for additional clinical trials to better evaluate treatments for IPF.
- These future trials ideally should use patients with biopsy-proven IPF/UIP in the early stages of disease. These trials should have three arms: a placebo arm, an oral corticosteroid arm and a third arm using the agent of interest, either as a single agent or together with oral corticosteroids.
- Such trials would need to examine a number of clinically relevant outcomes in randomized trials over a considerable period of time (3–5 years). The outcomes of interest should include survival, changes in lung function and quality-of-life indices.

Practice points

- IPF is a specific form of chronic fibrosing interstitial pneumonia limited to the lung, associated with the histological pattern of UIP on surgical lung biopsy.
- Although current guidelines, based upon consensus, indicate prednisone associated with azathioprine or cyclophosphamide as the basis for IPF treatment, it is commonly observed that these drugs are ineffective in most of these patients.
- Using the methodologies of the Cochrane collaboration, no high-quality studies on oral corticosteroids, the most commonly used medical therapy for IPF, have been identified. Furthermore, only few small studies have used non-steroid immunosuppressive agents, and the results have been disappointing.
- In a recent randomized, double-blind, placebo-controlled, multinational trial IFN-γ therapy did not significantly affect the primary end point of survival. Further analysis of this cohort of IPF patients after a follow-up period of 3 years suggests that those patients with less severe disease could have a greater benefit from therapy with IFN-γ. Therefore, further trials using IFN-γ in IPF patients might provide in the future additional evidence regarding its usefulness.
- Because of its poor prognosis, there is a major need for additional clinical trials to better evaluate new therapies for IPF.

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