Current and Future Treatment Options in Idiopathic Pulmonary Fibrosis

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Abstract: Idiopathic pulmonary fibrosis (IPF) is a chronic condition of unknown aetiology with deteriorating respiratory function leading to respiratory failure. Sequential acute lung injury leads to progressive fixed tissue fibrosis, architectural distortion and loss of function. An excess of profibrotic cytokines and/or a deficiency in antifibrotic cytokines have been implicated in the pathological process as has excessive oxidation. At present no specific therapy is available. Corticosteroids alone or in combination with immunosuppressive drugs such as azathioprine, colchicine, and cyclophosphamide have been used with limited success. Interferon-gamma-1b showed a significant improvement in pulmonary function only in one study. Pirfenidone, cyclosporine and acetylcysteine may also prove to be of benefit but data from studies are limited. Novel drugs, mainly antifibrotic, anticytokine and immunoregulatory, are currently being investigated in various trial phases. Most recently, endothelin receptor antagonists (e.g., bosentan) have been shown to have possible beneficial effects in early stages of IPF. After a short overview on the current hypothesis on pathophysiology in IPF this review will discuss the present and possible future therapeutic options in IPF.

Keywords: Acetylcysteine, azathioprine, glucocorticosteroid, idiopathic pulmonary fibrosis, treatment.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is one of the most common interstitial lung diseases ranking second behind sarcoidosis. Prevalence ranges from 15 to 250 per 100,000 depending on the country, age, and gender [1-4]. The disease is insidious and progressive. Median survival is 2 to 3 years after diagnosis. Although consensus statement of the American Thoracic Society and the European Respiratory Society has defined diagnostic criteria the diagnosis of IPF remains problematic [5]. Often diagnosis is made by an interactive approach of different specialists including clinicians, radiologists, and pathologists. The consensus statement aims at defining IPF. This is an important step to compare treatment regiments. Studies in the past have often included mixed groups of patients with IPF and NSIP (non specific interstitial pneumonia). This is important because it is now clear that NSIP has a much better prognosis than IPF. In addition, NSIP shows a good response to corticosteroids while IPF does not [6]. At present there is no therapy available to effectively influence the course of IPF. However, with ongoing research deeper insight into pathogenesis of IPF has evolved. Hopefully, this knowledge will eventually lead to the development of efficacious therapies for IPF. After a short overview on the current concepts of IPF pathogenesis this review will summarize present and future treatment options for IPF.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF IPF

IPF belongs to the group of idiopathic interstitial pneumonias (IIP). IIP are a subgroup of diffuse parenchymal lung diseases (DPLD) or diffuse interstitial lung diseases [7]. IPF is defined as a specific form of chronic fibrosing interstitial pneumonia limited to the lung and associated with the histologic appearance of usual interstitial pneumonia (UIP) on surgical (thoracoscopic or open) lung biopsy [5]. The definite diagnosis of IPF in the presence of a surgical biopsy showing UIP includes several criteria that are listed in Table **1**. In the absence of a surgical biopsy the diagnosis of IPF can be made by using ATS/ERS criteria which are listed in Table **2**. The differential diagnoses of IPF include the other IIP and DLPD (Table **3**).

Table 1. Diagnostic Criteria of IPF in the Presence of Surgical Biopsy Showing UIP

Exclusion of other known causes of interstitial lung disease
Abnormal pulmonary function studies including evidence of restriction and/or impaired gas exchange
Abnormalities on chest X rays and/or HRCT

Table 2. ATS/ERS Diagnostic Criteria of IPF in the Absence of Surgical Biopsy

Major Criteria	Minor Criteria
Exclusion of other known causes of interstitial lung diseases	Age > 50 years
Restriction and/or impaired gas exchange on pulmonary function studies	Insidious onset of otherwise unexplained dyspnea on exertio
Bibasilar reticular abnormalities with minimal ground glass opacities on HRCT scans	Duration of illness ≥ 3 months
Transbronchial lung biopsy or bronchoalveolar lavage (BAL) showing no features to support an alternative diagnosis	Bibasilar, inspiratory crackles (dry or "Velcro" type in quality)

The presence of all major criteria and at least three minor criteria increases the likelihood of an IPF.

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Table 3. Differential Diagnosis of IPF

DPLD of known causes (e.g., drugs or association e.g., collagen vascular disease)
IIP other than IPF (e.g. NSIP)
Granulomatous DPLD (e.g. sarcoidosis)
Other forms of DPLD (e.g. histiocytosis X)

PATHOGENESIS

Our understanding of the pathogenesis of IPF has evolved during the last years. More than 30 years ago an initial hypothesis on the development of IPF was proposed. That model suggested that chronic inflammation (alveolitis) led to fibrosis [8, 9]. However, this concept was questioned by the finding that the degree of tissue inflammation correlated poorly with fibrosis or outcome. Moreover, immunosuppressive anti-inflammatory treatment has no significant effect [10]. This led to an alternative hypothesis that is summarized in Fig. (**1**).

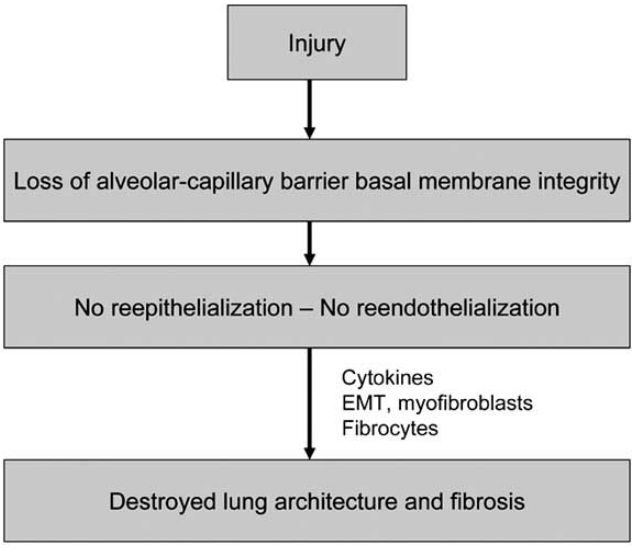

Fig. (1). Current concept IPF pathogenesis. For details refer to text. EMT: epithelial-to-mesenchymal transformation.

At present IPF is believed to develop as a consequence of epithelial injury with abnormal wound healing (Fig. **2**). Inflammation is not necessary for fibrosis [11]. Several mechanisms have been implicated in this concept.

The loss of the alveolar-capillary barrier basement membrane (BM) integrity represents the "point of no return" in the development of pathologic fibrosis. This barrier consists of the type I alveolar epithelial cell, the endothelial cell, and their respective BMs. In a normal lung the alveolar-capillary barrier is repaired after acute lung injury and tissue integrity and function is rapidly restorated. Early after an injury haemorrhage and plasma extravasation is observed as well as coagulation and release of inflammatory mediators [12, 13]. Inflammatory cells, fibroblasts, myofibroblasts, endothelial cells, and epithelial cells are activated by these mediators. Deposition of extracellular matrix (ECM) after acute inflammation is an essential event. If the BM is intact and the injurious stimulus is removed the deposition of ECM is remodelled/reabsorped and reepithelialization and reendothelialization occurs [12, 13]. In contrast, in patients with IPF loss of type I epithelial cells and endothelial cells is observed. Alveolar structures and collapse and fusion of BMs is present because of the loss of alveolar-capillary barrier. Type II alveolar epithelial cells and endothelial cells proliferate without structured matrix. In addition, fibroblast and myofibroblast recruitment and proliferation lead to end stage fibrosis [14-19] (Fig. **3**).

Several cytokines such as transforming growth factor (TGF)-β, connective tissue growth factor (CTGF), platelet derived growth factor (PDGF), and interleukin(IL)-13 as well as chemokines are important players in the pathogenesis of IPF. TGF-β is strongly associated with progressive fibrosis in IPF [20, 21]. It can drive EMT (epithelial mesenchymal transition) and fibroblast-to-myofibroblast differentiation [22]. In addition, TGF-β is the most potent inducer of ECM production known to date. CTGF stimulates fibroblast matrix production and myofibroblast differentiation [23]. PDGF has mitogenic and chemoattractive effects on mesenchymal cells including fibroblasts [24]. The Th2 type cytokine IL-13 stimulates fibroblast collagen production. It is not totally clear whether this occurs independently of TGF-β [25, 26]. In IPF there as a predomination of Th2 type cytokines. Moreover, IL-13 can stimulate production of FIZZ (found in inflammatory zone)-1. The biological function of FIZZ-1 is unknown but it can stimulate myofibroblast differentiation *in vitro* [27, 28]. All of these cytokines provide potential therapeutic targets. In addition to cytokines chemokines are abundantly expressed in pulmonary fibrosis [29]. CCL2 (monocyte chemoattractant protein-1) for example can induce TGF-β1 and procollagen gene expression [30]. Moreover, levels of CCL2 are increased in IPF [31].

Data from the literature also suggest that pathogenesis of IPF is related to a persistent presentation of an "antigen" that leads to chronic inflammation and destruction of lung parenchyma resulting eventually in lung fibrosis [32-35].

Given the importance of myofibroblasts and fibrocytes in the pathogenesis of IPF interest has been focussed on these cells. The classic concept states that tissue injury induces resident fibroblasts to proliferate and express constituents of ECM. A more recent theory implies that expression of TGF-β in case of tissue injury induces transition of epithelial cells to a mesenchymal phenotype, the fibroblast/myofibroblast [22, 36-37]. There is also evidence in the literature that circulating fibrocytes are mesenchymal progenitor cells that home and extravasate into site of lung injury [18] (Fig. **3**).

Most recently, severe endoplasmatic reticulum stress of alveolar type II cells has been shown to play an important role in induction of apoptosis of these cells [38].

THERAPEUTIC OPTIONS

Therapeutic options in IPF are limited. At present there is no treatment available that could effectively reduce fibrosis. Most treatment regimens used today aim at suppressing inflammation to inhibit destruction of lung parenchyma and fibrosis. A still unresolved problem is established fibrosis. Fibrotic tissue cannot be removed or replaced by healthy

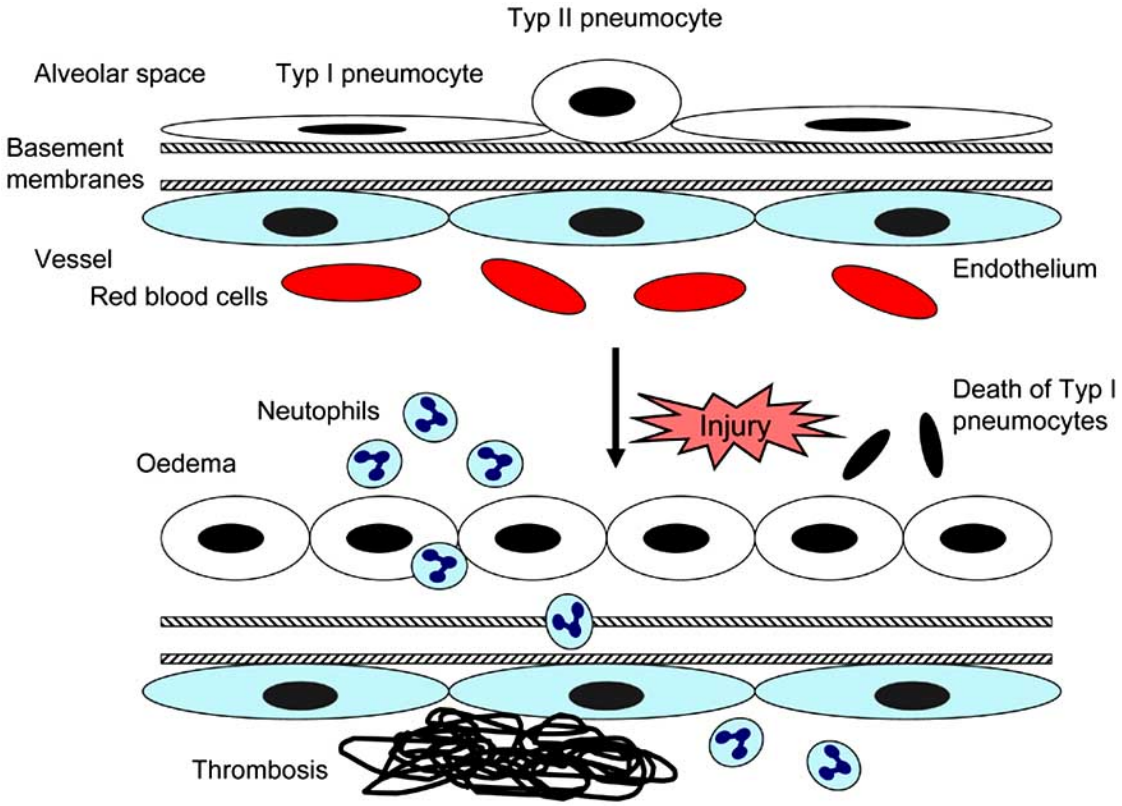

Fig. (2). Lung injury leads to death of type I pneumocytes, influx of neutrophils, oedema, and thrombosis.

lung tissue. Advances in our understanding of the underlying pathogenetic mechanisms will hopefully lead to development of effective and efficacious agents. Table **4** summarizes the different treatment approaches.

Another point of concern is how to treat stable IPF and exacerbations. Facing no real alternative options exacerbations are most often treated with high dose corticosteroids or cyclophosphamide. However, there is no convincing evidence that those therapies improve outcome [39].

CURRENT TREATMENT OPTIONS

As mentioned above present medical therapy for IPF is limited. Best supportive care including rehabilitation, oxygen therapy, pulmonary rehabilitation, opiates, antireflux therapy is strongly advised. Lung transplantation is an option in selected patients. No drug therapy to date has proven any substantial surviving benefit or modification of the course of disease. A combination therapy of prednisone (tapering from 0.5 mg kg/day to 10-20 mg/day), azathioprine (2 mg/kg, maximum 200 mg/day) and N-acetlycysteine (600 mg three

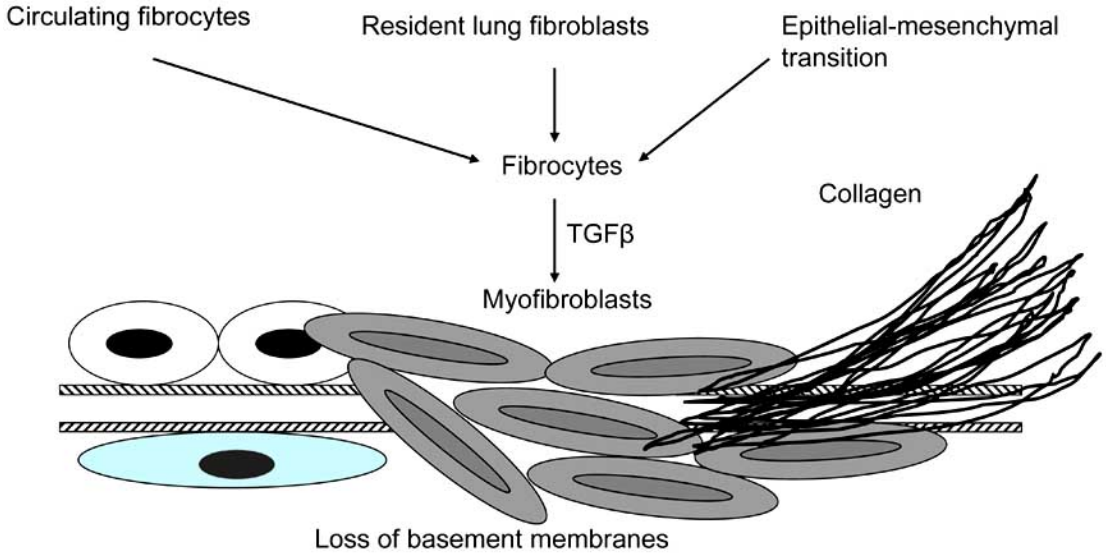

Fig. (3). The loss of the alveolar-capillary barrier prevents recovery. Fibrocytes from different sources become myofibroblasts that produce collagen and extracellular matrix. TGFβ: Transforming growth factor-β.

times a day) has been shown to have significant better treatment effect than prednisolone and azathioprine alone. Therefore combination therapy is recommended [40]. At present the PANTHER-IPF (Evaluating the effectiveness prednisone, azathioprin, and N-acetlycysteine in people with idiopathic pulmonary fibrosis) is comparing the effect of a combination therapy, N-acetlycysteine alone and placebo (NCT00650091). This trial will investigate patients with mild to moderate IPF. Primary end-point will be change in VC after 60 weeks.

Table 4. Therapeutic Approaches to Treat IPF

Mode of Action	Examples
Antiinflammatory/ immunosuppressive	Glucocorticosteroids, azathioprine, cyclophosphamide, pirefenidone, IFN-γ, N-acetylcysteine, thalidomide, Anti-TNFα antibodies, BIBF-1120, zileutin, imatinib
antifibrotic	MS80, endothelin receptor antagonists, anti-TGFβ antibodies, FG-3019, imatinib
Anticoagulation	Heparine, phenprocoumon
Blockade of circulating fibrocytes	Anti-CXL12 antibodies

IMMUNOSUPPRESSIVE TREATMENT IN IPF

Glucocorticosteroids

Glucocorticosteroids have a broad spectrum of anti-inflammatory and immunosuppressive effects. Based on the former hypothesis of chronic inflammation leading eventually to fibrosis the use of steroids seemed logical. Phan and colleagues used an animal model of bleomycin-induced pulmonary fibrosis to test the effect of glucocorticosteroids [41]. In their experiments methylprednisolone prevented the increase in bleomycin-induced lung collagen deposition and partially suppressed total lung collagen synthesis, without affecting the net rate of lung collagen synthesis expressed per mg of DNA. Several clinical trials assessed the effect of steroid treatment on IPF. A recent meta-analysis by Richeldi and co-workers has evaluated the efficacy of steroid therapy in adult patients with familial and sporadic IPF [42]. The authors identified seventeen articles including a total of 726 patients with treatment duration of 2 weeks to 36 months as potential eligible for meta-analysis. However, those were not randomized controlled trials or controlled clinical trials. Therefore the authors excluded all and concluded that at present there is no evidence for steroid treatment in IPF [42]. At present corticosteroids are not recommended as monotherapy for IPF.

Azathioprine

Azathioprine is a purine analog inhibiting adenine deaminase which itself impairs the proliferation of cells, especially leukocytes and lymphocytes. Azathioprine has been used as therapy for IPF primarily in patients failing or experiencing adverse effects from corticosteroids. Anecdotal responses were noted in uncontrolled studies [43]. The combination of azathioprine plus corticosteroids was associated with modest improvement and enhanced survival in some patients [44]. Until now most studies had limitations in design and interpretation of results (e.g. uncontrolled, small numbers of subjects, lack of adequate details to assess response, or inclusion of patients with conditions other than IPF [43, 45-46]. Raghu and co-workers enrolled 27 patients in a prospective, double-blind, randomized, placebo-controlled study to compare the therapeutic effect of combined prednisone/ azathioprine with prednisone plus placebo [44]. In these cases no further classification of the IPF subtypes were done. At a one year follow up the authors could not show any significant difference in clinical measures or mortality. A more recent study of Hoyles and co-workers also did not show any advantage in clinical outcome after treating patients with prednisone, cyclophosphamide and addition of oral azathioprine or placebo [46]. Patients though enrolled in this study suffered from scleroderma associated lung fibrosis but not from idiopathic interstitial pneumonia. 45 patients were enrolled in this multicenter, prospective, double-blind, randomized, placebo-controlled study. The primary endpoints of this trial were changes in FVC of predicted and the changes in DL_{CO}. There was no statistically significant improvement in the end points between the treatment group and the placebo group [47]. Serious side effects like myelosuppression, liver toxicity, nausea, joint pain and an increased risk for malignancies does not justify the routine use of azathioprine as a monotherapy in the management of IPF due to a lack of statistical significant studies.

Cyclophosphamide

This alkylating agent is in most instances orally absorbed and activated by liver enzymes to several cytotoxic compounds suppressing the function of immunomodulatory cells like leukocytes and lymphocytes. There is some data on small nonrandomized trials and case reports in the treatment of idiopathic interstitial pneumonia showing little benefit. Statistically not convincing data exist to show a superiority of cyclophosphamide over other cytotoxic agents in treating IPF. However, no studies have directly compared cyclophosphamide with other immunosuppressive or cytotoxic agents [48-52].

High-dose intravenous cyclophosphamide administered over a maximum of 4 weeks (dose range from 500mg up to 1800 mg) has been tried in open trials of refractory IPF [50, 53]. Results are generally unimpressive. The poor response to pulsed cyclophosphamide therapy may likely reflect late course disease when treatment was initiated. In a prospective trial Johnson and colleagues [48] showed that there was no benefit of high dose prednisone *vs* low dose prednisone plus cyclophosphamide. Among this heterogeneous group of IPF no statistically significant markers could be obtained regarding clinical course of the disease or mortality. In addition, a large retrospective analysis from Collar and co-workers [54] compared a combination therapy of corticosteroid and cyclophosphamide patients who meet the definition of IPF. Patients were identified retrospectively and treatment addressed on an intention-to-treat basis. A total of 164 patients were included and half of them where treated, whereas half did not receive any immunosuppressive or

immunomodulatory therapy. There was no significant difference in survival between treated and untreated patients. The lack of treatment persisted even in the group with histologic proven diagnosis of IPF (n = 24). Those data clearly showed that combined corticosteroid and cyclophosphamide therapy had no impact on survival in patients with IPF. No valid studies have compared oral with pulsed cyclophosphamide for IPF yet.

Toxicity associated with cyclophosphamide remains a major impediment to the routine use of this agent. Especially the increased risk of infections, myelosuppression, hepatotoxicity and not to forget hemorrhagic cystitis and the increased risk for several malignancies reinforces the importance of careful consideration of this cytotoxic agent. As with azathioprine, there is no evidence to justify the routine use of cyclophosphamide alone or in combination with steroids for the management of IPF.

Methotrexate

In a systemic review of the PUBMED database no study or data could be found about methotrexate in the treatment of IPF. In contrast, several trials propose that the use of methotrexate e.g. in the treatment of rheumatoid arthritis induces the development of interstitial lung disease [55-57]. However, some favourable use of methotrexate was published for interstitial lung disease combined with scleroderma and polymyositis-induced lung fibrosis [58, 59]. Again, it has to be emphasized that the routine use of methotrexate for the therapy of IPF is definitely not recommended.

Colchicine

Colchicine inhibits collagen formation from fibroblasts and suppresses the release of alveolar-macrophage-derived growth factor and fibronectin by alveolar macrophages from patients with pulmonary fibrosis. Based on animal and *in vitro* studies colchicine may be able to attenuate fibrosis [60, 61]. However, several clinical trials failed to demonstrate a positive effect of colchicines on lung function or survival in IPF [62-66]. In the study by Douglas and co-workers 26 patients with IPF were randomized to receive either high-dose prednisone (n = 12) or colchicine (n = 14) [62]. Patients with high-dose steroid therapy showed a trend to more rapid decline in lung function and shorter survival. However, both treatment regimens did not result in an objective improvement. The authors discussed colchicine as a potential alternative to high-dose steroids. Selman and colleagues compared the effect of colchicine and/or D-penicillamine with prednisone, in comparison to prednisone alone [63]. Fifty-six IPF patients were included in this study. Patients received either colchicine/prednisone (n=19), D-penicill-amine/prednisone (n=11), D-penicillamine/colchicine/pred-nisone (n=11), or prednisone alone (n=15). Response to therapy was assessed by changes in lung function test results as measured by total and vital lung capacities, arterial blood gas analysis at rest breathing room air, and survival. No significant differences either in lung function tests or in arterial gases were found in any group relative to the baseline measurement. Survival was not significantly improved in any of the groups. A retrospective analysis reviewed the clinical records of 487 patients seen at Mayo Clinic Rochester [64]. Surgical open lung biopsy was performed in 20.3% to obtain the diagnosis. 167 patients received colchicine alone, 71 patients were treated with a combination of colchicine and prednisolone. No significant effect on survival was observed with colchicine. Peters and colleagues retrospectively analysed the outcome of 23 patients being treated with colchicine [65]. Clinical and pulmonary function parameters improved in five patients (22 percent) following colchicine, nine (39 percent) remained stable, and nine (39 percent) worsened. Another study compared 22 patients with IPF being treated with colchicine as first line therapy to 22 historical patients with IPF who received prednisone as initial single-drug treatment [66]. No significant differences were noted between both groups. However, a trend towards a more rapid decline in lung function in the prednisone-treated group was observed. The most important side effect of colchicines in all studies was diarrhoea. In summary, the present data are insufficient to recommend colchicine as treatment option for IPF.

ANTIOXIDATIVE TREATMENT

N-Acetylcysteine

Oxidative stress and oxidant-antioxidant imbalance has been suggested to play an important role in the pathogenesis and progression of IPF [67-74]. Oral N-acetylcsteine (NAC) reduced collagen deposition in the lungs of bleomycin-induced lung fibrosis in mice [75]. Meyer and co-workers were able to show that glutathione levels in the bronchoalveolar lavage fluid of IPF patients could be oral administration of N-acetylcysteine (NAC) [70]. The IFIGENIA (Idiopathic Pulmonary Fibrosis International Group Exploring *N*-Acetylcysteine I Annual) trial looked at the effect of high dose NAC (600 mg tid) in patients with IPF [76]. This was a double-blind, randomized, placebo-controlled multicenter study. 182 patients received either NAC (92) or placebo (90). This therapy was given in addition to standard treatment including prednisone plus azathioprine. Therapy was NAC attenuated the decrease in vital capacity and DL_{CO} after 12 months which were defined as primary endpoints. However, no significant difference in mortality was observed between both groups (9% in the NAC group, 11% in the placebo group). No significant difference in adverse effects was observed between both groups. Interestingly, patients in the NAC group had a significantly lower rate of myelotoxic effects. This may be due to a protective effect of NAC against myelotoxic effects of immunosuppressive therapy [76]. NAC may preserve vital capacity and DL_{CO} in IPF patients when added to prednisone and azathioprine better than standard therapy alone. Whether this effect lasts longer than 12 months has to be further evaluated. However, since NAC is not expensive and has demonstrated a favourable effect it should be given to patients with IPF. Most recently, Behr and colleagues performed additional analysis with the data from the IFIGENIA trial [77]. They confirmed that vital capacity and DL_{CO} did not significantly change in trial completers on NAC whereas in non-completers the indices worsened but less pronounced than in the placebo group. Interestingly baseline DL_{CO}, total lung capacity, and PaO2 was significantly lower in non-completers compared to

completers implicating that disease might have been much worse in that group. This notion is also supported by the finding that the composite physiology index (CPI) was significantly lower in the completer group. The CPI represents the degree of disease [78]. A CPI of less than 50 points means less severe disease. It is not surprising that patients with less severe disease had a better prognosis. However, the authors speculate that patients with less pronounced IPF may have a more favourable outcome with triple therapy. This remains to be investigated in future studies.

TREATMENT OF ACUTE EXACERBATION OF IPF

Acute exacerbations of IPF (AE-IPF) are defined by an acute onset of dyspnea (< 1 month) with worsening hypoxia and progressive infiltrates seen in the absence of heart failure or infection [39]. Pathologic studies revealed diffuse alveolar damage (DAD) on the underlying fibrotic pattern of UIP in nearly all case of AE-IPF [80, 81]. No specific aetiology of AE-IPF has been identified yet. Infections are supposed in some patients. Several treatment strategies have been employed in AE-IPF. High-dose pulse corticosteroid therapy has been tried similar to idiopathic ARDS. Kondoh and colleagues treated three patients with AE-IPF with high doses of corticosteroids and were able to shown an improvement in oxygenation [80]. In a study by Akira and co-workers patients with AE-IPF were classified according to CT scans into three groups with peripheral parenchymal opacification (n = 6), multifocal parenchymal opacification (n = 6), and diffuse parenchymal opacification (n = 5) [82]. 50% of patients with multifocal pattern responded to steroid therapy whereas all patients with peripheral pattern showed some degree of improvement. Cyclosporin ahs been tested in small, uncontrolled series in conjunction with glucocorticosteroids. Four of seven patients showed a response and three patients had a prolonged survival [83]. Data on cyclophosphamide are lacking. Although pirfenidone lowered the rate of AE-IPF (placebo group, 13.9%; pirfenidone group, 0%) in one study (see below) its efficacy in AE-IPF remains unclear. Anticoagulant therapy may be beneficial in AE-IPF. However, this has to be further evaluated. In conclusion, at present there is no effective therapy of AE-IPF available. The prognosis of AE-IPF remains poor. A recent systematic review found that a 1-month and 3-month mortality of AE-IPF around 60% and 67%, respectively [84].

TREATMENT OF PULMONARY HYPERTENSION IN IPF

Pulmonary hypertension (PH) is more and more often found in IPF. Based on data from the literature the prevalence of PH in IPF may be up to 84% [85]. This number may overestimate the rate in real life but it emphasizes that IPF is often associated with PH (group 3 according to Dana Point classification). Although a number of powerful drugs have been introduced in the treatment of pulmonary arterial hypertension in the last few years almost no data are available on their effects on PH in IPF. Endothelin receptor antagonists have been investigated as anti-fibrotic agents in clinical trials (see below) but those IPF patients had no PH. Since similar pathogenetic mechanisms can be found in IPF and pulmonary arterial hypertension it is tempting to speculate that those agents may also have a beneficial effect on IPF. Data from ongoing trials will hopefully answer these questions. At present PH in IPF should be treated by treating the underlying disorder. Oxygen, diuretics, and anticoagulants may be helpful in treating right heart failure. Lung and combined heart lung transplantation remains the ultimate therapy (see below).

EXPERIMENTAL AND FUTURE TREATMENT OPTIONS

Interferon-γ

Interferon-γ (IFN-γ) has been described as a key mediator in antagonizing TGF-β expression and activity thus limiting fibroblast proliferation, differentiation and collagen synthesis. In a murine model of bleomycin-induced pulmonary fibrosis daily treatment with IFN-γ reduced mRNA expression of TGF-β, collagen I, and collagen III. In addition, IFN-γ attenuated the increase in lung collagen levels [86].

Ziesche and co-workers treated 18 patients with pulmonary fibrosis who had been unresponsive to corticosteroids or other immunosuppressants with prednisolone alone (N = 9) or prednisolone plus IFN-γ 1β (N = 9) [87]. In that study combination therapy of prednisolone plus IFN-γ 1β increased TLC and PaO2. In contrast, in group with prednisolone monotherapy lung function deteriorated. There are some limitations of the study. The major point is that most of the patients had not IPF but other pulmonary fibrotic diseases such as NSIP. Therefore results from that study cannot be easily transferred on IPF patients.

Two large clinical trials have evaluated the effect of IFN-γ 1β treatment in IPF. Raghu and co-workers investigated the effect of subcutaneous IFN-γ 1β in IPF patients that were unresponsive to corticosteroid therapy (GIPF-001 study) [88]. In this multinational, multicenter, placebo-controlled trial 330 patients were included. Patients were treated over a median of 58 weeks. IFN-γ 1β did not significantly improve progression-free survival as well as lung function, gas exchange or quality of life. A trend towards longer survival was observed in the IFN-γ 1β group (10% of the patients died compared to 17% in the placebo group). *Post hoc* analysis revealed an increased survival in patients with a baseline FVC > 62% of predicted. Treatment with IFN-γ 1β was associated with more adverse side effects but treatment discontinuation rates were similar in both groups.

The INSPIRE study was a multicenter, randomized, placebo-controlled trial [89]. A total of 826 patients with IPF were randomized to receive either IFN-γ 1β (N = 551; 200 mg s.c. three times per week) or placebo (N = 275). This study was prematurely stopped at the second interim analysis because IFN-γ 1β treatment did not show a minimum beneficial effect on survival (the primary endpoint). 15% of patients in the treatment group and 13% of patients in the placebo group had died. More patients in the IFN-γ 1β group reported flu-like illness.

A smaller study by Antoniou and colleagues compared the effect of IFN-γ 1β and colchicine in IFP over a period of

two years [90]. That study included 50 IPF patients (31 IFN-γ 1β, 18 colchicine). Lung function was moderately impaired (mean FVC 71.8% of predicted and 70.7% of predicted, respectively). After a median follow-up period of 25 months 15.6% in the IFN-γ 1β group and 38.8% in the colchicines group had died (P = 0.028). The survival benefit was only apparent in patients with a baseline FVC > 71% of predicted. In that subgroup only patients in the colchicine group died. Thus it is not clear whether IFN-γ 1β improved survival by stabilizing IPF or whether colchicine treatment itself was associated with higher mortality. Treatment with IFN-γ 1β significantly improved FVC compared to colchicine treatment only after 24 months. Other lung function parameters and PaO2 showed no significant difference between both groups. The authors speculated that IFN-γ 1β may be most effective in mild-to-moderate IPF. However, based on the data from the above mentioned larger clinical trials this hypothesis cannot be supported.

Based on the present data from the literature the use of IFN-γ 1β as therapy for IPF cannot be recommended.

Anticoagulation

Vascular injury in the presence of inflammation in IPF has been reported by several authors [91-93]. Microvascular injury has been suggested as an important step in the evolution of IPF [93]. Microvascular injury leads to exposition of neointimal tissue factor. This factor is a strong prothrombotic stimulus leading to rapid coagulation. Cella and colleagues found increased plasma levels of tissue factor pathway inhibitor (TFPI) in IPF patients [94]. This may be due to extensive release from mesenchymal cells.

Pulmonary embolism has been documented as cause of death in IPF. However, it is rarely observed as cause of acute exacerbation. In a review by Panos and colleagues pulmonary embolism was the cause of death in only 3.4% [95]. A more recent study including 86 IPF patients reported pulmonary embolism in 7 patients (8.1%) and deep venous thrombosis in one patient (1.1%) [96]. It has to be taken into account that those patients were severely impaired and referred for lung transplantation. Pulmonary hypertension is another important vascular problem in IPF that is discussed at another site in this article.

Kubo and co-workers investigated the effect of an anticoagulant therapy in patients with IPF [97]. In that study 56 patients were randomized to receive prednisolone alone or prednisolone and anticoagulant therapy with warfarin. Re-hospitalized patients in the anticoagulant group were treated with low-molecular-weight heparin. The survival in the anticoagulant group was significantly increased. Improved survival was associated with reduced exacerbation rate. However, no significant difference was observed for hospitalization-free days between the two groups. This study had some limitations. It was not blinded. 6 out of 31 patients declined anticoagulant therapy (19.4% drop out). Pulmonary embolism was not excluded as cause for acute exacerbation by CT imaging or other radiological methods. No information is given on probable pulmonary hypertension in those patients. It has also to be taken into account that the patients in that study were not severely affected by their IPF (mean FVC 71% and 69% of predicted, mean PaO_2 71 mmHg and 69 mmHg, mean DL_{CO} 63% and 59% of predicted) [97]. In addition, single therapy with corticosteroids is not considered the therapy of choice for IPF. Despite these limitations the study of Kubo and colleagues provides interesting data on the possible use of anticoagulant therapy in IPF. Larger clinical trials are needed to address this issue. This has led to the initiation of the ACE-IPF (Anticoagulant effectiveness in idiopathic pulmonary fibrosis) study. This phase III clinical trial will compare the effect of warfarin and placebo on survival time, bleeding complication, and decline in VC (NCT00957242). This study will end in November 2011.

Pirfenidone

Pirfenidone is a derivate of pyridone (5-methyl-1-phenyl-2-[1H]-pyridone) with anti-inflammatory, antioxidant and antifibrotic activity [89, 90]. Animal experiments demonstrated antifibrotic effects of this drug [100, 101]. Pirfenidon reduces expression of profibrotic cytokines (e.g. PDGF, TGF-β) [102, 103], inhibits expression of proinflammatory cytokines (e.g. TNF-α, IL-6) as well as influx of inflammatory cells [104-107] and leads to down-regulation of procollagen gene expression [103]. Kakugawa and co-workers showed that pirfenidon reduced heat shock protein (HSP) 47-positive cells and myofibroblasts in a murine model of bleomycin-induced fibrosis [108]. HSP47 is a collagen-specific molecular chaperone that is involved in collagen processing and/or secretion.

Based on these promising results from animal and cell culture experiments pirfenidone has been tested as an antifbrotic agent in IPF patients. Two open-label studies investigated the effect of prifenidone (40 mg/kg body weight) in a total of 54 patients [109, 110]. In the study by Raghu and colleagues mean age was 62 years and most patients received combination treatment of prednisone with immunosuppressants and oxygen supplementation prior to pirfenidone. Lung function was moderately impaired and diffusion capacity was severely reduced (mean FVC 58.8%, mean DL_{CO} 34.3%). However, the ranges of FVC (26% to 108% of predicted) and DL_{CO} (8% to 104% of predicted) were wide. One- and 2-year survival was 78% and 63% [109]. Compared to survival rates of the natural history of IPF these results are encouraging. At one-year follow up 48% of the patients were in stable condition and 23% had even improved regarding FVC. Patients were deteriorating lung function prior to treatment had a stabilization with prifenidone. The study be Nagai and co-workers included 8 males with IPF (n = 6) and systemic sclerosis associated UIP (n = 2). Mean age was 61 years. Lung function was moderately impaired (mean FVC 54%, range 37.1% to 83.6% of predicted). Diffusion capacity was severely decreased (mean DL_{CO} 33%, range 23.8% to 60.6% of predicted). In that study pirfendione had no significant effect on survival after 2 years. No significant deterioration of lung function parameters and oxygen saturation was observed [110]. In both studies adverse side effects of pirfenidone were described as mild. Adverse effects leading to discontinuation of pirfenidone occurred in 11% and included rash and photosensitivity, nausea and emesis [109].

Azuma and co-workers performed a placebo-controlled trial of pirfenidone in IPF [111]. In that study 107 patients

with IPF were evaluated for treatment with either pirfenidone (n = 72) or placebo (n = 35). However, 27 patients were not able to perform a 6 minute exercise test (6MET) on the treadmill. Since change in the lowest oxygen saturation during 6MET was the primary endpoint of the study an amendment was made not to negatively influence study results. Only patients being able to complete the 6MET (n = 80; pirfenidone: 55, placebo: 25) were included into analysis. The primary endpoint of the study was not reached. There was no significant difference in the change in the lowest oxygen saturation at 6 and 9 months between the pirfenidone and the placebo group. The decline in VC was significantly reduced in the pirfenidone group compared to placebo. However, no significant differences were observed for TLC, DL_{CO} and resting PaO_2 between both groups. In the placebo group the rate of acute exacerbations was significantly increased (5/35 *vs* 0/72; P = 0.0031). Adverse effects were common in both groups (pirfenidone: 98.6%; placbo: 88.9%). Photosensitivity occurred in almost 44%, stomach discomfort in 30%, anorexia in 32%, and nausea in 22% of patients in the pirfenidone group. The study was terminated before the one-year period due to exacerbation rate in the placebo arm [111]. Therefore all results from that study have to be interpreted with care.

Most recently, a multi-centre, double-blind, placebo-controlled, randomised phase III clinical trial was conducted in Japanese patients with well-defined IPF [112]. 275 patients were randomized to receive high-dose (1800 mg per day) or low-dose (1200 mg per day) pirfenidone or placebo. The primary end-point was change in VC after 52 weeks. Secondary end-points included progression-free survival and lowest oxygen saturation during a 6MET. There was a significant difference in decline of VC between the high-dose group and the placebo group (-90 ml *vs* -160 ml; P = 0.0416). A significant difference between the two groups was also observed for progression-free survival. However, no clear information was given about survival in the groups. 63% of patients in the high-dose group completed the study. 73% of the patients completed the study in the low-dose group and 70% in the placebo group. No major cause of withdrawal could be identified in the groups. Adverse effects were most common in the high-dose group including photosensitivity, anorexia, dizziness, upper respiratory tract infections, and γ-GT elevation.

Pirfenidone has been approved for treatment of IPF in Japan. However, at present data are limited to animal and cell culture experiments and four studies (two open label, two placebo-controlled). Further clinical trials are needed to better define the effect of pirfendione and to evaluate its safety profile (eg. photosensitivity). At present one trial with 750 patients evaluates these aspects of pirfenidone (NCT0062038). This trial will end May 2011.

Endothelin Receptor Antagonists

Endothelin (ET)-1 is a potent vasoconstrictor and leads to proliferation of smooth muscle cells, inflammation, fibrosis and endothelial dysfunction in the pathogenesis of pulmonary arterial hypertension [113-116]. ET-1 has also profibrotic activities. It promotes fibroblast synthesis of collagen types I and III [115]. Moreover, ET-1 expression has been described in fibrosing alveolitis [117]. In a rat model of bleomycin-induced pulmonary fibrosis the dual ET (ET_A and ET_B) receptor antagonist bosentan decreased collagen deposition in the lungs [118].

The BUILD (Bosentan use in interstitial lung disease)-1 trial investigated the effect of bosentan in 74 patients with IPF and compared it to placebo (n = 84) for 12 months [119]. Although bosentan failed to improve the walking distance in the 6 minute walking test (6MWT, defined as primary endpoint) a positive trend towards the second endpoints (time to death, time to disease progression) was observed in the treatment group. Interestingly this effect was statistically significant in the group of patients that had undergone surgical biopsy to prove the diagnosis of IPF. Those patients may probably be treated in the beginning of the disease and inhibition of ETR may be most effective in the early course of IPF. However, these results have to be interpreted with care since this group was small (49 on bosentan, 50 on placebo) and statistical analysis for performed as post hoc analysis. Based on these data the BUILD-3 trial was initiated to test whether selected IPF patients (< 5% honeycombing on HRCT and histologically proven diagnosis) may benefit from treatment with bosentan (NCT00391443). Bosentan also had no significant effect on health-related quality of life (HRQL) or dyspnoea in the whole group [120]. However, as for the other parameters mentioned above patients who underwent surgical biopsy for diagnosis treatment effects on HRQL and dyspnoea could be observed.

Data on the effect of the selective ETR_A antagonsists sitaxentan and ambrisentan have not been published yet. However, the ARTEMIS trial is currently investigating the effect of ambrisentan in IPF (NCT00768300). A new, tissue-targeting dual endothelin receptor antagonist, macitentan, is currently investigated in a phase II trail in idiopathic pulmonary fibrosis (NCT00903331).

At present ETR antagonists cannot be recommended as treatment for IPF apart from clinical studies. Data from large studies on the effect of these agents in patients with IPF and pulmonary hypertension are not available at the moment. The BUILD-3 trial and other trials with ETR antagonists will hopefully help to define which group of IPF patients will benefit from this therapy.

Anti-TNFα Treatment

Tumor necrosis factor (TNF)α is an important mediator of growth and collagen secretion of interstitial cells [121]. Piguet and Vesin treated bleomaycin- and silica-induced lung fibrosis in mice with a human recombinant soluble TNF receptor rsTNF-β [122]. They were able to demonstrate that rsTNF-β reduced lung collagen content. In a more recent paper Fujita and colleagues described a protective effect of TNFα on bleomycin-induced lung fibrosis in mice [123]. However, TNFα levels are elevated in patients with IPF [124, 125]. Raghu and co-workers conducted a multicenter, randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of the recombinant soluble TNF receptor etanercept in IPF [126]. In that study 88 IPF patients received either etanercept (25 mg twice a week) or placebo. Mean FVC was 63.9% of predicted. After 48 weeks of treatment no significant difference in change of FVC and DL_{CO} was observed between both groups. However, a non-

significant attenuation of disease progression was observed with etanercept. The authors concluded that further evaluation of etanercept is warranted. However, there were four deaths in the etanercept group and two deaths in the placebo group. Although this difference was not statistically significant it reminds us that inhibition of TNFα can cause serious side effects and can support infections. No case of tuberculosis was observed in that study. At present etanercept must be regarded as an experimental treatment approach.

MS80

MS80 is a sulphated oligosaccharide that has been extracted from seaweed. MS80 can bind to TGF-β1 and may thus have anti-fibrotic effects. Jiang and Guang showed that MS80 inhibited TGF-β1-mediated fibroblast proliferation and collagen deposition *in vitro* [127]. In addition, these authors were able to demonstrate anti-fibrotic activity of MS80 in a rat model of bleomycin-induced pulmonary fibrosis. No studies with humans have been published yet.

ACE Inhibitors and Statins

In addition to their blood pressure lowering effect angiotensin converting enzyme (ACE) inhibitors have been shown to block murine models of lung fibrosis [128-131]. Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme-A reductase and are used as lipid lowering agents. However, several studies have indicated that statins also exert anti-inflammatory effects [132, 133]. Simvastatin blocks CTGF expression in fibroblasts [134]. One study by Nadrous and colleagues retrospectively analyzed the effect of ACE inhibitors and statins on IPF in 478 patients [135]. These findings have to be interpreted with care because that study was a retrospective analysis and a single centre study. No prospective studies have been published so far.

Zileuton

Leukotrienes (LT) have been suggested to play an important role in the pathogenesis of pulmonary fibrosis. Expression of LTB4 and LTC4 is increased in the lungs of patients with IPF [136]. In the mouse model of bleomycin-induced pulmonary fibrosis LTs are increased after intratracheal application of bleomycin. Conversely, lipoxygenase-5 knock out mice are protected from bleomycin-induced fibrosis [137]. Inhibition of 5-lipoxygenase with zileuton or using MK-571, a cys-leukotriene receptor antagonist reduced inflammation and lung damage in mice treated with bleomycin [138]. One open label trial compared the efficacy of zileuton to prednisone/azathioprin (NCT00262405). That study started in January 2001. No results are available so far.

Thalidomide

Thalidomide is a derivative of glutamic acid. It was originally synthesised as a sedative and anti-emetic. However, it is had to be withdrawn because of teratogenic effects. Thalidomide has also anti-inflammatory and immunomodulatory effects [139-142]. In addition it inhibits angiogenesis [143]. Ye and co-workers showed that thalidomide reduced lipopolysaccharide-stimulated release of IL-18, IL-8, and TNFα from alveolar macrophages of IPF patients [144]. In the mouse model thalidomide ameliorated histological changes in bleomycin-induced lung fibrosis and decreased expression of TGF-β [145]. Horton and colleagues reported a positive effect of thalidomide on intractable cough in 11 patients with IPF [146]. However, no data are given concerning lung function. One clinical phase II study has investigated the safety, feasibility and efficacy of 400 mg of thalidomide administered daily for one year in patients with IPF who have failed or are not candidates for treatment with corticosteroids and/or cytotoxic drugs (NCT00162760). No study results have been published yet.

Antagonizing Transforming Growth Factor-β

As mentioned above TGF-β plays an important role in the pathogensis and is considered as a central mediator of fibrosis. Therefore inhibition of TGF-β may be a reasonable approach to treat IPF. A Monoclonal antibody (GC 1008) that neutralizes TGF-β1, TGF-β2, and TGF-β3 has been tested in a phase I study (NCT00125385). However, results have not been published so far according to MEDLINE. An alternative approach is to block $av\beta_6$ integrin with antagonists or antibodies. Latent TGF-β is activated by $av\beta_6$ integrin [147]. Therefore inhibition of $av\beta_6$ integrin may suppress TGF-β activation. Based on data from animal models an ALK-5 kinase inhibitor, SD-208, or decorin may also offer therapeutic approaches to antagonize TGF-β [148, 149].

Blockade of Connective Tissue Growth Factor

CTGF is considered to be a downstream mediator of TGF-β (see above). An anti-CTGF antibody, FG-3019, has been evaluated in a phase I trial (NCT00074698). In this yet unpublished study FG-3019 was well tolerated and safe (FibroGen, San Francisco, USA).

Imatinib

Imatinib mesylate is a tyrosine kinase inhibitor that blocks botch the PDGF receptor and c-Abl. Animal studies demonstrated inhibition of mesenchymal cell proliferation [150, 151]. This led to a phase II/III study. Daniels and colleagues performed a placebo controlled double blind study with 119 IPF patients over 96 weeks [152]. In that study imatinib had no significant effect on change of FVC or DL_{CO} compared to placebo. There was also no significant difference in survival between both groups.

BIBF-1120

BIPF-1120 is an indolinone derivative that blocks VEGF receptor (VEGFR), PDGFR and FGFR kinase activity in enzymatic assays. *In vitro* it also inhibits mitogen-activated protein kinase and Akt signaling pathways in different cell types contributing to angiogenesis, endothelial cells, pericytes, and smooth muscle cells. Cell proliferation is inhibited and apoptosis is induced [153]. This may also be an attractive therapeutic approach to IPF. A phase II study is

currently investigating the effect of BIBF-1120 in IPF (NCT00514683).

All Trans Retinoic Acid

All trans retinoic acid (ATRA) has been shown to prevent lung fibrosis in animal models [154]. This may provide the rationale for a potential use in IPF. However, no study is currently registered.

Blockade of Circulating Fibroblast Precursor Cells

Phillips and co-workers showed that CD45(+) collagen I(+) CXCR4(+) (CD45(+)Col I(+)CXCR4(+)) cells are termed circulating fibrocytes that are recruited to the lungs after instillation of bleomycin in an animal model [155]. This effect is mainly mediated *via* CXCL12 and in that study antagonizing CXCL12 with an antibody attenuated pulmonary fibrosis. Therefore blocking CXCL12 may offer a potential treatment target. However, at present it is not clear whether circulating fibrocytes actually can differ into myofibroblasts.

NON PHARMACOLOGIC TREATMENT OF IPF

Oxygen Therapy

Dyspnoea has an important impact on quality of life. Oxygen therapy is advised in patients with hypoxia. However, there is no evidence that oxygen supplementation influences the quality of life and survival in patients with IPF or other ILD [156]. Polonski and co-workers compared 10 IPF patients with oxygen and 8 patients without oxygen [157]. In that study oxygen had a lowering effect on pulmonary artery pressure. At present oxygen therapy in IPF should be considered in patients with persisting hypoxaemia with a pO_2 below 7.3 kPa or below 8 kPa with clinical evidence of pulmonary hypertension.

Rehabilitation

Although rehabilitation and physical exercise have been proven useful in several diseases information on its effects in ILD is sparse. Holland and Hill performed a meta analysis that included two studies with a total of 85 patients (43 with training and 42 as control group) [158]. Physical training had no adverse effects. Improvement in 6 minute walking distance and in quality of life was seen in IPF patients. One study showed no significant effects of physical training on clinical variables or survival at six months [159]. At present physical training can be regarded as safe for patients with IPF. Short term improvement can be observed in functional exercise capacity and quality of life. However, longer-term effects are less clear.

Non Invasive Ventilation

Respiratory failure in IPF may require mechanical ventilation. However, the outcome of patients with IPF receiving invasive mechanical ventilation is poor. Rangappa and Moran retrospectively analyzed the outcome of 24 patients with IPF admitted to the ICU [160]. 19 patients were mechanically ventilated. 13 of these 19 patients had non-invasive ventilation before mechanical ventilation, and four received only non-invasive ventilation. 16 ventilated patients died. Another 6 died in the hospital and only two patients were discharged. Median survival was 16 days from ICU admission. Another retrospective study investigated 34 IPF patients with acute respiratory failure [161]. 15 patients underwent mechanical ventilation (MV) whereas 19 subjects were treated with non-invasive ventilation (NIV). Both ventilatory strategies temporarily increased oxygen supply as measured by an increased PaO2/FiO2. Overall mortality rate was 85% with 100% for invasive MV and 74% for NIV. MV does not seem to be beneficial in end-stage IFP patients. NIV may provide relief from dyspnoea and avoid aggressive approaches.

Apart from end-stage disease NIV may probably increase exercise tolerance and decrease dyspnoea. Moderno and colleagues investigated the effect of proportional assist ventilation (PAV) in 10 patients with IPF during cardiopulmonary exercise testing [162]. In that study PAV led to a lower heart rate during sub-maximal exercise compared to no support or only continous positive airway pressure (CPAP).

Lung Transplantation

Currently, the best treatment option for IPF is lung transplantation. IPF represents the largest proportion of ILF in patients listed for lung transplantation in North America (almost 20%) [163]. The 1-year and 5-year survival rates following lung transplantation for IPF are 74-79% and 40-54%, respectively [164]. There is no significant difference between single and bilateral lung transplants. The introduction of the lung allocation score in the United States in 2005 has reduced 1 year waiting-list mortality from 21% to 11% [165]. However, the optimal timing for lung transplantation in IPF patients remains uncertain. TL_{CO} seems to be a feasible parameter for prediction of survival. IPF patients with a TL_{CO} below 39% predicted should be considered for transplantation [166].

CONCLUSION

Despite increasing knowledge about underlying pathophysiologic mechanisms in IPF medical treatment is still unsatisfactory. However, with recent advances in our understanding of this disease new treatment targets have been discovered and will hopefully provide new therapeutic approaches to this fatal disease.

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