IPF management, recent advances and future directions

Dr. Sunil Sharma

Senior Resident

Department of Pulmonary Medicine

Introduction

- Idiopathic Pulmonary Fibrosis (IPF) is the most common form of interstitial lung diseases of unknown origin.
- It is associated with an extremely poor prognosis for survival in most patients.
- Life expectancy after diagnosis varies, but is on average less than 5 years.

Introduction

- The mainstay of therapy has been the use of corticosteroids with or without immunosuppressive drugs.

Chest 123 (3): 759-761 (2002).

- Therapies with anti-inflammatory drugs are associated with toxicity and do not provide objective benefit

ANTI-INFLAMMATORY AGENTS

- Anti-inflammatory therapies continue to be used despite there being little evidence of inflammation in the pathogenesis of IPF

- Although corticosteroid with or without immunosuppressive drugs were the mainstay of therapy for IPF for decades, their efficacy is unproven and toxicities are substantial .

  Am. J. Respir. Crit. Care Med. 171 (9): 939-940 (2005).

  Ann. Intern. Med.134:136-151 (2001).

- In a majority of cases of IPF, corticosteroid therapy is only partially effective, and most patients deteriorate despite therapy.

- There is no controlled trial using corticosteroids alone for the treatment of IPF

  Cochrane Database Syst. Rev. 3:CD002880 (2003).

- Any conclusive evidence supporting the use of corticosteroid therapy for the treatment of IPF is lacking

  Eur Respir. J.626:693-702 (2005).

- Given the poor prognosis of the disease and the lack of readily available alternatives and efficacious treatment, a therapeutic trial with anti-inflammatory medications is still justified

  Thorax 54:S1-S30 (1999).

- IPF respond better to therapy if they exhibit more inflammation and less fibrosis

ANTI-FIBROTIC AND ANTI-CYTOKINE AGENTS

- Trend toward using anti-fibrotic treatment, based on the concept that the disease is a fibrotic process with a lack of significant inflammation

- Anti-fibrotic drugs that interfere with or modulate further progression of lung fibrosis may have potential to improve respiratory function

Mayo Clin. Proc. 72(2):285-287 (1997)

ANTI-FIBROTIC AND ANTI-CYTOKINE AGENTS

- Anti-cytokine therapeutic strategies are directed at abrogating the activities of the targeted cytokines that have diverse regulatory activities in several processes that comprise fibrosis.

- This has been attempted by targeting one or more key steps in cytokine synthesis and binding to cognate receptors.

ANTI-FIBROTIC AND ANTI-CYTOKINE AGENTS

- The major anti-fibrotic and anti-cytokine agents that have been used in the treatment of IPF include:
  - colchicine
  - penicillamine
  - pirfenidone
  - TGF β antagonist
  - anti-tumor necrosis factor α (TNF α)
  - interferon-γ (IFN- γ) and
  - connective tissue growth factor antagonist

Expert Opin.Emerg. Drugs 10:707-727 (2005).

Colchicine

- Inhibits collagen formation from fibroblasts and may increase collagen degradation .
- Suppresses the release of alveolar macrophage–derived growth factor and fibronectin by alveolar macrophages.
- Clinical studies have not shown it to be more effective than glucocorticoids

Chest. 1993;103:101-4.

D-Penicillamine

- Inhibits collagen synthesis by interfering with collagen cross-linking.
- Suppresses T-cell function .
- Reduced fibrosis induced by radiation and bleomycin.
- Limited studies have not shown efficacy in idiopathic pulmonary fibrosis.

Semin Respir Crit Care Med. 1994;15:77-96.

Pirfenidone

- Pirfenidone is an anti-fibrotic agent that inhibits TGF- β induced collagen synthesis in vitro.
- Decreases lung fibroblast proliferation, and downregulates pro-fibrotic cytokines
- Can diminish BIPF by downregulating platelet-derived growth factor (PDGF) expression

  Am. J. Respir. Crit. Care Med.153:A403 (1996).
- In clinical trials with IPF patients, pirfenidone was able to stabilize both respiratory function and symptomology.
- A multiple center study is currently underway.

TGF- β Antagonist

- Anti-TGF- β antibodies and TGF- β soluble receptors could partially inhibit fibrosis in bleomycin model .
- Although efficient in animal models, humans could develop immune reactions against the antibodies.
- GC1008, an antibody that neutralized TGF β, is being investigated for safety in treating patients with IPF

Pulm. Pharmacol. Ther.19:Mar 3 E Pub (2006).

TNF- α Antagonist

- TNF-α has been found to be significantly elevated in BIPF.
- Anti-TNF- α antibodies and TNF- α soluble receptors could inhibit fibrosis in animal models .
- Anti-TNF- α antibodies can inhibit TNF- α -induced cytokine networks such as TGFβ, interleukin-5 (IL-5), and eosinophil recruitment in BIPF.

J. Immunol.153:4733-4741 (1994).

TNF- α Antagonist

- A clinical phase 1 trial has reported improvement of lung function after treatment with a soluble TNF- α receptor in patients with IPF.

- A phase II double-blind, parallel, placebo controlled randomized study of the efficacy and safety of a compound that blocks TNF- α in IPF patients is underway.

- This compound works by binding to TNF- α cell surface receptors, thus inhibiting the initiation of intracellular signaling

IFN- γ -1b

- IFN- γ -1b regulates both macrophage and fibroblast function.
- It down regulates molecules associated with fibrosis, inflammation, and angiogenesis.

N. Engl. J. Med. 341(17): 1302-1304 (1999).

- In addition, IFN- γ therapy reduced TGF β expression in lung biopsies from IPF patients.

IFN- γ -1b

- Prolonged survival has now been suggested in three controlled clinical trials of IFN- γ -1b in the treatment of IPF .

Chest 128:203-206 (2005).

- A phase III randomized, placebo-controlled trial studying survival outcomes in IPF with IFN- γ -1b is currently underway.

IFN- γ -1b

- Multicenter, randomized, placebo-controlled trial in IPF patients who had failed to respond to corticosteroids.

- This study showed no significant difference in the composite primary end point of progression-free survival (defined by either a decrease of at least 10% in the predicted FVC or an increase of at least 5 mm Hg in the alveolar-arterial oxygen pressure gradient at rest, or death) or the secondary outcomes of pulmonary function and quality of life.

- However, *post hoc* analysis did reveal increased survival in a subset of patients who had a baseline FVC 62% of predicted.

N Engl J Med 2004; 350:125–133

IFN- γ -1b

- Antoniou et al, reported that long-term treatment with IFN- γ -1b appeared to have a beneficial effect on survival, outcome, and predicted FVC in a well defined population of patients with mild-to-moderate IPF.

Eur Respir J 2006; 28:496–504

- Strieter et al. undertook a study assessing blood and lung biomarkers following IFN- γ -1b treatment.

- They observed that IFN- γ -1b can down-regulate molecules involved with fibrosis, inflammation, and proliferation, while up-regulating molecules associated with antiangiogenesis and antimicrobial defense.

Am J Respir Crit Care Med2004; 170:133–140

IFN- γ -1b

- Follow-up phase III trial (International Study of Survival Outcomes in Idiopathic Pulmonary Fibrosis With Interferon-γ -1b Early Intervention [INSPIRE]) was being conducted by Inter- Mune (Brisbane, CA).

- INSPIRE trial has been terminated early.

IFN- γ -1b

- Among the 826 randomized patients (including 115 deaths), there was no statistically significant difference between treatment groups for overall mortality (14.5% in the Actimmune (InterMune) group as compared to 12.7% in the placebo group).

- This overall survival result crossed their redefined stopping boundary for lack of benefit of Actimmune relative to placebo.

Connective Tissue Growth Factor Antagonist (Anti-CTGF)

- CTGF has a crucial role in the IPF pathway by triggering the production of collagen and fibronectin, which causes fibrotic lesion development.

- Human monoclonal antibodies that neutralize the activity of CTGF and modulate fibrosis in lung and kidney have been developed.

Connective Tissue Growth Factor Antagonist (Anti-CTGF)

- An open label, phase 1, safety and tolerability dose-escalating study of FG-3019, a therapeutic antibody designed to block the profibrotic activity of CTGF, has been recently completed in patients with mild-to moderate IPF.

- The drug was found to be safe and well tolerated.

  Expert Opin.Emerg. Drugs 10:707-727 (2005).

- A phase II trial of FG-3019 in IPF is currently underway.

Interleukin-13

- Interleukin 13 is prototypic T-helper type 2 (Th2) cytokine that is profibrotic.

- IPF-imbalance in T-helper type 1/Th2 cytokine expression, with Th2 cytokines predominating.

- In animal models IL-13 can stimulate fibroblast collagen production independently of TGF-β

J Immunol 2004; 172:4068–4076

- Study by Fichtner-Feigl et al. has shown that signaling through IL-13Rα2, originally thought to be a decoy receptor for IL-13, results in the production of TGF-β

- IL-13 can also stimulate production of FIZZ (found in inflammatory zone)-1 by airway epithelial cells.

J Immunol2004; 173:3425–3431

- FIZZ-1 can stimulate myofibroblast differentiation *in vitro*.

Am J Pathol 2004; 164:1315–1326

Interleukin-13

- Since epithelial-mesenchymal crosstalk is thought to be important for the formation of fibroblastic foci, FIZZ-1 may play a significant role in this process, downstream of IL-13.

- These data suggest that therapies targeting either IL-13 or the IL-13R α 2 receptor may be of interest.

- Study in mice has shown that a recombinant fusion protein composed of IL-13 and a derivative of pseudomonas exotoxin has efficacy in the bleomycin model of lung fibrosis.

J Immunol 2003; 171:2684–2693.

RECEPTOR ANTAGONIST

- Soluble cytokine receptors or cytokine-binding proteins that could compete with cellular receptors for any available secreted cytokine should effectively inhibit the cytokine's biological activities.

-Decorin

-Imatinib Mesylate (PDGF Receptor antagonist)

-Endothelin Receptor 1 Antagonist

Decorin

- Decorin is a small proteoglycan that binds and reduces biological activities of all isoforms of TGF β

  Biochem.J. 302:527-534 (1994).

- Aadenovirus mediated delivery of decorin cDNA has been shown to inhibit the fibrotic response.

  Am. J. Respir. Crit. Care Med. 163:770-777 (2001).

- The advantages of decorin as a potential therapeutic agent are
  - aerosol administration
  - minimal risk of immunological reactions.

Imatinib Mesylate (PDGF Receptor Antagonist)

- Imatinib mesylate inhibits activation of the PDGF receptor significantly, and reduces BM fibrosis in humans.

Eur. J. Cancer. 38(Suppl.5):S28-S36 (2002).

- A phase II randomized, double blind, placebo-controlled study of the clinical effects of imatinib mesylate given orally to patients with IPF has been completed.

- The efficacy of the biological agent has been encouraging , but susceptibility to infections has been a major concern.

Endothelin Receptor 1 Antagonist

- The endothelial cell-derived endothelin-1 (ET-1) is a potent mitogen for endothelial cells and vascular smooth muscle cells.

- ET-1 is strongly upregulated in IPF lungs and is expressed by epithelial cells.

- Studies have suggested that inhibition of this mediator could have anti-fibrotic effect .

- ET-1 and its receptors act as angiogenic regulators, representing a new target for anti-angiogenic therapy

Am. J. Pathol. 157:1703-1711 (2000).

- Bosentan, a non-selective ET A and B receptor antagonist, is being studied in a multi-center phase II/III study in IPF patients.

INHIBITION OF SIGNAL TRANSDUCTION

- Smad 7 is a major inhibitory regulator
- TGF β regulates tissue remodeling by expression of its intracellular signaling molecule Smad 3 and 7 which is down regulated during the process of lung fibrosis.
- Over expression of both Smad 7 and IL-7 antagonize TGF β signaling and attenuate fibrosis in BIPF in mice

J. Clin. Invest. 104:5-11 (1999).

- Thus, it may be possible to modulate the intracellular signaling pathway of TGF- β.

ANTI-APOPTOSIS

- Current evidence suggests that increased and continuous epithelial cell apoptosis, and decreased fibroblast/myofibroblast apoptosis occurred in the process of PF

- Myofibroblasts from patients with fibrotic lung disease secrete soluble factors (angiotensin peptides) that induce apoptosis of human AEC.

- Myofibroblast induced epithelial cell apoptosis via an oxidant-mediated mechanism may promote
  - epithelial injury,
  - aberrant repair responses, and
  - progressive fibrosis

FASEB J.19:854-856 (2005).

- Animal studies have shown that administration of amiodarone induces both apoptosis of AEC and lung fibrosis

- This effect may be inhibited by captopril (angiotensin converting enzyme inhibitor)

Am. J. Physiol., Lung Cell. Mol. Physiol. 279:L143-L151 (2000).

- Although the mechanisms of AEC apoptosis in PF are not completely understood, the roles of several molecules have been suggested, including
  - Fas activation,
  - Angiotensin pathways,
  - Activation of T cell-derived perforin and IL-13 stimulation,
  - Activation of TGF-β

J. Clin. Pathol. 57:1292-1298 (2004).

Induce Apoptosis in Fibroblasts

- HMG-CoA reductase inhibitors (statins) induce apoptosis in normal and fibrotic lung fibroblasts.

- Anti-fibrotic effect of statins is related to their ability to inhibit the expression of CTGF.

Am. J. Respir. Crit. Care Med.169:A706 (2004).

ANTIANGIOGENESIS

- Heterogeneity in vascularization in IPF may, on the one hand support fibroproliferation, and on the other hand, inhibit normal repair mechanisms.

- If neovascularization plays a key role in abnormal matrix remodeling, therapy directed at either inhibition of angiogenic or augmentation of angiostatic CXC chemokines could be helpful in IPF.

  Am. J. Respir. Crit. Care Med. 170:207 (2004).

- An imbalance in the levels of angiogenic chemokines as compared with angiostatic chemokines favoring net angiogenesis has been demonstrated with IPF .

  J. Immunol. 159:1437Y1443 (1997).

- An increase in an angiostatic chemokine (IFN-inducible T-cell α chemoattractant/CXCL11) is seen in bronchial biopsies after IFN-γ 1b treatment.

- Increased levels of the angiogenic IL-18 have been found in bronchoalveolar lavage fluid (BALF) samples from IPF patients

Sarcoidosis Vasc. Diffuse Lung Dis.21:105-110 (2004).

- Thus, therapy directed at attenuation of angiogenic or enhancement of angiostatic CXC chemokines might present a novel therapeutic option for the treatment of IPF .

MATRIX METALLOPROTEINASES (MMPS) INHIBITOR

- Both intra-alveolar and interstitial fibroblasts secrete ECM proteins, including collagens, fibronectin, elastic fibers and proteoglycans.

- IPF is characterized by an excessive amount of collagen deposited in the lung. IPF fibroblasts produce a number of ECM protein and integrin molecules.

- Abundant Col-1 can be identified in areas of mature fibrosis, while Col-III is detected in areas of early fibrosis.

Thorax 36:645-653 (1981).

- Matrix metalloproteinases (MMPs) have been implicated in the remodeling of ECM.

- The control of MMPs is achieved by tissue inhibitors of metalloproteinases (TIMPs).

- Higher expression of TIMP compared with MMPs in IPF patients.

  Am. J. Physiol. 279:L562-L574 (2000).

- An imbalance between MMPs and their inhibitors seems to play an important role in remodeling the ECM during fibrotic process .

- **Batimastal** (BB-94), a synthetic inhibitor of MMPs, has been shown to significantly reduce lung fibrosis in an animal model.

  Am. J. Respir. Cell Mol. Biol. 28:12-24 (2003).

- **Relaxin** alone or in combination with IFN-γ reduces collagen synthesis by scleroderma-derived fibroblasts.

- A randomized, double-blind, placebo-controlled trial has been performed in patients with systemic sclerosis.

  Ann. Intern. Med. 132:871-879 (2000).

- A combination of MMP inhibitors and anti-fibrotic agents may help to reduce fibrosis.

ANTIOXIDANT AGENTS

- **N-acetyl Cystine (NAC)**
- **Nitric Oxide Synthase Inhibitors (Aminoguanidine)**
- **Cysteine Pro-drugs**

N-acetyl Cystine (NAC)

- NAC, a derivative of the cysteine amino acid, has been demonstrated to augment the synthesis of anti-oxidant glutathione (GSH).

  N. Engl. J. Med. 353:2285-2287 (2005).

- GSH plays an important role as a defense mechanism against intra and extracellular oxidative stress.

- It scavenges free radicals and contributes to the reduction of hydrogen peroxide and lipid hyperoxide.

- IPF is characterized by GSH deficiency .

- A phase III multiple center, randomized, double-blind, placebo controlled trial was designed to examine the efficacy of NAC in IPF

N. Engl. J. Med.353:2229-2242 (2005).

- NAC slowed the deterioration of forced vital capacity and diffusion capacity after 1 year to a statistically significant extent.
- There was a high dropout rate in both arms and there was no difference in mortality.
- There was a significant reduction in bone marrow toxicity in the NAC group.
- This suggests that NAC may confer protection from the toxic side effects of azathioprine.

Nitric Oxide Synthase Inhibitors (Aminoguanidine)

- Activated macrophages produce both nitric oxide (NO) and peroxynitrite, contributing to the cellular injury mediated by ROS.

- High level of NO exists in BALF, and over-expression of inducible nitric oxide synthase (iNOS) also exists in BIPF in animal models .

- The combined treatment of taurine and niacin significantly reduces lung fibrosis in animal models and blocks the production of NO in BALF.

Nitric Oxide 4:399-411 (2000).

- Strategy which minimizes the production of abnormal levels of NO could be promising.

- Aminoguanidine, a specific inhibitor of iNOS, abrogated BIPF in mice without systemic toxicity.

Cysteine Pro-drugs

- The depletion of GSH in IPF patients may place the alveolar space at increased risk of additional injury caused by ROS.
- Since exogenous administration of GSH is relatively ineffective and toxic, cysteine pro-drugs have been used to achieve this goal.
- A new cysteine pro-drug, Z2196 (2RS, 4R-2-methylthiazolidine carboxylic acid), attenuated BIPF successfully, providing readily bioavailability of cysteine

Am. J. Respir. Crit. Care Med. 162:1561-1568 (2000).

TISSUE-RE-GENERATOR

- The procoagulant/fibrinolytic balance in the broncheoalveolar space is important in the lung repair process, and AEC are key contributors to that balance.

- Recently, there has been focus on the role of HGF in the lung repair process.

- HGF is a multipotent growth factor produced by pulmonary fibroblasts that stimulates the migration and morphogenesis of various epithelial cells, and has an antiapoptotic effect on alveolar and bronchial cells .

- HGF plays an important role in regulating the growth of lung epithelium, and in regeneration of the lung as a paracrine or endocrine factor in lung injury and fibrosis

- in vivo studies have shown that either continuous systemic injection or intratracheal administration of recombinant human HGF (rhHGF) attenuated lung fibrosis in BIPF in animal models

Am. J. Respir. Crit. Care Med. 162:2302-2307 (2000).

- From the therapeutic point of view, because HGF has both antiapoptotic and fibrinolytic potential, it is one of the ideal therapeutic agents for lung fibrosis .

- HGF gene therapy would be ideal from the clinical point of view

Lab. Invest. 84:836-844 (2004).

FIBROBLAST DIFFERENTIATION INHIBITORS

- Myofibroblasts arise from the differentiation of fibroblasts under the effect of TGF- β, PDGF, and other fibrogenic cytokines.

- Role of the phosphatase and tensin homolog (PTEN) which is mutated in multiple advanced cancers is being studied in the lung repair process.

- PTEN inhibits cell proliferation and induces apoptosis.

Cell 95:29-39 (1998).

- PTEN expression is downregulated in fibroblasts isolated from IPF patients.

- There is an inverse correlation between PTEN and α -SMA expression in fibroblast foci of lung tissue from IPF patients.

- PTEN inhibition increases α -SMA expression both in fibroblasts in vitro and PF in vivo.

- Inhibition or loss of PTEN is both necessary and sufficient to induce myofibroblast differentiation, including proliferation, α -SMA expression, and collagen production.

- Reconstitution of PTEN into PTEN knocked-out cells inhibits myofibroblast differentiation,whereas the overexpression of PTEN suppresses any myofibroblast differentiation that may be induced by TGFβ .

- These results suggest that PTEN may play a crucial role in myofibroblast differentiation both in vitro and in vivo.

Am. J. Respir. Crit. Care Med. 173:5-6 (2006).

- Therefore, from the therapeutic point of view, targeting PTEN may well prove to be a novel treatment strategy for IPF.

Anticoagulants

- In 2005, Kubo et al published the results of a nonblinded, randomized trial of 56 patients with IPF administered prednisolone alone or prednisolone plus anticoagulation (oral warfarin for outpatients or low-molecular-weight heparin for hospitalized patients).

Chest 2005; 128:1475–1482

- They reported a significant increase in survival in the anticoagulant group, with 63% survival at 3 years in the anticoagulant group vs 35% in the nonanticoagulant group.

- Both groups had a comparable incidence of acute exacerbations, but mortality associated with acute exacerbation was lower in the anticoagulant group (18% vs 71%).

- Increased local procoagulant activity is a characteristic feature of IPF , with extravascular generation of tissue factor, factor VIIa, factor Xa, and thrombin.

- These coagulation factors can all exert cellular effects through the activation of proteinase-activated receptors (PARs), particularly PAR1.

- Expression of this receptor is increased in IPF

Am JPathol 2005; 166:1353–1365

- And in patients with pulmonary fibrosis associated with scleroderma.

Am J Physiol Lung Cell MolPhysiol 2005; 288:L190–L201

- PAR1 activation on lung fibroblasts up-regulates PDGF, CTGF,and procollagen expression and drives myofibroblast

- These data suggest that activation of the coagulation system (an early event in lung injury and maintained in fibrosis) can link to many of the profibrotic mechanisms described and may also be relevant in terms of the beneficial effects observed with anticoagulant therapy reported by Kubo et al.

Proc Am Thorac Soc 2006; 3:389–393

- phase I clinical trials are underway in Germany to assess the effects of inhaled heparin in patients with IPF

- Given the central role of PAR1 in transducing the proinflammatory and profibrotic effects of several coagulation proteinases, the development of PAR1 receptor antagonists will be of considerable interest.

Role of stem cell

- Endogenous tissue stem cells are undifferentiated cells that reside in tissues and participate in regeneration after injury.
- The adult lung is a vital and complex organ that normally turns over slowly.
- Injury models have suggested that different regions of the respiratory system are derived from diverse stem or progenitor cells, with differing strategies for maintenance and repair.

Role of stem cell

- Studies have suggested potential lung tissue derivation from extrapulmonary BM-derived stem cells.
- Endothelial, epithelial and mesenchymal elements, contribute to repair and regeneration in response to injury.
- These cells proliferate from endogenous reparative cells of normal lung resident cells or may be derived from BM-derived progenitors.

- A key element in repair is vasculogenesis, and the proliferation of surviving endothelial cells at the sites of injury.

- The presence of BM-derived circulating stem/reparative cells also has been shown to play a role in vasculogenesis in tissue repair and remodeling.

EMBO J. 18:3964-3972 (1999).

- Fibroblasts/myofibroblasts are considered to be key contributors of pulmonary fibrosis.

THERAPEUTIC POTENTIAL OF STEM CELLS IN LUNG DISEASES

Possible intervention is to

- Block Bone Marrow-derived Fibroblast Recruitment
- Use of Stem Cells for Cellular Therapy in Lung Injury

Non pharmacological approach

- **Lung transplant**
- **Supplemental Oxygen**
- **Pulmonary Rehabilitation**

LUNG TRANSPLANT

- Lung transplant remains the only therapeutic intervention of proven benefit in IPF.

- Transplant has been reserved for patients at the advanced stages of IPF and the 5-year survival data approach 50 percent.

- Many patients show improvement with single lung transplantation

  FASEB J. 15:2215-2224 (2001).

- This procedure can prolong life and may improve the quality of the patient's life.

- However, many patients die because of the shortage of donated organs, rejection, infections, other complications, and the high cost associated with organ transplant.

Supplemental Oxygen

- Patients with hypoxemia (PaO_2 less than 55 mmHg or SpO_2 less than 88 percent) at rest or during exercise can be managed with supplemental oxygen.

- In patients with COPD, supplemental oxygen relieves exercise-induced hypoxemia and improves exercise performance.

- In one study that examined QOL in IPF patients, no difference was found between patients receiving supplemental oxygen compared to those who were not receiving oxygen.

pulmonary rehabilitation

- Patients with IPF should be encouraged to enroll in pulmonary rehabilitation programs.

- Although not yet shown to be effective in the IPF population, recent evidence suggests the possibility of benefit from a tailored exercise program.

- Overall quality of life is impaired in IPF, with specific defects in areas of physical health and perceived social independence.

- Therefore, it has been suggested that pulmonary rehabilitation programs for IPF be designed to include education and psychosocial support elements with the goal of improving coping skills affecting a better quality of life.

Conclusion

- Conventional treatment of IPF with corticosteroids and immunosuppressive agents has unproven benefit and significant side effects.

- As the understanding about the pathogenesis of IPF has increased, it has led to identification of new therapeutic approaches.

- Profibrotic growth factors and cytokines seem to be important intermediaries in driving disease progression, and consequently, modulating their activity seems to be an attractive approach.

- Several agents with antifibrotic, immunomodulatory, or antioxidant properties are now being evaluated in randomized, controlled trials of patients who have IPF.

Conclusion

- IFN γ-1b has shown evidence that it may prolong survival in patients who have IPF, particularly among those with more preserved lung function .

- N-acetylcysteine stabilized the decline in lung function as compared with placebo, although it did not prolong survival.

- Other agents including bosentan, pirfenidone, etanercept, imatinib, inhaled iloprost, and FG-3019 currently are being evaluated in randomized, controlled studies.

- These studies will provide the clinical evidence necessary for identifying optimal treatment strategies

Conclusion

- New therapeutic strategies should have as a target the different pathways of pathogenesis of IPF.

- Current therapeutic approaches target at
  - apoptosis,
  - Epithelial replacement,
  - procoagulant activity,
  - growth factors production,
  - fibroblasts/myofibroblasts,
  - angiogenesis,
  - Th1 and Th2 cytokines and
  - oxidative stress.

- The emergence of pioneering technologies, such as DNA microarrays, could provide us with novel pathogenetic insights and identify potential therapeutic targets in a disease for which therapy is still elusive and ineffective.

Respir Res 2004;5:26.

A suggested algorithm for treatment and follow up for idiopathic pulmonary fibrosis