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Review Article

Pharmacotherapy in idiopathic pulmonary fibrosis

Gaurav Acharya[1], Sunil Arya[2], Shivani Badal[3], Dewesh Kumar[4]*, Saurabh Samdariya[5]

[1]Department of Anesthesiology, Mahatma Gandhi Memorial Medical College & MY Hospital, Indore, Madhya Pradesh, India, [2]Department of Pediatrics, Mahatma Gandhi Memorial Medical College & MY Hospital, Indore, Madhya Pradesh, India, [3]Department of Obstetrics and Gynecology, Regional Institute of Medical Science, Imphal, Manipur, India, [4]Department of Community and Family Medicine, AIIMS, Jodhpur, Rajasthan, India, [5]Department of Radiation Oncology, AIIMS, Jodhpur, Rajasthan, India

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***Correspondence to:**
Dr. Dewesh Kumar,
Email: dr.dewesh@gmail.com

ABSTRACT

Idiopathic pulmonary fibrosis or cryptogenic fibrosing alveolitis is a form of chronic, progressive interstitial lung disease causing scarring of lung tissue and usually affect adults. Treatment is usually aimed at controlling inflammation and thus slowing the process of fibrosis. With only few patients responding to treatment and the disease being ultimately fatal with poor progression, the underlying lesion was considered to be fibrotic rather than inflammatory. Fibrotic foci, deposition of collagen, and lack of inflammatory cells are a predominant finding. Pirfenidone and N-acetyl cysteine are the only effective pharmacotherapy available till date. Interim results of PANTHER Trial clearly indicate more risk with triple therapy. However, in Indian patients, trial of steroid therapy may be tried when there is doubt of chronic hypersensitivity pneumonitis. BIBF 1120 has also shown positive results in Phase II clinical trial and shows a positive response in deteriorating lung function. Supplemental oxygen, education of patient, pulmonary rehabilitation, and *Streptococcus pneumoniae* and influenza vaccine are the most important supportive care. Pulmonary rehabilitation should be used as a treatment in the majority of patients.

Keywords: Idiopathic pulmonary fibrosis, Pirfenidone, N-acetyl cysteine, Interstitial lung disease

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) or cryptogenic fibrosing alveolitis is a form of chronic, progressive interstitial lung disease causing scarring of lung tissue and usually affect adults. Treatment is usually aimed at controlling inflammation and thus slowing the process of fibrosis. With only few patients responding to treatment and the disease being ultimately fatal with poor progression, the underlying lesion was considered to be fibrotic rather than inflammatory.[1] Fibrotic foci, deposition of collagen, and lack of inflammatory cells are a predominant finding.[2]

PHARMACOLOGICAL INTERVENTIONS

Pirfenidone

This novel drug is the latest area of research as anti-fibrotic agent. Pirfenidone (5-methyl-1-phenyl-2-(1H)-pyridone) inhibits transforming growth factor beta stimulated collagen deposition, causes a reduction in extracellular matrix, and blocks the proliferation of fibroblast.

The CAPACITY (clinical studies assessing pirfenidone in IPF: research of efficacy and safety outcome) Program was designed to confirm the effect of pirfenidone on lung function.[3] In 2008, Japanese Ministry of Health, Labor, and Welfare approved use of pirfenidone for management of IPF and in 2011, European Commission approved its use for mild to moderate IPF.[4] As measured by change in forced vital capacity (FVC), use of pifnidone has not been approved by FDA due to lack of efficacy and survival benefits[5] and has demanded a Phase III clinical study ASCEND (NCT01366209) currently underway in USA. The most common side effect includes rash, photo sensitivity, dyspepsia, abdominal pain, nausea, anorexia, fatigue and lethargy, diarrhea, constipation, itching, dryness, and hyper pigmentation of the skin, headache, and weakness.

N-acetyl cysteine (NAC)

It is an anti-oxidant agent and precursor of glutathione. It restores depleted levels of glutathione, thus preventing lung injury from excessive production of oxidants. This theory is supported by low levels of glutathione in bronchoalveolar lavage fluid.

IPF International Group Exploring NAC I Annual Trial, in which azathioprine/NAC was compared to azathiprine/prednisolone/placebo, has shown a lower rate of fall in vital capacity and single breath carbon monoxide diffusion capacity (DLCO) in favor of NAC group, thus helping the treatment.[6] However, there is no significant difference in type or severity of adverse effect and mortality.

The multicenter PANTHER Trial (prednisolone, azathioprine and NAC: a study that evaluates response in IPF) has shown that triple therapy should not be used.[7] However study is ongoing between mono therapy with NAC and placebo.

Tyrosine kinase inhibitor

Activation of various signaling pathway by several tyrosine kinase receptors in IPF has been shown to cause fibrosis. Inhibition of these receptors helps in slowing the progression of IPF.

Imatinib is a tyrosine kinase inhibitor that is being used in IPF. It acts against platelet derived growth factor receptor (PDGFRs) and has shown to have no effect on lung function and survival of the patient.[8]

BIBF 1120 (Nintedanib)

It is a potent inhibitor of vascular endothelial growth factor receptor, PDGFR, and basic fibroblast growth factor receptor. BBIF 1120 was used for treatment of IPF in Phase II trial to improve pulmonary fibrosis with BBIF 20 (8). BBIF 20 showed a significant effect on lung function decline compared to placebo. Total lung capacity was preserved, annual rate of lung function decline was reduced, and patient showing significant reduction in FVC were also less.

Sildenafil (phoshodiesterase 5 inhibitor)

Being a potent vasodilator, it increases the blood flow to a healthy part of the lung in patients with advanced IPF, thus improving gas exchange. Sildenafil was tested against placebo in sildenafil trial of exercise performance in IPF.[9] There was improvement in dyspnea and quality-of-life especially in patient with right ventricular systolic dysfunction.

Anticoagulation

Use of anticoagulation on prophylactic and therapeutic basis has shown to ameliorate fibrosis. Efficacy of warfarin was tested in Anticoagulant Effectiveness in IPF Trial, which showed increased mortality. At present, nebulized heparin is under trial.

Gastroesophageal reflux (GER) and microaspiration

GER is an important risk factor to IPF and is found in 90% of patients with IPF. Use of antireflux medications has shown a decrease in fibrosis score on chest computed tomography. These medications are independent predictors of lower mortality.[10]

NON PHARMACOLOGICAL INTERVENTION

Supportive care

Supplemental oxygen, education of patient, pulmonary rehabilitation, and *Streptococcus pneumoniae* and Influenza vaccine are the most important supportive care. Pulmonary rehabilitation should be used as a treatment in the majority of patients as advised by ATS/ERS/JRS/ALAT official statement on IPF 2011.[11]

To get maximum physiological benefit, high intensity exercise, i.e., more than 60% maximum work rate should be done for at least 20 sessions 3 times a week.

Stem cell therapy

Autologous adipose stem cells are instilled into both lower lobes of the lung via the bronchoscope. No serious side effects and an improvement of FVC were observed in Phase I trial.[12]

Lung transplant

Lung transplant is most frequently done for IPF and is the second most common cause of transplant after chronic obstructive pulmonary disease. Transplant is done in patients with usual interstitial pneumonia and any of the following:[13]

- DLCO ≤39% of the predicted
- ≥10% decrement in FVC over last 6 months
- SpO_2 <88% during MWT
- HRCT shows honey combing (fibrosis score >2).

CONCLUSION

Pirfenidone and NAC are the only effective pharmacotherapy available till date. Interim results of PANTHER Trial clearly indicate more risk with triple therapy. However, in Indian patients, trial of steroid therapy may be tried when there is doubt of chronic hypersensitivity pneumonitis. BIBF 1120 has also shown positive results in Phase II clinical trial and shows a positive response in deteriorating lung function.

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