Review Article

Ambroxol hydrochloride in the management of idiopathic pulmonary fibrosis: Clinical trials are the need of the hour

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is a debilitating lung disease of unknown etiology. Its pathogenesis remains poorly elucidated but aberrant wound healing is central to its pathology. It has a median survival time of 3 to 5 years. None of the treatment modality or drugs tried in its management has so far changed the overall outcome. Recent *in vitro* and experimental studies have shown that ambroxol hydrochloride exerts several newer actions, namely the surfactant stimulatory, anti-imflammatory and anti-oxidant actions, in addition to its being a secrrtolytic and mucokinetic agent. The anti inflammatory and anti-fibrotic properties of the drug are due to its ability to block the release of oxidant stress markers, cytokines, leukotrienes, MPO activity, hydroxyproline content, nitic oxide and/or collagen I & III mRNA in the local milieu while preserving the SOD and GSH-PX activities. In human studies also, the agent was able to block the expression of TGF-beta and TNF-alpha in plasma and preserving the carbon monoxide diffusion capacity of the lungs in lung cancer patients on radiation therapy. Thus, ambroxol may have the potential to check the dysregulated healing process that is typical of IPF. This, coupled with its safety profile for human use, warrants clinical trials of the drug in the management of IPF.

KEY WORDS: IPF, Ambroxol, aberrant wound healing

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INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a debilitating lung disease of unknown etiology. Clinical manifestations of the disease include persistent dry cough and shortness of breath on exertion. The symptoms of the disease limit the physical activity and reduce the patient's quality-of-life (QoL). The course of the disease is variable and is difficult to predict, but it is generally a progressive deterioration with a median survival time of 3-5 years.[1] Acute exacerbations may occur in some patients and are often fatal. Its pathogenesis remains poorly elucidated and controversial and none of the treatment modality or drugs tried in its management has so far convincingly changed the outcome of the disease.

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This short clinical commentary is an attempt to briefly overview the existing literature on the pathogenesis and therapy of IPF and to discuss a possible role for ambroxol hydrochloride in its management.

PATHOGENESIS OF IPF

Wilson and Wynn[2] have reviewed the pathogenesis of IPF. A three phase model of wound repair has been put forward namely (1) injury; (2) inflammation; and (3) repair. Dysregulation at one or more of these phases is considered at the center stage of the disease process. According to this theory, chronic inflammation can lead to an imbalance in the production of chemokines, cytokines and growth factors and disrupt cellular recruitment. These changes coupled with excessive pro-fibrotic interleukin-13 and/or transforming growth factor-β1 (TGF-β1) production can turn a well-controlled healing response into a pathogenic fibrotic response. However, it is now being increasingly realized that IPF can't be entirely explained on the basis of this simple paradigm of injury, inflammation and repair.

King *et al*.[3] have recently reviewed the pathogenesis of IPF. Accordingly, the disease is being described as a

heterogeneous pathological process of multi-factorial origin and is the outcome of an aberrant wound healing, i.e., an increase in the number of fibroblasts and myofibroblasts. This change occurs mainly through a process of epithelial mesenchymal transition[4] [Figure 1], but pericytes and mesothelial cells also act as a source for fibroblasts and myofibroblasts. Angiogenesis and vascular remodeling also contribute to the pathology.

Epithelial injury, destruction of type I alveolar epithelial cells (AECs) and aberrant activation of type II AECs occur in response to a host of environmental factors namely smoking, chronic micro-aspiration and viral infections. These environmental factors interact with genetic factors like polymorphism in the promoter region of mucin 5B gene and mutations of telomerase and result into an increased secretion of mediators such as platelet-derived growth factor, TGF-β1, tumor necrosis factor-α (TNF-α), endothelin-1 and matrix metalloproteinases (MMPs) in the local milieu. These mediators in turn initiate and perpetuate the process of inflammation and scarring.

THERAPEUTIC STRATEGIES FOR IPF

The recent clinical trials in the management of IPF can be summarized as under:

Prednisone, azathioprine and N-acetylcysteine (NAC)

Patients with mild to moderate IPF were enrolled to receive either of a combination of prednisone, azathioprine and NAC, NAC alone or placebo. Change in forced vital capacity (FVC) during the following 60 week was set as the primary outcome of the study, but at the time of planned midpoint interim analysis, it was found that patients in the combination group (77 patients) had increased deaths ($P = 0.01$) and hospitalization ($P < 0.001$) without any evident physiological or clinical benefits as compared to placebo group (78 patients).[5] Accordingly, the combination therapy has been terminated prematurely, but the study is still ongoing with the remaining two groups.

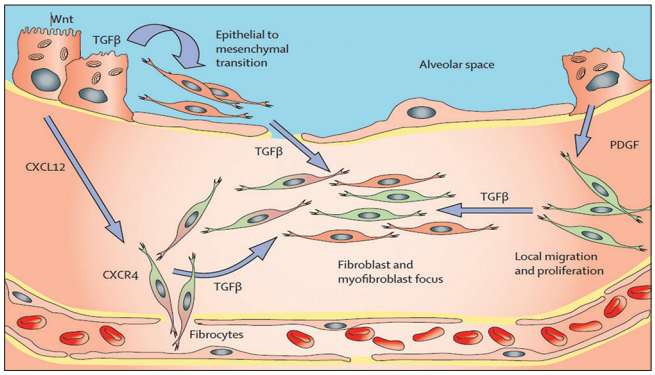

Figure 1: The process of epithelial mesenchymal transition mediated by the cytokines, chiefly transforming growth factor-beta1. The later can be checked by ambroxol (Taken from, King TE Jr, *et al.* Lancet, 2011 with permission from Elsevier)

Inhaled NAC monotherapy

A total of 100 cases with mild to moderate IPF were enrolled to assess the efficacy of inhaled NAC. Seventy six patients completed the study. Inhaled NAC did not improve the outcome of the patients in terms of FVC change at 48 weeks or other secondary variables except that there was a slowdown of FVC decrement in a subset of patients with initial FVC <95% of predicted and diffusing capacity for carbon monoxide (DLCO) <55%.[6] This study had several drawbacks in terms of study design with no double-blinding, omission of evaluating survivals and dropout rate of 24%.

Pirfenidone

Widely known as CAPACITY trial, it consisted of two studies: The 004 and the 006 trials. The 004 trial had three study groups, namely the high-dose pirfenidone, the low-dose pirfenidone and the placebo group. The 006 trial had two study groups, namely the high pirfenidone and the placebo group. Primary endpoint was the change of FVC (%) at 72 weeks. The 004 trial showed a significant decrease in decline in FVC% in the high-dose pirfenidone group as compared with the placebo group ($P = 0.001$), but the 006 trial revealed no significant difference between the two study groups ($P > 0.5$).[7]

Tyrosine kinase inhibitor

A total of 432 IPF patients were put on four different dosages of tyrosine kinase inhibitor BIBF1120 (50 mg/day, 50 mg bid, 100 mg bid and 150 mg bid) or placebo for 12 months. Primary end point was annual decrease of FVC. The BIBF1120 150 mg bid group showed a lower annual rate of decline in FVC as compared with the placebo group (0.06 L/year vs. 0.19 L/year, $P = 0.01$). The 150 mg bid group also had fewer acute exacerbations as compared with the placebo group ($P = 0.02$) and a better QoL in terms of the St. George's Respiratory Questionnaire (SGRQ) scores, but suffered a higher rate of adverse reactions and discontinuation of the drug.[8]

Bosentan

A total of 616 patients with established biopsy diagnosis of IPF but without extensive honeycombing on high-resolution computed tomography were enrolled for this study. The primary outcome of the study was a simultaneous FVC decrease of more than 10% and a decrease in DLCO or an acute exacerbation and the secondary endpoints included a health-related QoL and transition dyspnea index. The Bosentan group failed to show any advantage over the placebo.[9]

Warfarin

A total of 145 IPF patients were enrolled to receive either warfarin or placebo. Primary endpoints included deaths, admissions or time to decline in FVC of more than 10%. Since there were unexpected surplus deaths in the warfarin group (unrelated to bleeding), the study was terminated prematurely.[10]

Thalidomide

Twenty three subjects with IPF were treated with low-dose of thalidomide or placebo for 12 weeks in a crossover double-blind trial, with a washout interval of 2 weeks. Thalidomide group had better QoL in terms of decreased cough and SGRQ scores. However, this study has the limitation in terms of treatment duration of only 12 weeks and a small number of patients from a single center.[11]

Losartan

This study included 20 subjects with IPF. The primary endpoint was FVC% change after 12-months of losartan administration. Of the 17 patients who could be evaluated, 12 (71%) revealed stable (FVCs within 5% change) or improved (FVC increase of more than 5%) status. Secondary endpoints such as forced expiratory volume in the first second % change in 1 year, DLCO% change and 6-minute walk test distance (6MWD) were also stable or improved in 58%, 71% and 65%, respectively. There was no incident of commonly anticipated hypotension. This investigation has limitations as the number of patients is too small.[12]

Stem cell therapy

Twelve subjects with mild to moderate IPFs were enrolled for intratracheal instillation of autologous adipose stem cells via bronchoscope to both lower lobes of lung monthly for 3 times. This non-randomized phase 1 trial is still ongoing for safety and toxicity evaluation. According to the interim findings, both the 6MWD and FVC showed improvement and no serious side-effects such as infection, allergic reaction, acute exacerbation, institutional admission or neoplasm has been noted. Second and third phase investigations are expected based on these results.[13]

Each of the above therapeutic modality has, so far, failed to establish a definite role for itself in the management of IPF in terms of a favorable outcome and/or the safety issues. This is possibly due to the fact that none of the above pharmaceutical agents/modalities have the potential to prevent or reverse the process of aberrant wound healing, which is responsible for the typical pathology of IPF. As a result, the IPF patients are increasingly being advised symptomatic treatment or only observation.

AMBROXOL

Ambroxol hydrochloride (C_{13} H_{18} Br_2 N_2 O) is an active N-desmethyl metabolite of bromhexine hydrochloride. Deletion of a methyl group and introduction of a hydroxyl group in a para-trans position of cyclohexyl ring have enriched ambroxol to acquire several new, but important pharmacological properties namely surfactant stimulatory, anti-inflammatory, anti-oxidant and local anesthetic effects in addition to the muco-kinetic and muco-ciliary effects of the parent compound. Recognition of the surfactant stimulatory and anti-inflammatory properties of the drug has led to the resurgence of interest in the molecule in the management of difficult to treat obstructive airway disorders,[14] but experimental and human studies indicate that the drug may find a role in the management of interstitial lung diseases as well.

Experiments on neutrophils, macrophases and mast cells have now shown that the drug has antioxidant and anti-inflammatory properties as well. This is possibly due to the fact that pulmonary surfactant and inflammatory mediators share phosphatidyl choline as their substrate. In animals exposed to tobacco smoke and other toxic inhalants, ambroxol acted as free radical scavenger and was capable of protecting these animals from the oxidative stress injury.[15] Further, it decreased the lipopolysaccharide (LPS) induced synthesis of cytokines, oxygen radicals and nitric oxide in alveolar macrophages.[16,17]

In acute lung injury models, the drug was able to decrease the damage to the lungs. The drug was also able to prevent LPS induced lung hemorrhage, edema, exudation, infiltration with neutrophills and release of cytokines in animal studies.[18] More recently Zhi *et al*.[19] have shown that ambroxol was able to block paraquat induced rise in oxidant stress markers namely malondialdehyde, superoxide and myeloperoxidase (MPO), cytokines namely TNF-α, monocyte chemoattractant protein-1, TGF-β1, MMP-2 and tissue inhibitor of metalloproteinase-1, total inflammatory cell count, hydroxyproline content and collagen I and III messenger ribonucleic acid (mRNA) in rat lungs while preserving the superoxide dismutase (SOD) and glutathione system (GSH-PX) activities. Ambroxol was also able to reduce the paraquat induced lung injury, i.e., the interstitial edema, inflammatory cell infiltration in the alveolar space and septum and pulmonary fibrosis.

Human studies on ambroxol

Ambroxol has been available in the market since 1973. Since then, the drug has been administered to thousands of patients. The reported adverse reactions are low and include skin rashes, nausea, vomiting, abdominal pain and dyspepsia. Anaphylactic reactions and allergic reactions are rare. Thus, the drug is safe for human use.

Recently, Xia *et al*.[20] showed that the expression of TGF-β1, as well as TNF-α in plasma did not rise in ambroxol treated lung cancer patients on radiation therapy as compared with the controls. The DLCO was also preserved in the ambroxol treated patients. This is the first direct clinical evidence of the protective role of ambroxol in radiation induced lung injury, i.e., an interstitial lung disease.

Potential role of ambroxol in IPF

No direct clinical data are yet available to show the efficacy of ambroxol in IPF but ample *in vitro* and experimental studies are now available that show that ambroxol is capable of exerting important anti-inflammatory and anti-oxidant actions. These actions of the drug are due to its ability to block the release of several oxidant stress markers, cytokines, leukotrienes, MPO activity,

hydroxyproline content, nitric oxide and/or collagen I and III mRNA in the local milieu while preserving the SOD and GSH-PX activities.[15-19] Even in human studies, the agent was to able to block the expression of TGF-β1 and TNF-α in plasma and preserving the DLCO of the lungs in lung cancer patients on radiation therapy.[20]

From the above experimental and the limited clinical evidence of the efficacy of the drug in preventing radiation induced lung injury, an interstitial lung disease, it is being hypothesized that ambroxol has the potential to check the process of epithelial mesenchymal transition, mediated chiefly by cytokine TGF-β1 as shown in [Figure 1] and thereby to check the typical dysregulated healing process of IPF. It, coupled with its safety profile for human use, warrants clinical trials of the drug in the management of IPF either alone or in combination to other drugs. This is more urgent as no treatment modality or drugs tried in its management have, so far, changed the outcome from the disease.

The most ideal patients to be included in these clinical trials will obviously be those who have mild disease with minimal fibrosis. Primary end points for these studies may include deaths, hospitalization, changes in FVC, 6MWD and changes in DLCO. Secondary endpoints may include a health-related QoL, transition dyspnea index and adverse reactions, if any. Expression of TGF-β1 in plasma can be the best biochemical marker for these studies.

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