Journal of Palliative Care & Medicine
ISSN: 2165-7386
Rindone and Rosset, J Palliat Care Med 2014, 4:5
DOI: 10.4172/2165-7386.1000193

Research Article Open Access

The Point on N-acetylcysteine in Idiopathic Pulmonary Fibrosis Treatment

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Received date: Apr 21, 2014, **Accepted date:** Oct 16, 2014, **Published date:** Oct 26, 2014

Abstract

Idiopathic pulmonary fibrosis (IPF) is still a non-curable disease. The suggested therapy consists of Pirfenidone combined with other drugs like azathioprine, and acetylcysteine. The New England Journal of Medicine published a new study that goes against the common use of N-acetylcysteine (NAC) to treat IPF patient. There are other studies that went in favor of N-acetylcysteine. The present study reviews the entire developments and sums up the reality by affirming that new studies should be done to demonstrate whether the NAC should be administered in combination with Pirfenidone or not, as the last study did not clarify this point.

Keywords: Acetylcysteine; Idiopathic pulmonary fibrosis; Pirfenidone

Introduction

The idiopathic pulmonary fibrosis is a chronic, progressive, fibrosing interstitial pneumonia of unknown cause that mostly affects elder people. Major symptom is of this disorder is the onset of progressive worsening of dyspnea connected to the loss of lung function. This disease has a poor prognosis since the median survival is three years after the diagnosis [1-6].

Pirfenidoneis is the only drug approved worldwide to treat IPF because of its fibrosis inhibition and collagen production actions induced by TGF-beta2. It also shrinks the inflammatory process by reducing the production of TNF-alfa and IL-1beta [3-4].

However, this drug not free from side effects, mostly leading to gastrointestinal problems. The patients treated with Pirfenidone have an eight months median survival improvement: 3.8 years vs. 3 years. Efforts were on to improvise the case with other drugs. N-acetylcysteine is amucolytic agent that acts both as precursor and reduced glutathione (GSH). It is a nucleophilic scavenger and an enzyme-catalyzed antioxidant. NAC regulates many cellular functions like apoptosis, cellular growth and the production of cytokine [5-8]. In humans NAC is used in some alveolitis and to avoid Paracetamoloverdose hepatotoxic effects. Therefore, GSH has a major role as a protector of biological structures and functions [9].

Overall, the anti-inflammatory action of NAC is well documented *in vitro* as well as *in vivo*.

Materials and Methods

The research had been conducted using PubMed library database. We have decided to refer: IPF [All Fields] AND ("acetylcysteine" [MeSH Terms] OR "acetylcysteine" [All Fields]) (49 results) that has included the research outcome of the other researches. We have not taken the Clinical cases into account and have considered the entire research data updated up to 26th September 2014.

The studies

Since 1990 IPF was linked to GSH deficiency in respiratory-tract. That was supposed to create a favorable environment for excessive fibroblast proliferation as demonstrated in bronchoalveolar lavage fluid (BAL) or calf serum (CS) cells in vitro [10].

A 1995 study on the glutathione deficiency observed lung epithelial lining fluid (ELF) and discussed the effects of intravenous NAC on lung glutathione levels in IPF. The Glutathione levels have significantly increased in bronchoalveolar lavage fluid (BALF) and ELF levels. The study concluded that it is possible and safe to improve lung glutathione levels among IPF patients with the help of antioxidant protection as there were no side effects [11].

Studying human fetal lung fibroblasts (HFL-1) Sugiura et al. proved that NAC can affect the TGF-betainvolved in IPF tissue by remodeling or fibrotic processes. TGF beta modulation abolished gel contraction in vitro, and regulated the production of fibronectin and VEGF as important mediators of tissue repair and remodeling [12].

TGF-beta1also induces alveolar epithelial-mesenchymal transition (EMT) on rat epithelial cell line (RLE-6TN) and in primary rat alveolar epithelial cells (AEC). NAC inhibits EMT and their changing into fibroblast-like morphology cells in vitro [12].

The NAC dose-dependent inhibitory effect on the expression of interleukin-8 (IL-8), matrix metalloproteinase-9 (MMP-9) and intercellular cell adhesion molecule-1 (ICAM-1) was demonstrated on bronchoalveolar lavage (BAL) cells of patients with IPF or sarcoidosis [13]. Cu A et al. demonstrated the effects of NAC onalveolar macrophages contained in BAL of IPF affected patient's culture in vitro. These cells were inhibited in their production of TNF-alpha, sTNFR, and TGF-beta1 and their pro-fibrotic and pro-inflammatory actions [14].

N-acetylcysteine could also alleviate the IPF induced in rats by regulating the lysyl oxidase activity [15]. Another work described NOX4 reduction resulting on myofibroblast differentiation inhibition and fibroblasts migration [16]. The efficacy of NAC on p63 total

suppression in lung tissues of IPF patientsat an early phase and while dexamethasone or pirfenidone showed no effects [17].

A multicenter, randomized and controlled clinical trial was conducted to evaluate the efficacy of NAC mono therapy among patients with early stage IPF. Seventy six patients were randomly divided in two groups: the NAC treatment group and the control group (no therapy). No significant differences in the FVC change were shown but with a post hoc exploratory analysis showed that NAC therapy was associated with stability of FVC among patients with initial FVC<95% or initial diffusing capacity of carbon monoxide <55 [18,19].

Sakamoto described the correlation between the uses of combined NAC therapy. His study described the difference between the two groups: one treated with Pirfenidone and NAC and the other without NAC. After six months the median change in FVC was 0 mL in the NAC group and -290 mL in the non NAC group and talking about the median survival period was 557 ± 66 days in the NAC group and 196 ± 57 days in the non NAC group (p=0.03) [20].

IFIGENIA is a very important study that compared the regimen consisting of azathioprine, prednisone, and acetylcysteine without NAC in the IPF therapy. They showed that the first one preserved the FVC and carbon monoxide diffusing capacity better than the second [21]. This study encouraged the researchers to evaluate the effects of NAC in treating IPF compared to the three drug regimen and this study was called PANTHER (Prednisone, Azathioprine, and N-Acetylcysteine: A Study That Evaluates Response in Idiopathic Pulmonary Fibrosis). PANTHER was interrupted because it was unsafe and the study continued with the NAC monotherapy and the placebo. The recent study concluded that acetylcysteine did not preserve IPF patients' FVC and it would result in mild-to-moderate impairment in pulmonary function [22].

Conclusions

Although NAC mono therapy's effects on IPF weren't demonstrated in the only study conducted in comparison with placebo [22], the same journal published another article which demonstrated a major efficacy of the NAC combined therapy [21]. It is therefore essential to recap all these findings, as it indicates that NAC may have some beneficial effects, especially among early stage IPF patients. Discussion of these data highlights the importance of a further research in this area. Since the most important studies (IFIGENIA and PANTHER) gave us contrasting elements, an overview on N-acetylcysteine use is needed especially in the combined therapy of IPF. Nevertheless, considering the lack of differences in side effects, the common use of NAC-based therapy can be continued.

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