Contents lists available at ScienceDirect

Respiratory Investigation

journal homepage: www.elsevier.com/locate/resinv

Original article

Efficacy and safety of inhaled N-acetylcysteine in idiopathic pulmonary fibrosis: A prospective, single-arm study

Ryo Okuda, Hidekazu Matsushima, Tomohiro Oba, Rie Kawabe, Minako Matsubayashi, Masako Amano, Tomotaka Nishizawa, Koujiro Honda*

Department of Respiratory Medicine, Saitama Red Cross Hospital, 8-3-33 Kami-ochiai, Chuo-ku, Saitama 338-8553, Japan

ARTICLE INFO

Article history:
Received 10 July 2015
Received in revised form
18 September 2015
Accepted 12 October 2015
Available online 15 December 2015

Keywords:
Forced vital capacity
Idiopathic pulmonary fibrosis
Inhalation
Krebs von den Lungen-6
N-acetylcysteine

ABSTRACT

Background: Idiopathic pulmonary fibrosis (IPF) is a progressive lung disease with few treatment options. The efficacy of N-acetylcysteine in patients with IPF remains controversial. The aim of this research was to investigate the efficacy of inhaled N-acetylcysteine.

Methods: This study was designed as a single-center, single-arm, prospective clinical trial. Each patient who had IPF received 352.4 mg of inhaled N-acetylcysteine twice daily.

Results: In total, 28 patients were enrolled. The mean values of the respiratory function parameters at the initiation of therapy were as follows: forced vital capacity (FVC), 2.27 L and %FVC, 76.2%. The mean change in FVC during 26 weeks prior to the inhaled N-acetylcysteine therapy was −170 mL, a significant decrease ($p=0.019$). The mean change in FVC during 26 weeks after the initiation of inhaled N-acetylcysteine therapy was −70 mL ($p=0.06$). When the patients were classified into two groups according to the degree of decline in FVC (≥100 mL vs. <100 mL) during the 26-week period prior to the initiation of therapy, inhaled N-acetylcysteine showed a greater efficacy in attenuating FVC decline in the ≥100-mL group than in the <100-mL group.

Conclusions: Inhaled N-acetylcysteine therapy was effective in patients with mild-to-moderate IPF and was more beneficial in patients who had greater declines in FVC before the initiation of therapy. (UMIN title: Efficacy and safety of inhaled N-acetylcysteine in idiopathic pulmonary fibrosis, UMIN000016706, 2015/03/04.)

Abbreviations: IPF, idiopathic pulmonary fibrosis; FVC, forced vital capacity; VC, vital capacity; DLco, diffusion capacity of the lung for carbon monoxide; UIP, usual interstitial pneumonia; KL-6, Krebs von den Lungen-6; SP-D, surfactant protein-D

*Corresponding author. Tel.: +81 48 852 1111; fax: +81 48 852 1132.
E-mail addresses: b980013@yahoo.co.jp (R. Okuda), himatsushima@sunny.ocn.ne.jp (H. Matsushima), obatomohiro@hotmail.co.jp (T. Oba), blackberry_wine1218@yahoo.co.jp (R. Kawabe), mizu_mina@hotmail.com (M. Matsubayashi), skyfield1021@gmail.com (M. Amano), tn1230bungo@yahoo.co.jp (T. Nishizawa), hondakojiro78@gmail.com (K. Honda).

http://dx.doi.org/10.1016/j.resinv.2015.10.001

1. Introduction

Among the interstitial pneumonias, idiopathic pulmonary fibrosis (IPF) has an extremely poor prognosis, with approximately half of the patients with the disease dying within 2–3 years after diagnosis [1].

Reactive oxygen species are thought to be among the factors precipitating fibrosis in IPF. N-acetylcysteine can not only cause the direct elimination of these reactive oxyradicals, but it also can exert antifibrotic activity by inhibiting the production of inflammatory cytokines such as TNF-α and IL-1 [2,3]. In cases of severe IPF, the levels of glutathione in the lower respiratory tract are deficient, leading to an oxidation–reduction imbalance [4,5]. N-acetylcysteine also is generally recognized to have the capacity to improve this oxidation–reduction imbalance via metabolically converting itself to the antioxidant glutathione.

The change in forced vital capacity (FVC) or vital capacity (VC) currently represents a highly reliable endpoint in the treatment of IPF [6]. The IFIGENIA trial, which was published in 2005, demonstrated significant differences between a three-drug regimen (oral N-acetylcysteine 600 mg three times daily, added to a standard regimen of prednisone and azathioprine) and a standard two-drug regimen (prednisone+azathioprine), with regard to the deterioration of VC and diffusion capacity of the lung for carbon monoxide (DLco) [7]. On the other hand, in the PANTHER-IPF trial, which was published in 2014, no significant difference was observed in FVC change between the oral N-acetylcysteine group and the placebo group [8]. Thus, the efficacy of oral N-acetylcysteine therapy in patients with IPF remains controversial. In addition, a few reports have dealt with the efficacy of inhaled N-acetylcysteine therapy. Inhaled N-acetylcysteine therapy may be more effective than oral N-acetylcysteine therapy from the standpoint of ensuring that N-acetylcysteine reaches the lower respiratory tract. We conducted this study to clarify the trend of FVC change in patients with IPF who were treated with inhaled N-acetylcysteine therapy.

2. Materials and methods

2.1. Study design

This study was designed as a single-center, single-arm, prospective clinical trial and was conducted at the Saitama Red Cross Hospital in Japan. N-acetylcysteine was administered by inhalation at the dose of 352.4 mg twice daily (b.i.d.) via an ultrasonic nebulizer (NE-U22, Omron, Tokyo, Japan).

2.2. Subjects

The diagnosis of IPF and inclusion of subjects in the present study were based on the following criteria: patient age ≥ 50 years, a usual interstitial pneumonia (UIP) pattern, or possible UIP pattern on high-resolution CT in accordance with the 2011 American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association official statement on IPF [1], and the exclusion of other clinically known causes of UIP, such as drug-induced pneumonitis, collagen vascular diseases, and hypersensitivity pneumonitis. Concomitant therapy with only pirfenidone was permitted if the dose had been stable for 26 weeks before the experimental therapy. To assess the therapeutic responses in each subject, the study population comprised patients with IPF who had undergone pulmonary function tests at least 9 weeks prior to the initiation of the treatment.

The criteria for withdrawal were as follows: discontinuation of treatment by the attending physician because the therapeutic effect was insufficient or because serious adverse events occurred and the patient withdrew consent. All patients provided written informed consent for participation in the N-acetylcysteine inhalation study. The present study was approved by the institutional review board of the Saitama Red Cross Hospital (IRB number, 20130109-2; date of registration, 2013/01/16).

2.3. Efficacy and safety analysis

The primary endpoint was an absolute change in FVC at week 26 after the initiation of N-acetylcysteine therapy. We compared FVC change during the 26-week period prior to the initiation of therapy and the change during the 26 weeks after the initiation of therapy. Other assessment variables were the changes in the percentage of DLco (%DLco) and the absolute serum levels of interstitial pneumonia markers such as Krebs von den Lungen-6 (KL-6) and surfactant protein-D (SP-D). FVC, %DLco, and the serum levels of interstitial pneumonia markers were measured at 13-week intervals. Pulmonary function tests were measured with Chestac-33 (Chest, Tokyo, Japan). The frequency of acute exacerbations of IPF after the initiation of therapy also was checked. Acute exacerbation of IPF was diagnosed in accordance with the current Japanese guidelines; these included the fulfillment of all the following criteria: exclusion of overt infections and other disorders such as heart failure, pronounced dyspnea, findings of a honeycomb lung with newly appearing ground-glass opacities and infiltrates on high-resolution CT, and a decrease of ≥ 10 mmHg in the peripheral arterial oxygen tension [9].

Safety evaluation was performed by assessing the frequency of adverse events occurring from the initiation of N-acetylcysteine therapy to week 30 in terms of the system organ class and severity grade according to the Common Terminology Criteria for Adverse Events Version 4.0 [10]. Any untoward events that caused an aggravation in severity by 1 grade or more from the baseline were recorded as adverse events in this study.

2.4. Estimation of sample size

The sample size of 15 patients was calculated to provide a paired t-test, a power of 80%, alpha error probability of 0.05 by the two-side test, and an effect size of 0.8. A minimum enrollment of 20 patients with an expected withdrawal rate of 30% was required.