

Case Report

Effect of an oral β_2 -adrenoceptor agonist in a patient with idiopathic interstitial pneumonia

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ABSTRACT

A 63-year-old man was referred to our hospital because of a dry cough. His chest roentgenogram revealed ground-glass opacities and honeycomb formations bilaterally in the lower lung fields. Pulmonary function tests showed a depleted lung volume and decreased arterial oxygen tension. He was clinically diagnosed as having idiopathic interstitial pneumonia (IIP). A β_2 -adrenoceptor agonist was administered because the patient's symptoms improved after its inhalation. Following treatment with an oral β_2 -adrenoceptor agonist, the dry cough disappeared, lung function tests remained unchanged and an improvement in arterial oxygen tension was observed. Although β_2 -adrenoceptor agonist therapy does not improve disease activity or progression in patients with IIP, its use may mitigate symptoms associated with the disease.

Key words: bronchial hypersensitivity, dry cough, KL-6, lung function test, methacholine, smooth muscle.

INTRODUCTION

A proliferation of extravascular and/or extrabronchial parenchymal smooth muscle cells is one of the characteristic histologic features of idiopathic interstitial pneumonia (IIP).¹ β_2 -Adrenoceptor agonists have a preventive effect on both the contraction of smooth muscles and the proliferation of smooth muscle cells.^{2,3} We are unaware of any studies describing the clinical course of

patients with IIP during long-term treatment with a β_2 -adrenoceptor agonist. Herein, we describe a case of a patient with IIP who underwent treatment with an oral β_2 -adrenoceptor agonist for 1 year. His clinical symptoms disappeared, his respiratory function tests did not worsen and his arterial oxygen tension improved following treatment.

CLINICAL SUMMARY

A 63-year-old man was admitted to our hospital to undergo follow-up tests of an abnormal chest roentgenogram and a severe dry cough. He had worked as a cattle breeder for 48 years and, thus, frequently handled hay feed for cattle. He was a life-long non-smoker. Chest auscultation revealed fine crackles over the lower lung fields bilaterally. His chest roentgenogram and chest computed tomography (CT) scan (Fig. 1) revealed ground-glass opacities and honeycomb formations throughout the lower lung fields. Laboratory findings showed normal hematologic, hepatic and renal function and no abnormalities in serum protein electrophoresis and immunoglobulins. In particular, the patient's serum IgE concentration was normal. The serum Krebs von den Lungen-6 (KL-6) concentration was 873 U/mL (normal upper limit 500 U/mL). Autoimmune antibodies and precipitating antibodies to mold antigens were not found. Pulmonary function tests revealed a reduced total lung capacity (TLC; 3.77 L, 75% of predicted) but normal carbon monoxide diffusing capacity (carbon monoxide diffusing capacity adjusted for alveolar volume (permeability index; DL/V_A) 4.64 mL/min per mmHg per L; 101%). Arterial blood gas analysis during breathing of room air in the sitting position showed the following: pH 7.418; P_aO_2 78 mmHg; P_aCO_2 46.4 mmHg; alveolar-arterial oxygen tension difference (A_aDO_2) 16.3 mmHg. Broncho-alveolar lavage fluid (BALF) findings showed a slightly increased neutrophil ratio (5.4%) and an

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Received 29 June 2000. Accepted for publication 19 November 2000.

increased CD4/8 ratio (4.11). Microbiologic analyses of BALF ruled out the possibility of infectious diseases. Findings of transbronchial lung biopsy showed slight lymphocyte infiltration in the alveolar septa, thickened alveolar walls, no foreign body depositions, no vasculitis and no granulomas. Transbronchial bronchial biopsy demonstrated an absence of eosinophil infiltration and no goblet cell hyperplasias in the bronchial epithelium. Bronchial hypersensitivity was examined using a method developed by Takishima *et al.* (Astograph™; Chest MI, Tokyo, Japan) involving continuous methacholine inhalation with simultaneous measurement of respiratory

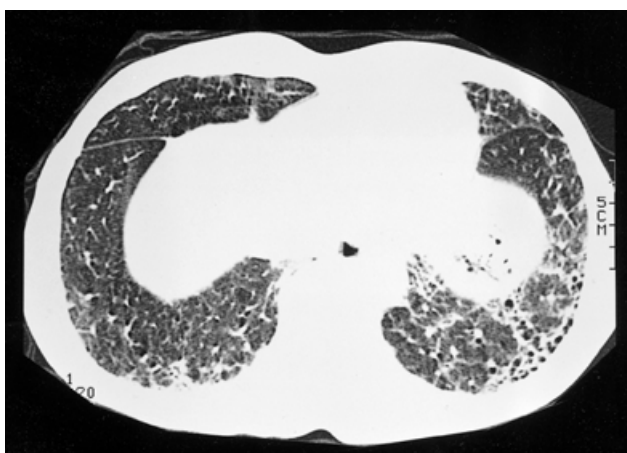


Fig. 1 Chest computed tomography scan. Note the ground-glass opacities and honeycomb formations in the lower lung fields bilaterally.

resistance (Rrs; cm H₂O/L per s). Baseline Rrs was 3.7 cm H₂O/L per s and no bronchial hypersensitivity was detected. Nevertheless, the patient's dry cough almost completely disappeared after inhalation of a β_2 -adrenoceptor agonist.

The patient was diagnosed as having IIP and underwent treatment with an oral β_2 -adrenoceptor agonist (salbutamol; 2 μ g/kg) in order to relieve the dry cough. After a follow-up period of 1 year, his dry cough had almost completely disappeared, TLC and DLV_A values were essentially the same (3.89 L (77%) and 4.62 mL/min per mmHg per L (100%), respectively) and the P_aO₂ and A_aDO₂ showed an improvement (95 and 4.1 mmHg, respectively). His serum KL-6 concentration improved to 580 U/mL, but was still above the normal upper limit.

Bronchial hypersensitivity test

To determine whether patients with IIP show bronchial hypersensitivity, we examined seven male and three female IIP patients in a study using the methacholine inhalation method. All patients approved of the study objective and all gave written informed consent to participate. The patients were all non-smokers and none had a history of corticosteroid treatment. There is a strong association between bronchial hyperresponsiveness and smoking⁴ and, thus, to exclude the influence of smoking, study participants were limited to non-smokers. The methacholine inhalation method is described below. Two-fold increasing concentrations of methacholine

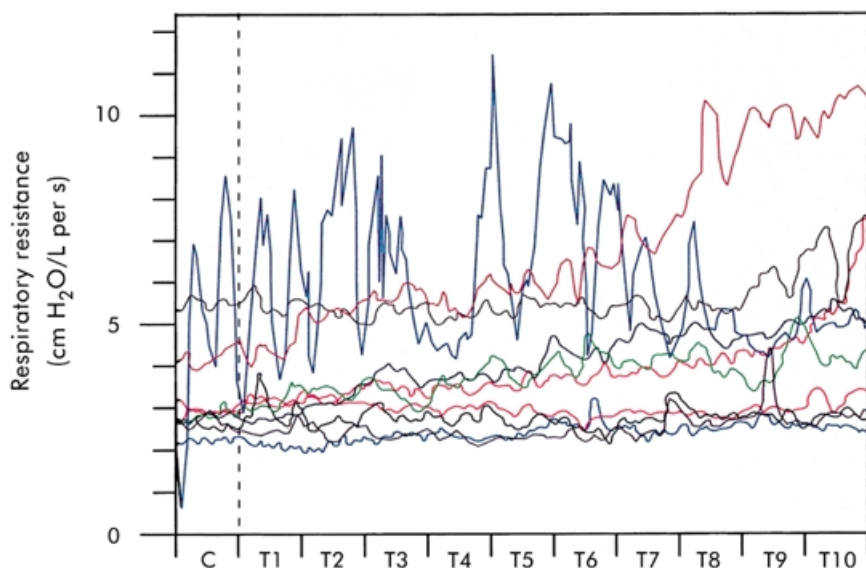


Fig. 2 Results of bronchial hypersensitivity test by continuous methacholine inhalation method. Note that none of the patients with idiopathic interstitial pneumonia showed bronchial hypersensitivity. Total methacholine concentration in 1 min inhalation (mg/mL) is as follows: T1 = 0.049, T2 = 0.098, T3 = 0.195, T4 = 0.391, T5 = 0.781, T6 = 1.56, T7 = 3.13, T8 = 6.25, T9 = 12.5 and T10 = 25.0. C, 0.9% NaCl inhalation; T, methacholine inhalation.

chloride diluted in physiologic saline, from 0.049 to 25 mg/mL, were inhaled from Bird micronebulizers (Bird Corp., Palm Springs, CA, USA) with an output of 0.15 mL/min. The particle size ranged from 0.5 to 4.0 μ m. The Rrs was measured by 3 Hz forced-oscillation method. After recording baseline Rrs (physiologic saline inhalation), methacholine was inhaled sequentially at 1 min. intervals. Respiratory conductance (Grs; the reciprocal of Rrs) was plotted and the cumulative dose of methacholine that decreased Grs to 65% of the baseline level was obtained as PD₃₅Grs from each dose-response curve. This parameter was measured in terms of a unit defined as 1 min inhalation of methacholine. Mean (\pm SEM) baseline Rrs was 3.6 ± 0.4 cm H₂O/L per s and none of the patients showed bronchial hypersensitivity (Fig. 2).

DISCUSSION

Because no standard treatment has yet been established for IIP, it is difficult for clinicians to select the appropriate timing of treatment and therapeutic approach, especially during the early stages of disease progression. In the present case, after 1 year of treatment with a β_2 -adrenoceptor agonist, the clinical symptoms disappeared, the respiratory function tests were unchanged and an improvement in arterial oxygen tension was observed. However, we could not discontinue and restart β_2 -adrenoceptor agonist treatment at the appropriate time to clarify its effectiveness. Because the patient underwent treatment for only 1 year, a longer observation period and a control study with and without the administration of a β_2 -adrenoceptor agonist is needed to clarify the efficacy of this drug and its possible contribution to the prognosis of patients with IIP. The present IIP patient was believed to be in a stable condition based on the respiratory function tests and roentgenographic findings. None of the clinical parameters improved completely in response to treatment with the β_2 -adrenoceptor agonist. Treatment with a β_2 -adrenoceptor agonist does improve clinical symptoms in patients with IIP, but cannot be concluded to have a positive impact on disease activity and progression.

A diagnosis of chronic farmer's lung disease was attractive given that the patient had worked as a farmer for 48 years. However, a negative precipitin reaction to

mold antigens and a lack of improvement in chest roentgenogram findings, despite the fact that the patient had been hospitalized for approximately 1 month and, thus, not exposed to mold and hay antigens suggested that this diagnosis was unlikely. An absence of eosinophilia in the peripheral blood and BALF, a normal serum IgE titer, no bronchial hypersensitivity to methacholine and bronchial biopsy specimen findings rule out the possibility of complications by bronchial asthma or eosinophilic pneumonia.

The fact that the patient's cough, which was resistant to antitussives and expectorants, was temporarily relieved by inhalation of a β_2 -adrenoceptor agonist at the time of the methacholine challenge test prompted us to attempt treatment with this drug. To ensure compliance, we chose oral tablets instead of regular inhalation. Numerous drugs have pharmacologic effects on smooth muscle hyperplasia and hypertrophy.^{5,6} Because β_2 -adrenoceptor agonists have an inhibitory effect on proliferation and a relaxing effect on the tone of smooth muscles, their use may be indicated in cases involving patients with IIP, given that they may mitigate some of the symptoms. The frequency of bronchial hypersensitivity in patients with IIP remains unclear. We are unaware of any studies on the relationship between IIP and bronchial hypersensitivity and, thus, further clinical investigation should be considered.

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