Mechanisms of Colchicine Effect in the Treatment of Asbestosis and Idiopathic Pulmonary Fibrosis


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Abstract. The objective of this study was to evaluate the mechanisms of colchicine action in pulmonary fibrosis. The study included 10 patients with pulmonary fibrosis (idiopathic pulmonary fibrosis 5, asbestosis 4, and scleroderma 1) who had been admitted to Bellevue Hospital Center, a tertiary care public hospital in New York City. We administered colchicine 0.6 mg orally for 12 weeks to patients with pulmonary fibrosis. Symptoms, high resolution CT scans, pulmonary function tests, and bronchoalveolar lavage parameters were compared prior to and after treatment. Results showed declines in dyspnea index, selective improvement in several CT scans, but no statistically significant change in BAL cells, cytokines, fibronectin, or hydroxyproline. However, there was a decline in hydroxyproline in the BAL fluid in 8/10 patients. We concluded that colchicine has a mild antifibrotic effect which may be in inhibiting collagen formation since there was no effect on the inflammation that accompanies fibrosis.

Key words: Colchicine—Asbestosis—Inflammation.

Introduction

Patients with idiopathic pulmonary fibrosis (IPF) or secondary to a known underlying disease process, usually have a progressive clinical syndrome which poses significant challenges in clinical management. Patients present with gradual onset of dyspnea, diffuse bilateral infiltrates on their chest radiograph, and restrictive

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lung dysfunction with hypoxemia and a decreased diffusion capacity. Standard treatment regimens for IPF, which usually include glucocorticoids with or without immunosuppressive agents, produce less than a 30% response rate in pulmonary function and are associated with significant adverse events and morbidity [2].

Colchicine, an inhibitor of collagen synthesis and secretion and promoter of collagenase activity, has recently been used to treat IPF. Several studies have shown that colchicine was well tolerated and at least as effective as other standard therapies [10, 27]. In a retrospective analysis, Peters et al. [27] reported that pulmonary function improved in 5 patients, was stable in 9, and declined in 9 over a mean period of 22 months follow-up. However, only 5 of 23 had colchicine as the sole therapy. Douglas et al. [10] compared 22 patients who had received colchicine as initial single-agent therapy to 22 historical patients with usual interstitial pneumonia (UIP) of similar severity who had been given prednisone. There was no significant difference in the decline rate of pulmonary function between the two groups. The third study by Douglas et al. [12] was a prospective clinical trial involving 26 patients with IPF [idiopathic UIP by high-resolution computed tomography (HRCT)] randomized to prednisone or colchicine. The prednisone group had more serious side effects and there was a nonsignificant trend toward more rapid decline in pulmonary function and shortened survival rate compared with the colchicine-treated group. Since this study suggested that both prednisone and colchicine were relatively ineffective as antifibrotic agents and may not be different than no therapy at all. Douglas et al. [11] then reviewed 487 patients’ records and their outcome at the Mayo clinic from 1994 through 1996. By multivariate analysis after adjusting for factors associated with worse outcome such as older age, male gender, lower diffusing capacity, and rapid worsening of pulmonary function, there was no significant difference in survival between those patients treated with colchicine or prednisone and those on no therapy. A prospective study of colchicine in 19 patients with biopsy-proven usual interstitial pneumonia, who were unresponsive or intolerant to corticosteroids, reported 1 sustained response, 7 stabilizations, and 11 deteriorations while on the drug [38]. Treatment was for 6 ± 0.9 months and response was evaluated by dyspnea, chest radiograph, and pulmonary function including exercise desaturation scores.

Asbestosis and IPF are both interstitial lung diseases (ILD) characterized by excessive interstitial matrix and activated alveolar macrophages (AMs) [31]. The AMs and alveolar spaces can be repetitively sampled with bronchoalveolar lavage to measure relevant mediators associated with fibrosis, e.g., matrix proteins, cytokines, and growth factors [31]. In this regard, AMs from 22 ILD patients were cultured in the presence of colchicine 0.5 μg/ml for ±24 hours and fibronectin release was inhibited 23 ± 4% and AM insulin-like growth factor by 68 ± 10% [29]. Fibronectin release was blocked by greater than 90% after 72 hours. These in vitro effects were achieved at doses as low as 10 ng/ml, suggesting in vivo efficacy.

We instituted a clinical trial of colchicine as the sole therapy in patients with asbestosis, IPF, or scleroderma in order to assess the biochemical response to this