

Angiotensin-converting Enzyme Inhibitors in the Treatment of Sarcoidosis and Association with ACE Gene Polymorphism: Case Series

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ABSTRACT

Angiotensin-converting enzyme (ACE) is used as a marker for sarcoid disease activity.¹ We present an observational study of four African-American patients all of whom demonstrated improvement in their sarcoidosis after treatment with ACE inhibitors for hypertension. [Indian J Chest Dis Allied Sci 2013;55:105-107]

Key words: Angiotensin-converting enzyme, ACE gene polymorphism, Sarcoidosis.

INTRODUCTION

Angiotensin-converting enzyme (ACE) is used as a marker for sarcoid disease activity.¹ We have earlier reported remission of cutaneous and lymphatic sarcoidosis in a patient treated with an ACE inhibitor for acute congestive heart failure.² We now report a prospective observational series of four African-American patients who all demonstrated improvement in manifestations of sarcoidosis after treatment with an ACE inhibitor, benazapril for associated hypertension. The initial presentation and manifestation of the patients varied, more specifically, all presented with pulmonary sarcoidosis of which two also had concomitant vocal cord lesions and two with cutaneous lesions. The improvement in pulmonary sarcoidosis was demonstrated by improvement in pulmonary function tests (PFTs) and the improvement in vocal cord involvement was demonstrated by improvement in speech. Furthermore, all the patients described were tested for ACE gene polymorphism which has been shown to be associated with sarcoidosis.³

CASE REPORT

The four African-American patients described in this series were on treatment for hypertension with ACE

inhibitor, benazapril (10-20 mg) once daily. All the patients were investigated for ACE gene polymorphism and were found positive. Patient no. 1 and 2 had one copy of gene (D) and patient no. 3 and 4 had two copies of gene (DD). The patients earlier reported by us² were also tested and found to have two copies of gene (DD).

Case 1

A 47-year-old female with a history of hypertension had a lymph node biopsy in the year 2001 to confirm sarcoidosis that manifested with cutaneous pulmonary, vocal cord, and sinus lesions (Figure 1). She has a history of amphetamine abuse. The patient was treated with prednisone and an inhaled corticosteroid for her pulmonary sarcoidosis initially and then benazapril was added. Subsequently, the patient demonstrated improvement in her cutaneous and vocal cord lesions and a drop in ACE levels measured in the serum.

Pulmonary function tests done in May 2007 and in April 2008 showed an improvement in forced expiratory volume in first second (FEV₁) from 38% to 43% while the diffusion capacity increased from 40% to 45%. However, the vital capacity decreased from 69% to 55%, which is possibly occurred due to vocal cord involvement.

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Figure 1. Magnetic resonance imaging of neck showing vocal cord thickening in Case 1.

Case 2

A 53-year-old female was diagnosed to have pulmonary sarcoidosis by mediastinoscopy in 2003. She was treated with prednisone and a steroid inhaler and went into remission after six months but also developed diabetes. She then developed cutaneous lesions diagnosed on biopsy four years later (Figure 2A, B) followed by hoarseness of voice due to sarcoidosis involvement of the vocal cord and epiglottis diagnosed via laryngoscopy (Figure 3). She was advised benazapril for hypertension and continued insulin for her diabetes. Oral prednisone was continued periodically over short courses for

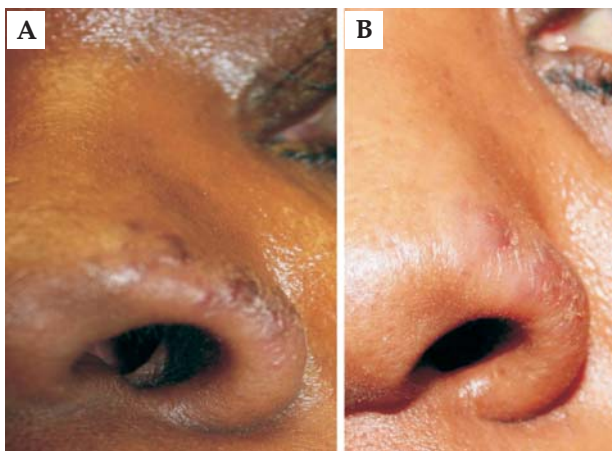


Figure 2. Photograph of the patient (A) before treatment showing active nose lesion and (B) after treatment showing healed nose lesion.

pulmonary sarcoidosis exacerbations. One year after the addition of benazapril, she had remission of her cutaneous and vocal cord lesions and also showed improvement in her pulmonary functions.



Figure 3. Computed tomography of neck showing vocal cord thickening in Case 2.

Pulmonary function testing done in September 2007 and in May 2008 showed no change in vital capacity. Diffusion capacity decreased from 62% to 55% and FEV₁ decreased from 82% to 71%. Clinically, the patient demonstrated significant improvement in exercise capacity.

Case 3

A 47-year-old female, daughter of the patient reported earlier by us,² was diagnosed to have pulmonary sarcoidosis in 2006 by mediastinoscopy, and was treated with oral prednisone and steroid inhaler for one-and-a-half years followed by the latter alone. She also had sinus involvement with sarcoidosis diagnosed by biopsy in 2010. The patient was treated with benazapril for hypertension from 2008 onwards with improvement in her pulmonary functions noted after addition of this medication.

Pulmonary function testing done in October 2007 and October 2008 showed an increase in vital capacity from 76% to 98% of predicted, while the FEV₁ improved from 93% to 103% of normal predicted.

Case 4

A 49-year-old male was diagnosed to have pulmonary sarcoidosis by open lung biopsy in 1992. The patient was treated with a steroid inhaler and oral prednisone off and on. The patient was started on benazapril in July 2008 and showed improvement in pulmonary functions within six months of starting

this medication. The vital capacity improved from 80% to 88% and FEV₁ improved from 79% to 90%, respectively. Diffusion capacity showed a marginal decrease from 25.8% to 24.4%.

DISCUSSION

Sarcoidosis is a systemic inflammatory disorder of unknown aetiology in which an unidentified agent stimulates a cellular response that results in characteristic granulomatous formation secondary to activation of the monocyte/macrophage system.⁴ This results in the production of ACE, which converts angiotensin I to angiotensin II resulting in production of proinflammatory substances including chemokines, cytokines (IL-6) and adhesion molecules, such as ICAM-1 and VCAM-I.⁵ The resulting process is best described as immunologically induced inflammation via intercellular cross talk.⁶

Evidence to support the use of ACE inhibitors in sarcoidosis comes from Mizuno *et al*⁷ who showed down regulation of monocytes and macrophages lineage cells via ICAM-1 and P2XL receptors in an experimental model with captopril and allopurinol. Allopurinol has been reported demonstrating a response in cutaneous sarcoidosis.⁸

ACE inhibitors have also been found to influence remodelling of myocardial tissue after myocardial ischaemic events.⁹ ACE inhibitors specifically bind zinc an essential co-factor for some matrix metalloproteinases implicated in the metabolism of elastin and collagen.¹⁰

These findings suggest that ACE inhibitors may not only decrease inflammation in granulomatous disease but also influence remodelling of areas including pulmonary or skin tissue leading to decrease in fibrosis and damage of involved tissues.

ACE gene polymorphism is associated as a genetic risk factor for sarcoidosis.¹¹ Severity increases with homozygotes (DD) polymorphism as compared to heterozygotes (D).¹¹

All of our five patients including the earlier reported one had positive gene polymorphism, and showed a response to ACE inhibitors suggesting that ACE gene polymorphism may be a marker for ACE inhibitor treatment.

Rosenbloom *et al*¹² also showed in an experimental model that ACE inhibitors should prevent pulmonary fibrosis.

This is a small observational report from a Community Hospital and has only five African-American patients indicating a race bias. Further, no control group was studied. Previous and current

treatment with corticosteroids may have confounded the results. However, the encouraging results make a strong case for a systematic randomised controlled study of ACE inhibitor as therapeutic agent in sarcoidosis.

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