Oral curcumin supplementation in patients with atopic asthma

Dennis H. Kim, M.D., Joshua F. Phillips, M.D., and Richard F. Lockey, M.D.

ABSTRACT

Oral curcumin is recognized to have anti-inflammatory properties and has been used by ancient traditional medicine for centuries to treat a variety of diseases. In vitro *studies have confirmed the ability of curcumin to inhibit allergic inflammatory cytokine responses from lymphocytes; however, there are no* in vivo *studies of curcumin to treat inflammation associated with allergic asthma. This study was designed to determine the effect of oral curcumin supplementation on patients with stable, persistent, atopic asthma. Adult patients with stable, persistent asthma with evidence of allergic sensitization were randomized to receive 1000 mg of curcumin twice daily or placebo. Subjects were followed for 6 months and performed monthly spirometry (pre- and postbronchodilator); Asthma Control Test (ACT) scoring; and measurements for fractional excretion of nitric oxide (NO), serum eosinophil count, leukocyte count, total IgE, specific IgE to* Dermatophagoides pteronyssinus *(Der p) and* Dermatophagoides farinae *(Der f), use of rescue albuterol, and dose of inhaled corticosteroid. Nine patients were randomized into the treatment arm and six were randomized into the placebo group. No differential response was seen in the treatment and placebo groups regarding the primary end point, postbronchodilator forced expiratory volume in 1 second (FEV_1). Similarly, all secondary end point evaluations were not significantly different. Despite* in vitro *evidence that curcumin has anti-inflammatory properties and can inhibit allergic cytokine responses from lymphocytes* in vitro*, curcumin, 1000-mg, twice daily supplementation did not significantly affect postbronchodilator FEV_1, ACT scores, use of rescue bronchodilator, dose of inhaled corticosteroid, exhaled NO, serum IgE, total white blood cell count specific IgE to Der p or Der f, and blood eosinophils in patients with persistent atopic asthma.*

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Curcumin (diferuloylmethane) is a naturally occurring polyphenolic molecule that is derived from the root of the *Curcuma longa* plant. It has been used for many centuries, particularly in India and China, for homeopathic medical treatment of conditions including arthritis, urinary afflictions, and asthma.

Laboratory evaluation of curcumin indicates antioxidant properties, and numerous molecular targets, including transcription factors AP-1 and NF-$\kappa\beta$, have been identified. As such, it inhibits the secretion of both proinflammatory (TNF-α and IL-6) and anti-inflammatory (IL-10) cytokines.[1] Curcumin also decreases the expression and release of eotaxin, monocyte chemotactic protein 1, and monocyte chemotactic protein 3 from IL-1β–stimulated human airway smooth muscle cells.[2] When added to *Dermatophagoides farinae* (Der f)–stimulated lymphocyte cell cultures from allergic asthmatic patients, curcumin inhibits Der f–induced lymphocyte proliferation and production of IL-2, IL-4, IL-5, and granulocyte macrophage colony-stimulating factor.[3] Ram *et al.* showed that curcumin decreases airway constriction and hyperreactivity in guinea pigs (20 mg/kg) when coadministered with ovalbumin.[4]

There are no *in vivo* studies using curcumin to treat asthma inflammation. Therefore, we performed a randomized, double-blinded, placebo-controlled pilot study to evaluate the effects of oral curcumin supplementation versus placebo, on adult patients with a history of stable persistent asthma and allergic sensitization. A daily dose of 2000 mg was chosen based on previously published data of potential side effects, drug absorption, and biological effects when given as an oral supplement in patients with Alzheimer's dementia.[5] Curcumin capsules were purchased from Sabinsa Corp. (Piscataway, NJ) and their appearance was identical to placebo.

This study enrolled adult males and nonpregnant female patients aged 18–60 years with a history of physician-diagnosed asthma for 1 year or longer, forced expiratory volume in 1 second (FEV_1) of $\geq$60%, current use of low-or-medium–dose inhaled corticosteroids,[6] $\geq$1 puff of short-acting β-agonist in the past

From the Division of Allergy and Clinical Immunology, University of South Florida College of Medicine and James A. Haley Department of Veterans' Affairs Hospital, Tampa, Florida

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Address correspondence and reprint requests to Dennis Kim, M.D., Division of Allergy and Clinical Immunology, University of South Florida College of Medicine and James A. Haley Department of Veterans' Affairs Hospital, 13000 Bruce B. Downs Boulevard, VAR-111D, Tampa, FL 33612

E-mail address: dkim2@health.usf.edu

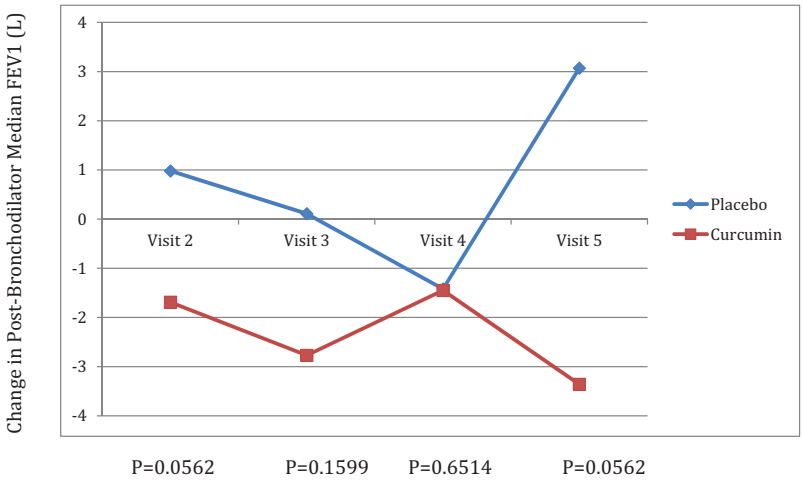

Figure 1. *Plot of median change in postbronchodilator forced expiratory volume in 1 second (FEV_1; percent predicted) of subjects receiving curcumin or placebo by visit (30-day intervals).*

Table 1 **Change in FEV_1 at each follow-up visit compared with baseline**

Group	No. of Patients	Variable	Mean (L)	SD (L)	Median (L)
Placebo	6	Visit 5	3.85	8.36	3.07
		Visit 4	1.66	8.40	−1.42
		Visit 3	2.89	10.42	0.11
		Visit 2	4.12	7.16	0.98
Curcumin	9	Visit 5	−4.60	5.80	−3.36
		Visit 4	−0.57	6.49	−1.45
		Visit 3	−4.67	8.71	−2.77
		Visit 2	−1.75	5.72	−1.69

FEV1 = forced expiratory volume in 1 s.

30 days, and a ≥2+ reaction by prick-puncture test (erythema larger than a nickel in diameter with wheal <3 millimeter) to *Dermatophagoides pteronyssinus* (Der p) or Der f. Subjects were excluded if there was a history of allergy or intolerance to curcumin, other chronic respiratory conditions (chronic obstructive pulmonary disease, pulmonary hypertension, interstitial lung disease, *etc.*), FEV_1< of 60%, and history of smoking in the past year or cumulative smoking of ≥10 pack-years. Other exclusive criteria included the use of oral corticosteroid in the preceding 1 month, high-dose inhaled corticosteroid for ≥2 weeks during the 4 weeks preceding the screening visit, long-acting β-agonists at screening visit, and use of short-acting β-agonist at >4 puffs/day on average during the preceding 2 weeks (other than before exercise). Additional exclusive criteria included the current use of allergen immunotherapy or any immunotherapy in the past year; current use of antileukotrienes; diseases, *i.e.*, medical or psychiatric or social problems that, in the investigator's opinion, would interfere with participation in the study or place the subject at risk; inability to swallow the study capsule; personal history of alcohol or illicit drug dependence in the last year; and inability to correctly use a peak flow meter.

The study was conducted between November 2008 through January 2010. All study methods and documents were approved by the Institutional Review Board of the University of South Florida, Tampa, FL.

During screening visit 1, subjects underwent baseline spirometry, Asthma Control Test (ACT) scoring, and skin-prick testing to Der f and Der p allergen extracts. Average ACT score for treatment and placebo groups were 19 and 18, respectively. Average postbronchodilator FEV_1 was 82% in the treatment and 78% in the placebo groups.

After a 2-week run-in period to confirm stable disease, subjects were then randomized; nine were entered into the treatment arm (curcumin at 1000 mg twice daily), and six were entered into the placebo group. Mean prebronchodilator FEV_1 at visit 1 for subjects in treatment and placebo arms were 2.29 and 2.87 L, respectively. Subjects also underwent induced sputum collection, exhaled nitric oxide (eNO), another ACT and phlebotomy to measure serum total IgE, total

blood eosinophil count, and serum-specific IgE to Der p1 and Der f1.

Two subjects in the treatment arm withdrew consent and were not included in the final analysis. The remaining subjects then returned for three follow-up visits, each 1 month apart, at which time they underwent spirometry, eNO, ACT scoring, phlebotomy for measurement of serum total IgE, blood eosinophils, specific antibody to Der f and Der p, and total white blood cell count. Subjects also maintained a daily diary to record the use of their rescue inhaler, symptoms such as coughing and wheezing, peak expiratory flow rates, dose of inhaled corticosteroids, and/or antibiotic or systemic corticosteroid. Bottles containing study drug were weighed to monitor for medication compliance.

Postbronchodilator FEV_1 was chosen to be the primary end point because it measures the best lung function that can be achieved by bronchodilator therapy on the day of the visit and therefore is a more stable measure in asthmatic patients than comparing visit-to-visit baseline FEV_1.[7] Primary end point analysis was done using Wilcoxon sum rank test instead of *t*-test because the data did not follow a normal distribution. Compared with baseline, the FEV_1 value at visit 5 in the treatment group decreased (mean = 4.6; SD = 5.8), whereas it increased in the placebo group (mean = 3.85; SD = 3.07; $p = 0.0562$). Overall, there was no statistically significant improvement in median values of FEV_1 among those subjects taking curcumin compared with placebo (Fig. 1; Table 1). Similarly, secondary end point evaluations of eNO, ACT scores, all of the serum analyses, rescue albuterol use, and dose of inhaled corticosteroid were also not significantly different (data not shown).

In conclusion, despite *in vitro* evidence that curcumin has anti-inflammatory properties and can inhibit allergic cytokine responses from lymphocytes *in vitro*, curcumin at 1000 mg twice daily supplementation did not significantly affect postbronchodilator FEV_1, ACT scores, use of rescue bronchodilator, dose of inhaled corticosteroid, eNO levels, or levels of serum IgE, total white blood cells, antibody specific to Der p or Der f, and blood eosinophils in patients with persistent atopic asthma. Future studies may benefit from a larger sample size, longer study duration, higher dose of curcumin, and/or improvements in oral bioavailability.

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