High-dose curcuminoids are efficacious in the reduction in symptoms and signs of oral lichen planus

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Background: Curcuminoids are components of turmeric *(Curcuma longa)* that possess anti-inflammatory properties.

Objective: We sought to study the efficacy of curcuminoids in controlling the signs and symptoms of oral lichen planus, at doses of 6000 mg/d (3 divided doses), and their safety at this dose.

Methods: Twenty consecutive, eligible patients who consented were enrolled into this randomized, double-blind, placebo-controlled clinical trial in 2007 through 2008. Measurement of symptoms and signs of oral lichen planus using the Numerical Rating Scale (NRS) and the Modified Oral Mucositis Index (MOMI), respectively; complete blood counts; liver enzymes; C-reactive protein; and interleukin-6 levels was done at baseline and day 14. Two-sided *P* values are reported.

Results: In the placebo group, the percentage changes from baseline in NRS (median [interquartile range] = 0.00 [−29 to 16.7], $P > .99$), erythema (0.00 [−10 to 16.7], $P = .98$), ulceration (0.00 [0.00 to 26.7], $P = .63$), and total MOMI scores (−3.2 [−13 to 9.09], $P = .95$) were not statistically significant, whereas they were statistically significant in the curcuminoids group: NRS (−22 [−33 to −14], $P = .0078$); erythema (−17 [−29 to −8.3], $P = .0078$), ulceration (−14 [−60 to 0.00], $P = .063$), MOMI (−24 [−38 to −11], $P = .0039$). The curcuminoids group showed a greater reduction in clinical signs and symptoms as compared with the placebo group, measured by percentage change in erythema ($P = .05$) and total MOMI score ($P = .03$), and proportion showing improvement in NRS (0.8 vs 0.3, $P = .02$) and total MOMI score (0.9 vs 0.5, $P = .05$). Adverse effects were uncommon in both groups.

Limitations: The small sample size resulted in limited power, particularly for multivariate analyses.

Conclusions: Curcuminoids at doses of 6000 mg/d in 3 divided doses are well tolerated and may prove efficacious in controlling signs and symptoms of oral lichen planus. (J Am Acad Dermatol 2012;66:752-60.)

Key words: anti-inflammatory; autoimmune; curcuminoids; herbal; oral lichen planus; turmeric.

Lichen planus is an autoimmune, mucocutaneous condition. It commonly involves the oral mucosa, which may be the only affected site. Oral lichen planus (OLP) can cause oral discomfort, and is characterized by white reticular changes, erythema, and ulcers.[1] Curcuminoids are components of the root turmeric (*Curcuma longa*), and have anti-inflammatory properties.[2] Clinical studies of curcuminoids have evaluated its use in conditions such as rheumatoid arthritis, postsurgical inflammation, and

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chronic uveitis.[2] Therefore, in 2003 through 2004 we conducted a randomized, double-blind, placebo-controlled trial of 2000 mg/d of curcuminoids in 33 patients with OLP.[3] We ended this study at the first interim analysis for futility. Data from this earlier study and observations from open-label use of curcuminoids in patients with OLP indicated that a starting dose of 2000 mg/d of curcuminoids was insufficient. Therefore we conducted the current randomized controlled trial using a higher dose of curcuminoids (6000 mg/d in 3 divided doses) in 20 patients with OLP.

The primary objectives of this study were to evaluate the efficacy of curcuminoids at a dose of 6000 mg/d in 3 divided doses in controlling the signs and symptoms of OLP, and the safety and tolerability of curcuminoids at this dose (specific aim 1).

In addition, we planned to evaluate the association of serum C-reactive protein (CRP) and serum interleukin (IL)-6 with clinical severity of OLP at baseline and over time (specific aim 2), and the effect of curcuminoids on these proteins (specific aim 3). We also planned to evaluate whether subgroups of patients with varying responses to curcuminoids could be identified by their baseline serum CRP or serum IL-6 levels (specific aim 4), and whether changes in these proteins could explain the mechanism of action of curcuminoids in OLP (specific aim 5).

CAPSULE SUMMARY

- Curcuminoids are components of turmeric *(Curcuma longa)* that possess anti-inflammatory properties.
- In a randomized, double-blind, placebo-controlled 2-week study of curcuminoids in 20 patients with oral lichen planus, a greater reduction in symptoms and signs was observed in the curcuminoids group as compared with the placebo group.
- Adverse effects included diarrhea but were uncommon.
- Curcuminoids at doses of 6000 mg/d in 3 divided doses are well tolerated and may prove efficacious in controlling signs and symptoms of oral lichen planus.

METHODS

Study design

This was a phase II randomized double-blind, placebo-controlled clinical trial.

Study population

A total of 23 patients with symptomatic OLP presenting to the oral medicine clinic at the University of California, San Francisco (UCSF) between October 2007 and November 2008 were screened for this study. Twenty of these patients met the eligibility criteria, signed a written consent form to participate, and were enrolled and randomized. Three patients had elevated liver enzymes at baseline and were excluded (Fig 1). This study was approved by the UCSF Institutional Review Board. An investigational New Drug Approval number was obtained from the Food and Drug Administration. This study was registered on clinicaltrials.gov in September 2007, identifier: NCT00525421.

Eligible patients were those older than 21 years; with a current clinical presentation of atrophic or erosive OLP, symptom score for OLP between 3 and 8 at enrollment (range of scale, using the Numerical Rating Scale [NRS]: 0 [no oral discomfort] to 10 [worst imaginable oral discomfort]); and who had not used topical or systemic glucocorticosteroids for at least 2 weeks. Exclusion criteria included pregnancy, lactation, patients on long-term glucocorticosteroid therapy, current orthodontic treatment, and history of gastroesophageal reflux disease, gastric ulcers, duodenal ulcers, gallstones (curcumin may cause gastric irritation and curcumin can stimulate gall bladder contractions[4]), or elevated liver enzymes above 2.5 times the upper limit of normal (curcumin can cause hepatotoxicity in some species such as mice and rat[2]).

The primary outcome of the study was change in symptom scores from baseline to 2-week follow-up. Secondary end points included changes in clinical signs, CRP, and IL-6 from baseline, and occurrence of adverse effects.

Subjects were recruited from the oral medicine clinic at UCSF. Patients were screened by a review of the medical history, medications used, current symptom score (for OLP), and an oral examination. At this time potential subjects were identified, written informed consent was obtained and consenting patients were scheduled for a blood draw on the same day. Those with liver enzymes within 2.5 times the upper limit of normal were enrolled and randomized. The study medication was sent to them by overnight mail, allowing a 12-day course of study medication taken before their 2-week follow-up visit.

A consecutive sample of eligible patients was enrolled into the study. Subject enrollment and follow-up is outlined in Fig 1.

Intervention

The study medication was a standardized extract of turmeric, which contains at least 95% curcuminoids, called "curcumin C3 complex." The turmeric rhizomes used for the manufacture of curcumin C3