

REPORT

Oral curcumin in the treatment of moderate to severe psoriasis vulgaris: A prospective clinical trial

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Background: There is a need for safe, inexpensive, and effective psoriasis therapies. Many anecdotal accounts of patients' successful treatment with the alternative medicine curcumin exist.

Objective: We sought to determine the safety and efficacy of oral curcumin in patients with psoriasis.

Methods: We conducted a phase II, open-label, Simon's two-stage trial of 4.5 g/d of oral curcuminoid C3 complex in patients with plaque psoriasis. End points included improvement in Physicians Global Assessment score, Psoriasis Area and Severity Index score, and safety end points throughout the study.

Results: The intention-to-treat analysis response rate was 16.7% (95% confidence interval: 2%, 48%) and both responders achieved a Psoriasis Area and Severity Index 75 score. There were no study-related adverse events that necessitated participant withdrawal.

Limitations: Small sample size and lack of placebo group are limitations.

Conclusion: The response rate was low and possibly caused by a placebo effect or the natural history of psoriasis. Large placebo-controlled studies are necessary before recommending oral curcumin as a psoriasis treatment. (J Am Acad Dermatol 10.1016/j.jaad.2007.12.035.)

Psoriasis is a common chronic inflammatory disease of the skin and joints, which affects about 2% of the general population.¹ Severe psoriasis is associated with significant decrements in health-related quality of life,² multiple

comorbidities,³ and increased cardiovascular risk⁴ and mortality.⁵ Treatment options for severe psoriasis are either time-consuming (eg, ultraviolet [UV]B or psoralen plus UVA therapy) or have the potential for organ toxicity with chronic use (methotrexate,

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Abbreviations used:

CI:	confidence interval
IQR:	interquartile range
PASI:	Psoriasis Area and Severity Index
PGA:	Physicians Global Assessment
UV:	ultraviolet

acitretin, cyclosporine).¹ Newer biologic therapies (infliximab, etanercept, adalimumab, efalizumab, and alefacept) are immunosuppressive and theoretically could increase the risk of infections and malignancies with long-term use, and are limited by their high cost.^{6,7} Despite the advent of multiple systemic therapy options for severe psoriasis, many patients with this disease are unable to achieve effective long-term control.^{8,9} Given the chronic nature of psoriasis and the need for long-term treatment, there exists an unmet need for effective, nontoxic therapies that are also convenient and affordable.

Given the limitations of traditional pharmacologic approaches in the treatment of psoriasis, patients frequently turn to complementary and alternative medicine therapies to manage their disease. It is estimated that 51% of patients with psoriasis use complementary and alternative medicine therapies to treat their skin despite limited or no scientific data on the safety and efficacy of these treatments.¹⁰ Curcumin (the active component of the Indian spice turmeric) is a complementary and alternative medicine therapy that has been successfully used to treat psoriasis based on anecdotal reports.¹¹⁻¹³ A strong scientific rationale suggests that curcumin may in fact be promising for the treatment of psoriasis. *In vitro* and animal studies have demonstrated the inhibitory effect of curcuminoids (term interchangeable with "curcumin") on immune pathways critical to the pathophysiology of psoriasis such as nuclear factor kappa B¹⁴⁻¹⁸ and downstream, inflammatory gene products such as Th-1 type cytokines (ie, tumor necrosis factor- α , interferon- γ) (45, 97-112).¹⁹⁻²² Furthermore, clinical trials²³ of curcumin have been conducted for a variety of indications and it has been shown to be safe in oral doses of up to 12 g.

Based on the physiologic effects of curcumin and the positive anecdotal reports of its benefit for psoriasis, we conducted a prospective, open-label, clinical trial to assess the safety and efficacy of oral curcumin in the treatment of chronic psoriasis vulgaris.

METHODS

Study patients

Our institutional review board approved the protocol and all patients gave written informed consent before any study-related procedures were

performed. The study was conducted in accordance with the Declaration of Helsinki and was registered at ClinicalTrials.gov before study initiation. Patients were eligible if they were at least 18 years old and had active but clinically stable plaque psoriasis that involved at least 6% of the body surface area and was of moderate plaque thickness as defined by a thickness score of 2 on the Psoriasis Area Severity Index (PASI). Patients were included if they were using a medically acceptable method of contraception throughout the entire study period. Patients with guttate, erythrodermic, or pustular psoriasis were excluded as were patients who used systemic treatments for psoriasis (eg, methotrexate, cyclosporine, alefacept, adalimumab, efalizumab, infliximab, etanercept, etretinate, systemic steroids, and psoralen plus UVA) within 3 months before day 0 or at any time during the study. Patients were excluded if they had used topical treatments or phototherapy for their psoriasis within 14 days before day 0 or at any time during the study. Patients who were pregnant or nursing a child, had clinically significant laboratory abnormalities at screening, or had significant uncontrolled comorbidities were excluded from the study. Patients for whom the dose of clonidine, digoxin, beta-blockers, lithium, or antimalarials had changed in the past month before enrollment were excluded from the study. Enrolled participants were required to avoid prolonged exposure to sun or UV light and discontinue nonmedicated emollients and medicated psoriasis shampoos 24 hours before each study visit.

Study drug

Curcuminoid C3 complex capsules contained 95% curcuminoids. Patients were given 500-mg capsules and were instructed to take 3 capsules 3 times a day by mouth.

Study design

This was a phase II, single-arm, single-dose, non-controlled, open-label, modified Simon's two-stage clinical trial of 4.5 g/d of curcumin administered orally in patients with chronic plaque psoriasis. The study took place at our department of dermatology. During this 16-week trial, patients were treated with 4.5 g/d of curcumin (3 pills of 500 mg, 3 times daily) for the first 12 weeks followed by a 4-week observation period after discontinuing the study drug. Histologic confirmation of psoriasis vulgaris was obtained for all enrolled participants. Patients were seen at a screening visit and then at baseline and weeks 2, 4, 8, 12, and 16 for safety and efficacy evaluations. The first participant was enrolled on January 25, 2006, and all study procedures were concluded on May 22, 2007.

Efficacy end points

The primary measure of efficacy was the proportion of patients who were classified as a responder using the Physicians Global Assessment (PGA) of change at week 12. A responder was defined as achieving a rating of good (50%-74% improvement), excellent (75%-99% improvement), or cleared (100% improvement) on the PGA compared with baseline. When necessary, baseline photographs were used in comparison with the current clinical examination to assess the PGA. Secondary end points included PASI scores and health-related quality of life as measured by the Skindex 29.^{24,25} Other outcome measures include PASI 75 and PASI 50, which correspond to 75% and 50% improvements in PASI scores from baseline, respectively, and have been shown to represent a meaningful end point in psoriasis clinical trials.²⁶

Safety end points

All patients who received at least one dose of study drug were included in the safety analysis. Safety data were obtained by patient interview (and examination if necessary) at all study visits and by collecting laboratory data on blood count, serum chemistries, and liver function tests at week-4 and week-12 visits.

Statistical analysis

To improve the efficiency of this early phase II study, the investigators used a Simon's two-stage design in which a planned interim analysis was performed to determine whether there was sufficient efficacy to warrant enrollment of additional participants. The following assumptions were made. First, we predicted that at least 50% of patients would achieve a response as defined above. Second, we determined that a response rate of 20% or less would not be promising for clinical use and that further study of oral curcumin at the doses used in this protocol would be abandoned. This lower limit of efficacy is similar to what is seen in placebo-controlled trials.⁶ Third, we assumed a type I error (significance level) of .05 and a type II error of .20. Thus, if the true response rate is less than 20%, the probability of recommending further investigation is limited to 5%, and if the true response rate is at least 50%, the probability of recommending further study is 80%.

The sample size calculations were performed using a program downloaded from the National Institutes of Health World Wide Web site (<http://linus.nci.nih.gov/~brb/Opt.htm>). The first stage of the trial enrolled 8 participants. According to the parameters defined above, if 3 or more of the

8 participants enrolled were classified as responders at week 12, this would justify enrolling an additional 10 participants for stage 2.

The primary analysis included all participants who were enrolled in the trial and received any study drug (intention to treat). Participants who withdrew from the study were classified as nonresponders and PASI and Skindex scores were treated as the last outcome carried forward when available. If no follow-up data were obtained because the patient withdrew before these measurements, the patient was classified as having no change in baseline PASI and Skindex scores. A secondary as-treated analysis (eg, per protocol) was performed in patients who completed the study up to week 12 and had taken at least 85% of their curcumin dose based on pill counts. The decision to continue or stop the trial after the first stage was determined by patients who were compliant with all study procedures up to week 12 (eg, per protocol analysis, selected as primary for the starting/stopping rules in the context of this early stage, exploratory study). Participants were classified as responders based on week-12 PGA scores and a response rate was calculated with 95% exact confidence interval (CI). Median PASI and Skindex-29 scores were calculated at baseline and week 12 including interquartile range (IQR) and comparisons were tested with a Wilcoxon rank sum for unpaired data and a Wilcoxon signed rank for paired data. Data analysis was performed using software (STATA, Version 10, StataCorp LP, College Station, Tex).

RESULTS

A total of 18 patients were screened, 12 of whom were enrolled and received the investigational drug at day 0. Of the 5 participants who did not receive drug, 3 were excluded because they did not have 6% or more of their body surface area covered with psoriasis and another patient was excluded because of anemia. One participant who was eligible for the study was lost to follow-up before receiving any study drug. Eight participants completed the trial up to week 16. Four of the 12 enrolled participants did not complete the trial; one was withdrawn by the investigators because of worsening of her psoriasis and 3 withdrew before week 12 because of lack of efficacy (Fig 1). Participants were instructed to take 3 pills 3 times a day for a total of 756 pills during 12 weeks. All participants who completed the trial were at least 85% compliant with the treatment regimen as determined by patient diaries, patient interview, and pill counts and the median number of pills missed was 15 (IQR 0, 47.5). Although widely accepted, these clinical methods for measuring compliance may overestimate actual compliance. Participants

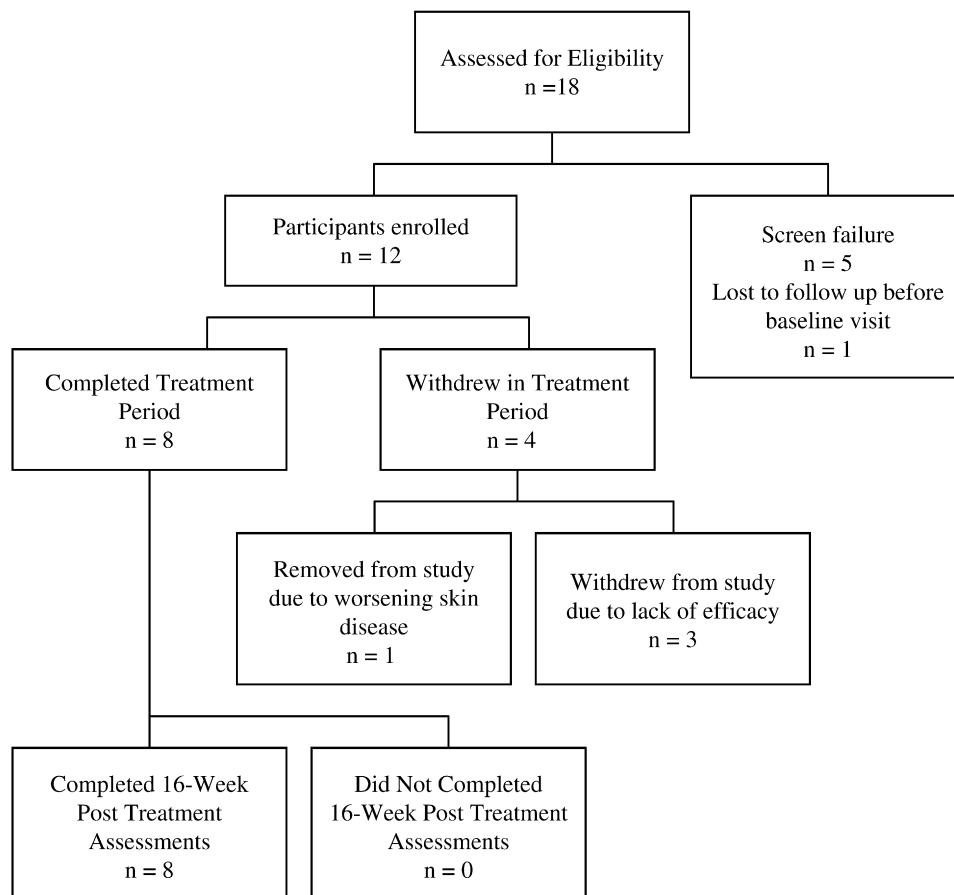


Fig 1. Flowchart of participant enrollment.

who failed to complete the trial had similar degrees of psoriasis severity as measured by PASI compared with patients who completed the trial, but non-completers had more impairment in health-related quality of life at baseline as measured by Skindex 29 ($P = .04$). Descriptive statistics and baseline data for enrolled patients are summarized in Table I.

Efficacy and quality-of-life end points

Intention-to-treat analysis, in which all participants who withdrew from the trial were classified as nonresponders, showed a response rate of 16.7% (95% CI: 2%, 48%) (Table II). The secondary as-treated analysis, which included only participants who completed the trial up to week 12, had a response rate of 25% (95% CI: 3, 65%). The study was terminated based on lack of sufficient evidence of efficacy, as only two patients who completed the trial achieved a response at week 12.

The two participants who were classified as responders achieved a score of excellent on the PGA, were seen during winter months, and were not exposed to sunlight during the trial based on patient report and physical examinations. No patients

received a score of cleared, good, or fair at week 12 whereas two participants received a PGA score of slight, 3 of unchanged, and one of worse at week 12 (Fig 2). Both responders achieved a PASI 75 at week 12, whereas no other patients achieved a PASI 75 or a PASI 50. Four weeks after discontinuation of curcumin therapy the responders maintained an excellent response based on PGA and PASI 75 at week 16. In those patients who completed the trial, the median Skindex-29 score was reduced by 0.35 (IQR 5.5, 5.0) (a lower score signifies improvement in quality of life). In subgroup analysis, the two responders had a median reduction in Skindex scores of 16 (IQR 5.1, 26.9) ($n = 2$) whereas nonresponders had a median increase (worsening) in Skindex scores of 2.5 (IQR 0, 5.6) ($n = 6$).

Safety end points

Ten of 12 patients who received study drug reported an adverse event for a total of 18 adverse events. The adverse events that were possibly related to the study drug were all mild and were either gastrointestinal upset or heat intolerance/hot flashes. Other adverse events that were mild to moderate in

Table I. Baseline demographic information

Patients	Age, y (median, IQR)	Sex (N, %)	Median (IQR) No. of prior systemic agents/ phototherapy used	Race	Baseline PASI (median, IQR)	Baseline Skindex (median, IQR)
Completed trial N = 8	50.5 (45, 55)	N = 7 (87.5%) male	1.5 (1, 2.5)	N = 7 White N = 1 Asian	13.7 (9.7, 17.2)	34.6 (18.5, 50.9)
Did not complete trial N = 4	50 (38.5, 62.5)	N = 2 (50%) male	1.5 (0.5, 2.5)	N = 2 White N = 1 Black N = 1 Other	14.6 (5.4, 8.3)	63.2 (52, 79.9)

IQR, Interquartile range; PASI, Psoriasis Area and Severity Index.

Table II. Summary of efficacy end points at week 12*

Efficacy outcome	Results of patients who completed trial (n = 8)	Results of intention-to-treat analysis (n = 12)*
Response rate based on achieving at least a PGA of good	25%, 95% CI (3%, 65%)	16.7%, 95% CI (2%, 48%)
PGA at wk 12 (median, IQR)	Unchanged-slight improvement (unchanged, fair-good)	Unchanged (worse-unchanged, slight improvement)
PASI 75 at wk 12	25%, 95% CI (3%, 65%)	16.7%, 95% CI (2%, 48%)
Change in PASI (baseline-wk 12) (median, IQR)	5.4 (0.65, 7.6) $P = .04$	0.65 (−1.25, 6.5) $P = .26$
Change in Skindex [†] (median, IQR)	0.35 (IQR −5.5, 5.0) $P = .9$	0.0 (−2.55, 4.95) $P = .63$

CI, Confidence interval; IQR, interquartile range; PASI: Psoriasis Area and Severity Index; PGA, Physicians Global Assessment.

Change in Skindex data was only available for one of 4 participants who withdrew and was 8.4. The other 3 participants were given a score of 0 to indicate no change.

*Change in PASI data of two of 4 participants who withdrew are available (−11.1 and −4.1) whereas the other two participants who withdrew had no follow-up PASI data and were given a score of 0 to indicate no change.

[†]Positive values indicate an increase in Skindex scores, suggesting a decrease in quality of life.

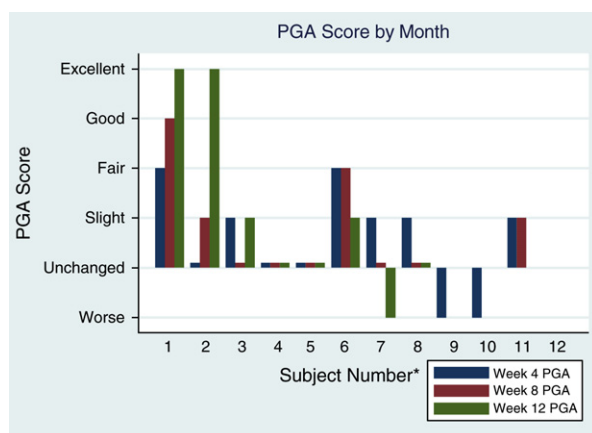


Fig 2. Physicians Global Assessment (PGA) scores by month. Week-12 PGA scores of good, excellent, and cleared are classified as responders. *Participants 9 to 12 withdrew before week 12 and PGA scores, when available, are shown for these patients for weeks in which they were evaluated.

intensity and judged unlikely to be related to the study drug were respiratory (n = 2), musculoskeletal (n = 3), and neurologic (n = 1) in nature. One patient

experienced worsening of her psoriasis at week 2 and developed near erythrodermic psoriasis before week 4. The patient had previously used extensive topical steroids that were discontinued 2 weeks before the start of the study drug. The investigator withdrew the patient so she could be treated with standard of care. Another patient underwent a kidney stone ablation procedure while enrolled in the study. The stone was diagnosed before the patient's enrollment in the study and the participant experienced the only serious adverse event when, during a transurethral ablation procedure, she experienced hypertension and respiratory distress and was hospitalized overnight for monitoring. Her symptoms resolved completely and she was discharged the following day. She was also the only participant to experience a significant laboratory aberration, which was a mild elevation in her liver enzymes at week 12 (aspartate aminotransferase 54, alanine aminotransferase 59) from baseline levels (aspartate aminotransferase 26, alanine aminotransferase 31) and the elevation in liver enzymes persisted at week 16 (aspartate aminotransferase 40, alanine aminotransferase 45).

DISCUSSION

As expected, 4.5 g/d of oral curcumin was well tolerated and safe in patients with psoriasis. All adverse events possibly related to the study drug were mild in nature and limited to gastrointestinal upset and heat intolerance or hot flashes. No participants were removed from the study because of study-related adverse events.

The efficacy of the study drug was low with an intention-to-treat response rate of 16.7% (95% CI: 2%, 48%) and did not justify continuation of the study based on our a priori termination rules. However, those who did respond achieved excellent responses of 83% and 88% improvement in PASI scores at week 12. The CI for the 16.7% response rate is wide as a result of the small sample size and, therefore, we cannot exclude the possibility that the response observed is caused by a placebo effect or the natural history of skin disease in these participants rather than efficacy of the drug itself. The lack of any evidence of meaningful response (eg, PASI 50) in all other participants argues that the true response rate is very low, limited to a small subset of patients with psoriasis, or not a result of curcumin but rather other factors that cannot be accounted for in an uncontrolled study.

Although in vitro curcumin has been shown to block pathways necessary to develop psoriasis, it is possible that oral administration will not produce a desired clinical effect because of low bioavailability. Orally administered curcumin has been shown to have low bioavailability in both animals and human beings.^{27,28} This relatively low bioavailability can be explained by the observation that curcumin is extensively reduced and conjugated in the intestinal tract. Animal experiments suggest that independent of dose, 40% to 90% of orally administered curcumin is excreted in stool.²⁹ We administered the highest dose of oral curcumin (eg, 4.5 g) we believed would be acceptable to patients based on the number and size of pills they would be required to swallow and recommendations from previous phase I trials.³⁰ This dose is substantially higher than what is achieved in diets high in turmeric, which corresponds to 60 to 100 mg of curcumin.³¹ It is possible that administering curcumin at higher doses or combining oral curcumin with agents that may enhance its absorption may result in better efficacy. Doses of curcumin of up to 8 g/d for up to 12 months have been safe in human beings and, therefore, higher doses may be considered for future studies.²³ Furthermore, new liposomal formulations of curcumin may enhance oral bioavailability and should be considered for future trials.³² Finally, curcumin may have efficacy when applied topically as demonstrated in one trial,

however, it stains the skin yellow and, therefore, may not be acceptable to patients.³³

In conclusion, oral curcumin was well tolerated by patients with psoriasis. The overall response rate was low and we cannot rule out that the responses were caused by a placebo effect or a natural disease remission. Nevertheless, excellent responses were observed in two patients and, therefore, large, placebo-controlled trials will be necessary to definitively prove or disprove oral curcumin as a potential therapeutic agent for psoriasis. For example, a placebo-controlled trial would need to enroll 254 participants to have statistical power of 80% to differentiate the response rate observed in our study from an expected PASI 75 response rate of 5% in the placebo group.⁶ Until such trials are performed, oral curcumin should not be recommended for the treatment of psoriasis given lack of proven efficacy. The results of our study further emphasize the need for rigorous prospective studies in assessing treatments for psoriasis.

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