

## FLUCONAZOLE FOR THE TREATMENT OF CUTANEOUS LEISHMANIASIS CAUSED BY *LEISHMANIA MAJOR*

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### ABSTRACT

**Background** Whereas certain oral antifungal azoles are well documented to have activity against leishmania, data on the efficacy of fluconazole for leishmaniasis are limited. We conducted a controlled trial in Saudi Arabia of fluconazole for the treatment of cutaneous leishmaniasis caused by *Leishmania major*.

**Methods** This randomized, double-blind, placebo-controlled trial assessed the efficacy of oral fluconazole, in a dose of 200 mg daily for six weeks, in the treatment of parasitologically confirmed cutaneous leishmaniasis. The primary outcome measure was the time to the complete healing of all lesions.

**Results** A total of 106 patients were assigned to receive fluconazole, and 103 patients were assigned to receive placebo. Follow-up data were available for 80 and 65 patients, respectively. At the three-month follow-up, healing of lesions was complete for 63 of the 80 patients in the fluconazole group (79 percent) and 22 of the 65 patients in the placebo group (34 percent; relative risk of complete healing, 2.33 [95 percent confidence interval, 1.63 to 3.33]). According to an intention-to-treat analysis, the rates of healing were 59 percent and 22 percent, respectively (relative risk, 2.76 [95 percent confidence interval, 1.84 to 4.12]). Sodium stibogluconate was offered to 11 patients in the fluconazole group who returned for follow-up (14 percent) and 33 of those in the placebo group (51 percent) in whom oral treatment was judged to have failed. According to a Kaplan–Meier analysis, the time to healing was shorter for the fluconazole group (median, 8.5 weeks, as compared with 11.2 weeks in the placebo group;  $P < 0.001$  by the log-rank test). Side effects were mild and similar in both groups.

**Conclusions** A six-week course of oral fluconazole is a safe and useful treatment for cutaneous leishmaniasis caused by *L. major*. (N Engl J Med 2002;346:891-5.)

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**L**EISHMANIASIS is a major cause of illness and death and a top priority for the tropical disease program of the World Health Organization. The worldwide incidence of leishmaniasis is about 1.8 million new cases annually.<sup>1</sup> Pentavalent antimony compounds remain the main therapeutic agents for various forms of leishmaniasis.

However, because of severe side effects and the requirement for parenteral administration, there has been an intensive search for alternative therapies, including oral agents for cutaneous leishmaniasis caused by *Leishmania major*.<sup>2</sup> The lesions of cutaneous leishmaniasis heal eventually — usually after several months. Mild disease is often managed with local care alone and may not require antimony therapy. However, a well-tolerated oral treatment would be useful, given the prolonged course of the infection and the disfiguring effects of unhealed skin lesions.

Certain azole antifungal drugs have activity against leishmania in vitro.<sup>3-5</sup> They inhibit the growth of leishmania in culture systems by inhibiting the cytochrome P-450–mediated 14 $\alpha$ -demethylation of lanosterol, blocking ergosterol synthesis, and causing accumulation of 14 $\alpha$ -methyl sterols.<sup>6</sup> In the treatment of cutaneous leishmaniasis caused by various species, the clinical effectiveness of the azole drugs has been varied.<sup>7-15</sup> Data are limited on the clinical efficacy against leishmania of fluconazole, a triazole antifungal agent available for oral and parenteral administration.<sup>16,17</sup> Its excellent safety profile and pharmacokinetic properties make it a suitable alternative therapy for cutaneous leishmaniasis. It has a long half-life, high solubility in water, and a concentration in skin that is 10 times that in plasma.<sup>18,19</sup> We conducted a randomized, double-blind, placebo-controlled trial in Saudi Arabia of the efficacy and safety of a six-week course of oral fluconazole for the treatment of cutaneous leishmaniasis caused by *L. major*.

### METHODS

#### Study Patients

Eligible patients were persons from the Al-Ahsaa and Riyadh regions of Saudi Arabia, where *L. major* is endemic, who had skin lesions that were suspected to be cutaneous leishmaniasis.<sup>20,21</sup> Criteria for inclusion were an age of more than 12 years, the presence of lesions of parasitologically confirmed leishmaniasis, and the non-use of antileishmania therapy during the previous two months. Criteria for exclusion were pregnancy, potential for pregnancy, breast-feeding, the presence of lesions on the face or ears, the

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presence of more than 10 lesions, a history of liver disease, an elevated serum creatinine concentration, abnormal results on liver-function tests, and allergy to fluconazole. Most of the patients were foreign construction workers or farmers originally from countries where cutaneous leishmaniasis is not endemic. One of five patients was a local national.

### Study Design and Procedures

The study was a randomized, double-blind, placebo-controlled trial. The use of a placebo group was justified in this trial for several reasons: cutaneous leishmaniasis caused by *L. major* is self-limiting and heals without treatment after several months; the criteria for inclusion and exclusion did not permit the enrollment of patients for whom antimony therapy was indicated according to the standard of care in the areas where *L. major* is endemic; and if the condition progressed at any stage, an independent, experienced dermatologist switched the patient to antimony therapy. The study protocol and consent form were approved by the Human Subjects Committee at the Harvard School of Public Health and the Licensing Committee at the Ministry of Health in Saudi Arabia. All the patients or their parents or guardians gave written informed consent.

To detect a difference of 22 percent in the rate of healing between the placebo group and the treatment group, assuming a healing rate of 45 percent in the placebo group, with a power of 90 percent and a two-sided type I error of 5 percent, 101 subjects were needed in each group.<sup>22</sup> To compensate for loss to follow-up, 25 percent more patients were to be enrolled in each group. Eligible, consenting patients enrolled in the study were randomly assigned to receive either fluconazole (Diflucan, Pfizer, New York) in the form of a 200-mg capsule once daily for six weeks or a matching placebo. Each coded package contained 42 capsules. The randomization sequence was generated from a random-number table.

At the time of enrollment, patients received a full physical examination, and blood was obtained for liver-function tests and a renal profile. The number of leishmania lesions was charted, along with a description of their appearance, their size in millimeters, their location, and the presence or absence of bacterial superinfection. The status of each lesion was documented every two weeks for six weeks, then every month for three months, and then every three months until the end of one year. Lesions with a secondary bacterial infection were treated with local care and topical antibiotics. If systemic antibiotics were required, agents with known or suspected activity against leishmania, such as rifampin, were not used.<sup>23,24</sup> An independent observer evaluated the rates of compliance and side effects by interviewing patients and counting their remaining capsules. There was clinical monitoring for adverse events in all patients. Nine patients had an additional liver-function test, the results of which were normal. The time to healing was defined as the number of weeks from randomization to the complete healing of the last skin lesion. Patients in whom oral therapy was thought to have failed were offered sodium stibogluconate. The study end points were the time to complete healing of all skin lesions, the need to switch to antimony compounds, and withdrawal from the study. The study was completed at the end of the leishmania season, by which time we had enrolled 209 of the 252 subjects we had intended to enroll.

### Parasitologic Studies

Parasitologic confirmation by smear and culture was attempted for all patients. Scrapings or a biopsy specimen from the edge of a lesion without apparent secondary bacterial infection was smeared on two slides and a portion was placed in a culture bottle. Smears were allowed to dry, fixed with methanol, stained with 10 percent Giemsa stain, and then examined for the presence of amastigote forms of leishmania. For culture, the collected material was inoculated into biphasic culture medium (nutrient agar [BKO 21, Biokar, Beauvais, France] containing 10 percent whole rabbit blood [vol/vol] overlaid with RPMI 1640 medium containing 100 µg of

gentamicin per milliliter). The inoculated cultures were incubated at 21°C for up to six weeks and examined biweekly for the presence of promastigote forms of leishmania. Any culture that yielded promastigotes was immediately subcultured in fresh biphasic culture medium, the liquid phase of which had been enriched with 10 percent heat-inactivated fetal-calf serum. Uncontaminated samples of promastigotes from the second or third passage of the subculture were inoculated into "sloppy Evans" medium.<sup>25</sup> Electrophoresis of the enzymes of leishmania parasites is used to classify isolates of leishmania into zymodemes. The parasites were characterized by the electrophoretic analysis of 15 enzymes with the use of the techniques and zymodeme nomenclature of Rioux et al.<sup>26</sup>

### Statistical Analysis

Epi Info software (version 6.02, Centers for Disease Control and Prevention, Atlanta, and World Health Organization, Geneva) was used for data entry. Statistical analysis was performed with the use of SAS software (SAS Institute, Cary, N.C.). Student's t-test was used to compare the two groups in terms of the means of continuous variables (e.g., age, duration of symptoms, number of lesions, and time to healing). Medians were compared by the Wilcoxon rank-sum test. The difference between the proportions of persons in each group in whom healing was complete was assessed by Fisher's exact test. The Kaplan-Meier method was used for the analysis of time to healing. To compare the two survival curves, the log-rank test was used. Multivariate analysis was carried out with the use of proportional-hazards regression to evaluate the effect of covariates on time to healing. All analyses were based on the intention-to-treat principle. The authors designed the study and had full access to the data without interference from the commercial sponsor.

## RESULTS

### Study Patients

Between October 1995 and June 1996, 248 patients were screened for the study, of whom 209 underwent randomization; 106 were assigned to the fluconazole group, and 103 were assigned to the placebo group. All patients had lesions that were parasitologically confirmed by smear, culture, or both, except for one patient in the placebo group, who was therefore excluded from the analyses. Of the 208 patients who were included, 63 (30 percent) received the container of capsules at the first visit and never returned for follow-up. Thirty-seven patients randomly assigned to receive placebo (36 percent) and 26 patients randomly assigned to receive fluconazole (25 percent) were lost to follow-up. The relative risk of loss to follow-up was 1.48 for the placebo group as compared with the fluconazole group (95 percent confidence interval, 0.97 to 2.25). The basic demographic data, and the number, size, duration, and condition of lesions in the patients who were lost to follow-up were not statistically different from those of the patients with data that could be analyzed. End points and follow-up data were available for 145 patients — 80 in the fluconazole group and 65 in the placebo group. There was no significant difference between the fluconazole and placebo groups in terms of age; the number, size, condition, or duration of lesions; or the use or nonuse of antibi-

TABLE 1. CHARACTERISTICS OF THE PATIENTS.\*

CHARACTERISTIC	FLUCONAZOLE GROUP (N=80)	PLACEBO GROUP (N=65)
Age — yr	31.2±7.3	31.1±7.9
No. of lesions	3.1±2.5	3.7±2.4
Duration of lesions before therapy — wk†	9.2±5.1	7.7±4.7
Size of lesions — mm	17±11	19±10
Use of antibiotics — no. (%)‡	32 (40)	34 (52)

\*Plus-minus values are means ±SD.

†P=0.07 for the comparison between groups.

‡The relative risk of the need for antibiotics was 0.76 (95 percent confidence interval, 0.54 to 1.09) in the fluconazole group as compared with the placebo group.

otics (Table 1). According to the multivariate analysis, there was no significant difference at base line between the two groups in terms of the combination of the mean number, duration, and size of lesions. All patients were followed for a mean of 72 days after the completion of therapy. None of the patients with complete healing had a relapse during a mean of seven months of follow-up.

At the time of the completion of therapy at six weeks, 23 of the 80 patients in the fluconazole group (29 percent) and 4 of the 65 patients in the placebo group (6 percent) had complete healing of all lesions (relative risk of complete healing, 4.67; 95 percent confidence interval, 1.70 to 12.83). When patients who dropped out of the study were included in an intention-to-treat analysis, 22 percent of the patients in the fluconazole group and 4 percent of those in the placebo group had complete healing at six weeks (relative risk, 5.53; 95 percent confidence interval, 1.98 to 15.44). At the three-month follow-up visit, 63 of the 80 patients in the fluconazole group (79 percent) had complete healing, as compared with 22 of the 65 patients in the placebo group (34 percent; relative risk, 2.33; 95 percent confidence interval, 1.63 to 3.33). According to an intention-to-treat analysis, in which it was assumed that treatment had failed in patients who dropped out of the study, 59 percent of the patients in the fluconazole group and 22 percent of those in the placebo group had complete healing (relative risk, 2.76; 95 percent confidence interval, 1.84 to 4.12). During follow-up, an antimony compound (sodium stibogluconate) was offered to 11 patients in the fluconazole group (14 percent) and 33 in the placebo group (51 percent) in whom oral therapy was considered to have failed

(relative risk of treatment failure, 0.27; 95 percent confidence interval, 0.15 to 0.49).

According to the Kaplan–Meier analysis (Fig. 1), the time to healing was shorter for the patients in the fluconazole group than for those in the placebo group (median, 8.5 weeks and 11.2 weeks, respectively; P<0.001 by the log-rank test). Age, the duration of symptoms before therapy began, the number, size, and condition of lesions, the use or nonuse of antibiotics, and compliance with the treatment regimen were evaluated by proportional-hazards regression and were not found to affect the time to healing.

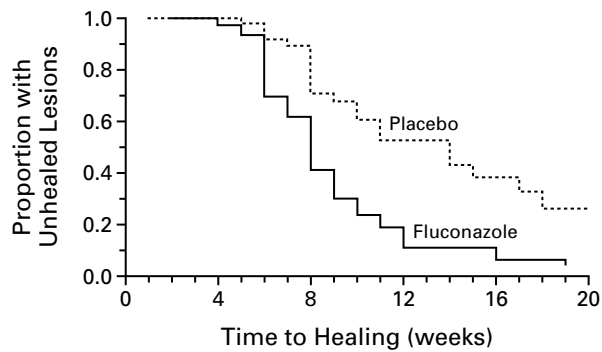
All 208 patients had evidence of leishmaniasis on a smear, a culture, or both. The parasite was grown from the samples obtained from 56 patients (27 percent) and in all cases was identified by isoenzyme electrophoresis as *L. major zymodeme* MON-26. No patient in either group had to stop therapy because of side effects. Mild and similar side effects were reported by patients in both groups.

## DISCUSSION

Cutaneous leishmaniasis of the Old World is endemic in the littoral zone of the Mediterranean, the Arabian Peninsula, the Middle East, East Africa, and other geographic areas. Events in the Middle East since the Persian Gulf War have led to more exposure of persons from nonendemic areas to the vector and the parasite, and the incidence of the disease has increased.<sup>27-30</sup> Because treatment with antimony agents is associated with side effects and with the inconvenience of parenteral administration, there has been a demand for oral alternatives.

We selected areas where *L. major zymodeme* MON-26 is endemic. Because of the criteria for inclusion and the limited number of women at risk for leishmania in the study areas, we had only one female patient. Indeed, fewer than 25 percent of reported cases of cutaneous leishmaniasis in Saudi Arabia occur among women.<sup>31</sup> We anticipated a high rate of loss to follow-up (and it was approximately 30 percent), because cutaneous leishmaniasis primarily affects construction workers and farmers, who are frequently unable to keep their follow-up appointments because of work or financial constraints. Although a greater number of patients in the placebo group were lost to follow-up, the difference was not statistically significant. Demographic characteristics and characteristics of the lesions of the patients who were lost to follow-up were similar to those of the patients for whom complete data were available.

We are not aware of any previous study that evaluated the clinical efficacy of fluconazole for cutaneous leishmaniasis. Sundar et al. described activity of fluconazole against visceral leishmaniasis in a report on 20 patients with Indian kala-azar who received



**Figure 1.** Kaplan–Meier Estimates of Proportions of Patients with Unhealed Lesions.

$P < 0.001$  by the log-rank test for the comparison between groups.

fluconazole, in 11 of whom the disease was apparently cured, by clinical and parasitologic standards.<sup>16</sup> However, all patients eventually had a relapse and were treated with antimony. Fluconazole has also been used successfully in combination with allopurinol to treat visceral leishmaniasis in immunocompromised patients.<sup>17</sup> In vitro studies have found that the activity of fluconazole against various leishmania species, including *L. major*, is poor. However, the drug's activity was evaluated with the use of promastigotes, a form of the organism that is not found in infected humans,<sup>3</sup> or with the use of amastigotes in a human macrophage culture system that had problems with cell lysis.<sup>4</sup>

The other azoles that have been studied for the treatment of cutaneous leishmaniasis of the Old World are ketoconazole and itraconazole. Several uncontrolled studies in which ketoconazole was used had mixed results.<sup>7,8,32</sup> Only one randomized, double-blind, placebo-controlled study examined the effect of itraconazole on cutaneous leishmaniasis.<sup>15</sup> In that study, Momeni et al. randomly assigned 131 patients to receive itraconazole or placebo for three weeks. At the end of the one-month follow-up period, 59 percent of the patients in the itraconazole group and 44 percent of those in the placebo group were cured. The difference was not statistically significant.

We evaluated the duration of disease before diagnosis and treatment, the number and distribution of lesions, the size of each lesion at the time of enrollment, and whether the lesions had secondary bacterial infection. Whether or not there was a response to the study drug was determined at the completion of therapy (at six weeks) and at three months. The rate of complete healing was 1.76 times as high in the flu-

conazole group as in the placebo group at six weeks and 2.33 times as high at three months.

Another variable we evaluated was the need to switch to antimony treatment at or after the completion of the study therapy. Patients in whom oral therapy was considered by the dermatologist to have failed because there was progression of disease or a lack of a satisfactory response were offered antimony; more than half of the patients in the placebo group were offered such treatment, as compared with only 14 percent in the fluconazole group.

The time to healing for each patient in whom all lesions were completely healed was also evaluated. Not only did more patients in the fluconazole group have complete healing at six weeks and at three months, but such healing was achieved sooner in that group. Time to healing was significantly shorter in the fluconazole group, according to the Kaplan–Meier analysis. Because the disease is self-healing in immunocompetent patients and all lesions will eventually heal, the two Kaplan–Meier curves will eventually meet. We used proportional-hazards regression to identify factors that could affect the time to healing. There was no significant effect of any of the independent variables, including age, the duration of symptoms before therapy began, the size of the lesions, the number and location of lesions, the presence or absence of secondary bacterial infection, and the use or nonuse of antibiotics.

Oral fluconazole as a treatment for cutaneous leishmaniasis caused by *L. major* is useful and well tolerated. It improves the chances that lesions will heal more rapidly. Other species causing cutaneous leishmaniasis may not be as responsive to fluconazole. Its activity against leishmania must be tested in patients in other areas of endemic disease. Because most lesions of *L. major* eventually heal without treatment, decisions regarding the administration of fluconazole must take into account the cost of medication and the ability of the patient to adhere to the treatment regimen.

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