Efficacy of Itraconazole in the Prophylactic Treatment of Pityriasis (Tinea) Versicolor

Jan Faergemann, MD, PhD; A. K. Gupta, MD, FRCPC; A. Al Mofadi, MD, FRCPC; A. Abanami, MD, FRCP(Edin); A. Abu Shareaah, MD; Greet Marynissen, PhD

Background: Pityriasis (tinea) versicolor has a high tendency to recur after being treated successfully. Prophylactic treatment to reduce recurrence is needed.

Objective: To determine whether recurrence of pityriasis versicolor could be prevented by prophylactic itraconazole treatment.

Design: Open treatment followed by a randomized, double-blind, placebo-controlled phase.

Setting: Multinational outpatient centers.

Patients: A total of 239 consecutive patients were included; 238 started open treatment. A total of 209 patients started prophylactic treatment: 106 in the itraconazole group and 103 in the placebo group.

Interventions: Open treatment: itraconazole, 200 mg once daily for 7 days. Prophylactic treatment: itraconazole, 200 mg, or placebo twice daily 1 day per month for 6 consecutive months.

Main Outcome Measures: Mycological cure rates at the end of open treatment and at the end of prophylactic treatment.

Results: Mycological cure at the end of open treatment was 92% (205/223). At the prophylactic treatment end point (6 months), mycological cure was 88% (90/102) in the itraconazole group and 57% (56/99) in the placebo group (P < .001). In open treatment, 11 patients were not able to be evaluated for efficacy. In prophylactic treatment, 4 patients in the itraconazole group and 4 in the placebo group were not able to be evaluated. Adverse events were reported during open treatment by 26 patients (11%) and during prophylactic treatment by 17 (16%) in the itraconazole group and 14 (14%) in the placebo group. No patients experienced any serious adverse events.

Conclusions: Prophylactic itraconazole treatment is efficacious for pityriasis versicolor after 6 months, as is itraconazole in the treatment of pityriasis versicolor.

Arch Dermatol. 2002;138:69-73

PITYRIASIS (TINEA) versicolor may be treated with topical or oral agents, with the latter being used especially when the disease is widespread or does not respond to topical measures. Systemic agents used for treating pityriasis versicolor include itraconazole, ketoconazole, and fluconazole.1,2

Itraconazole is a triazole antifungal agent with strong keratophilic and lipophilic properties.3 Similar to other azole antifungal agents, the mode of action of itraconazole involves inhibition of 14-α-demethylase, resulting in impaired sterol synthesis in fungal cell membranes. In vitro, itraconazole is active not only against yeasts such as Malassezia and Candida species but also against dermatophytes and nondermatophyte molds.4,5

When itraconazole is used to treat pityriasis versicolor, a suggested regimen is 200 mg/d for 7 days, with a minimum cumulative dose of at least 1000 mg being required for effective therapy.6,7 Four weeks after the start of therapy, cure rates of 80% to 90% have been reported.7 Although the fungal organisms may be nonviable, the color of the affected skin may take several weeks or months to normalize.

Pityriasis versicolor recurs at a variable rate in treated individuals, and 60% to 90% of patients relapse within 2 years in some series.8 Therefore, it is important to evaluate a prophylactic regimen that may be effective and safe in preventing the recurrence of pityriasis versicolor.

We evaluated the efficacy of treatment with itraconazole, 200 mg once daily for 1 week, and the efficacy of placebo-controlled prophylactic treatment with itraconazole, 200 mg taken 12 hours apart 1 day per month for 6 consecutive months, in terms of clinical and mycological outcome and frequency of recurrence of pityriasis versicolor. To our knowledge, this
PATIENTS AND METHODS

This multicenter, multinational trial was characterized by an open, active treatment phase with itraconazole, 200 mg once daily for 1 week, followed by 4 weeks without active therapy. In patients in whom pityriasis versicolor cleared, active treatment was followed by a double-blind prophylactic treatment phase with itraconazole, 200 mg, or placebo twice on 1 day per month for 6 consecutive months. Patients were randomly allocated to 1 of the 2 treatments in the prophylactic phase.

Patients who fulfilled the inclusion and exclusion criteria at the first visit (baseline) received itraconazole therapy for 7 days (treatment phase). Five weeks from the start of therapy (ie, 4 weeks after treatment), patients who were mycologically cured (no hyphae present) were randomized into the double-blind prophylactic phase to receive either itraconazole or placebo treatment for 6 months. Inclusion criteria for subjects included those aged 12 to 70 years who had a clinical diagnosis of pityriasis versicolor confirmed by mycological examination and who provided written informed consent before inclusion into the trial. Exclusion criteria for subjects included those with (1) known sensitivity to itraconazole or its excipients, (2) chronic mucocutaneous candidiasis or systemic fungal infection, (3) immunosuppression caused by disease or treatment, (4) any other disease or condition that in the investigator’s opinion should exclude the patient from the trial, and those who (5) participated in an investigational drug trial within 30 days of selection, (6) were pregnant or breastfeeding, and (7) were women of childbearing potential without adequate contraception. The following therapies were not allowed: (1) topical antifungal agents, topical corticosteroids, shampoos with active ingredients against Malassezia, or tar shampoos used within 2 weeks of the randomization visit or during the trial (topical corticosteroid nasal sprays or eye ointments were allowed during the trial); (2) systemic corticosteroid therapy either within 1 month of the randomization visit or during the trial; (3) systemic antifungal therapy within 2 months of the randomization visit or during the trial; (4) use of the enzyme-inducing drugs rifampin, phenytoin, rifabutin, carbamazepine, and isoniazid; and (5) use of some drugs metabolized by cytochrome P4503A4 with concomitant increase in their concentrations (eg, terfenadine, astemizole, cisapride, oral midazolam hydrochloride, triazolam, quinidine gluconate, pimozide, and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors). Other medications known to interact with itraconazole were monitored if they were being taken concurrently. Because absorption of itraconazole is impaired when gastric acidity is decreased, acid-neutralizing agents (eg, aluminum hydroxide) should be administered at least 2 hours after the intake of itraconazole. Itraconazole should be administered with 2 glasses of a cola beverage in individuals with achlorhydria or those taking acid secretion suppressors (eg, H2-antagonists and proton pump inhibitors).

Patients could be withdrawn from the trial if (1) a serious adverse event occurred or (2) the investigator considered it in the best interest of the patient for safety reasons. Patients were withdrawn from the trial if they withdrew their consent or if the randomization code was broken.

METHODS OF ASSIGNING PATIENTS TO TREATMENT GROUPS

All patients admitted to the trial entered the open treatment phase. Patients who were mycologically cured (no hyphae present) at the end of week 3 from the start of therapy were allocated to one of the treatment groups in the double-blind prophylactic phase using a predetermined randomization code generated at a central site. At each participating medical center, medication numbers were assigned consecutively starting with the lowest available number. Therefore, the investigator was not aware of the randomization code.

DETERMINATION OF SAMPLE SIZE

The primary variable was the mycological cure rate at the end of open treatment and at the end of prophylactic treatment. Mycological cure was described as negative findings on light microscopic examination. Mycological cure was expected to occur in 83% of patients who underwent itraconazole treatment in the first treatment phase, in 89% who expected to occur in 85% of patients who underwent itraconazole treatment, in 89% who underwent prophylactic treatment with itraconazole, and in 71% who underwent placebo prophylaxis. To be able to detect this difference with a power of 80% at the 5% level of significance, 74 patients are required in each treatment group. Assuming a mycological cure rate of 85%, 174 patients would be required to start the first treatment phase to have 148 patients to randomize between the groups receiving placebo and active therapy in the prophylactic phase. Twenty-nine patients who received treatment in the open phase did not continue into the double-blind prophylactic phase. Of these, 18 were not cured and 11 were lost to follow-up or were noncompliant. At the end of open treatment, mycological cure was recorded in 205 (92%) of 223 patients (Table 2). All patients randomized into the double-blind prophylactic phase were mycologically negative at the time of randomization. At the end of the prophylactic phase, 90 (88%) of 102 patients in the itraconazole group and 36 (57%) of 99 in the placebo group were still mycologically negative (P <.001) (Table 2).

CLINICAL GLOBAL EVALUATION

Findings were scored as cured, marked improvement, moderate improvement, unchanged, or deteriorated. Global
treatment phase of the study. To account for a dropout rate of approximately 10%, at least 194 patients needed to be recruited for the trial.

SAFETY ANALYSIS

An evaluation of adverse events was performed on all patients who received the trial medication at least once. An additional intent-to-treat analysis was performed on all randomized patients who had at least 1 administration of the prophylactic treatment medication and who had efficacy data after visit 2.

INITIAL CHARACTERIZATION OF PATIENT SAMPLE

For the open treatment phase, all data were tabulated and were descriptively presented with 95% confidence intervals. Comparability between treatment groups was evaluated with respect to the demographic and baseline data. For continuous data (eg, age), the Van Elteren test was applied. For nominal categorical data (eg, sex and race), the Cochran-Mantel-Haenszel test for general association was used. For ordinal categorical data (eg, clinical global evaluation scores), the Cochran-Mantel-Haenszel row mean scores differences test was used. All data were analyzed descriptively.

EFFICACY VARIABLES

The primary variable was the mycological cure rate at the end of open treatment and at the end of prophylactic treatment. Mycological cure was defined as no hyphae present. Samples for microscopy were always taken from the same area. The cure rate at the end of the open treatment phase was tabulated. Itraconazole and placebo prophylaxis were compared at the end of the prophylactic treatment phase using the Cochran-Mantel-Haenszel test for general association. The cure rate at the end of prophylactic treatment, between-group differences for dichotomous data were investigated using the Cochran-Mantel-Haenszel test for general association. Groups were compared for ordinal data using the Cochran-Mantel-Haenszel row mean scores differences test. Comparisons were performed for continuous data using the Van Elteren test. Within-group changes from randomization visit 2 were analyzed using the Wilcoxon signed rank test for ordinal and continuous data and the McNemar test for dichotomous data. Time-to-recurrence data were analyzed using the Mantel-Cox test.

ASSESSMENTS

For efficacy evaluations, patients had to be seen preferably by the same physician at each trial visit to maintain uniformity across clinical evaluations.

Primary Efficacy Variable

The primary efficacy variable was the mycological cure rate assessed at the end of weeks 5 and 29. Mycological cure was defined as negative microscopic results (negative potassium hydroxide preparation). For mycological evaluation, skin scrapings were taken from the active border of the lesion.

Secondary Efficacy Variables

Signs and Symptoms. Hyperpigmentation, hypopigmentation, itching, erythema, and latent desquamation were assessed according to absence or presence at each visit.

Clinical Global Evaluation. At each visit, findings from clinical evaluation were rated as follows: cured (absence of all symptoms vs baseline, except hyperpigmentation or hypopigmentation); marked improvement (clinical improvement ≥50% vs baseline); moderate improvement (clinical improvement >0% to <50% vs baseline); unchanged (no change in symptoms vs baseline); and deterioration (worsening of symptoms vs baseline).

Patient Compliance. Compliance was measured by patient self-assessment and by blister card reconciliation at the end of open treatment and during prophylactic treatment. Self-assessment consisted of the patient recording in a diary the number of capsules taken per dose of trial medication, the time of each intake, and the dates.

evaluation scores were significantly better in the itraconazole group compared with the placebo group when evaluated at the prophylactic treatment end point (P<.001). For all variables (erythema, hypopigmentation, desquamation, and itching), the itraconazole group showed significantly superior changes at the prophylactic treatment end point compared with the placebo group.

ADVERSE EVENTS

Adverse events were reported by 26 patients (11%) during open treatment and 31 (15%) during prophylactic treatment (17 patients [16%] in the itraconazole group and 14 [14%] in the placebo group).

Adverse events considered to be possibly, probably, or very likely drug related were reported in 10 patients during the open treatment phase and in 2 in the itraconazole group during the prophylactic treatment phase. All these adverse events were mild to moderate in intensity, except for severe pruritus in 1 patient. All patients continued in the trial except for 1 in open treatment who experienced urticaria and was withdrawn. Two patients in open treatment and 4 in the placebo group of prophylactic treatment were withdrawn from the trial because of adverse events. Moderate urticaria in 1 patient was the only adverse event leading to withdrawal that was considered to be very likely related to trial medication use. No patients experienced a severe adverse event.

The most common adverse events during open treatment were gastrointestinal tract complaints, which were reported by 9 patients (4%). There were no reports of gastrointestinal tract complaints during prophylactic treat-
ment. The most common adverse events during prophylactic treatment were upper respiratory tract infection (reported by 4 patients [4%] in the itraconazole group and 4 [4%] in the placebo group) and influenza-like symptoms (reported by 1 patient [1%] in the itraconazole group and 4 [4%] in the placebo group).

Itraconazole was effective in this study in the treatment of pityriasis versicolor, with mycological cure in 92% of patients evaluated 5 weeks after the start of therapy. The efficacy rate was consistent with that reported in previous studies. The excellent in vitro activity of itraconazole against Malassezia species and its high lipophilicity and accumulation in sebaceous glands support the high efficacy rates recorded when patients were evaluated 5 weeks after the start of therapy and for the placebo prophylactic group at the end of 6 months’ follow-up.

The high rate of recurrence, reaching as much as 60% in 1 year and 80% in 2 years, is an important consideration in pityriasis versicolor. Clinical disease manifests itself when there is conversion of the saprophytic (blasto) form of Malassezia species to the mycelial form. In immunocompetent individuals, factors predisposing to recurrence may be difficult to eradicate, including a tendency toward seborrhea and heavy sweating in the presence of high temperature and high humidity. There may be an inherited predisposition to the disease. A permanent cure may therefore be difficult to achieve, and this may explain the long-term nature of the disease. Consequently, a prophylactic regimen may help avoid recurrence of pityriasis versicolor. Prophylactic regimens using ketoconazole include 200 mg given on 3 consecutive days every month or a single dose of 400 mg taken once a month. Topical therapies have been used as a prophylactic, but patient compliance is lower, and no controlled studies have been reported in the literature, to our knowledge.

The present study was designed to determine whether recurrence of pityriasis versicolor could be prevented by administering prophylactic itraconazole, 400 mg once a month. To our knowledge, such a study has not been reported previously. Our results demonstrate that prophylactic therapy with itraconazole was effective in preventing development of the disease during the 6-month study.

There are no documented studies of topical prophylactic treatment in the literature, to our knowledge. Compliance with topical treatment is probably lower because it is more time-consuming and therefore more difficult to convince the patient to perform than oral treatment. This prophylactic treatment procedure with 1 treatment day per month with itraconazole could be used primarily in patients with frequent recurrences. The prophylactic regimen of itraconazole, 400 mg administered once a month, was not only effective but also safe and had high compliance.

Accepted for publication May 23, 2001.

This study was supported by an unrestricted educational grant from Janssen Pharmaceutica.

We thank the following individuals for recruiting patients for the study: T. Novak Gregurek (Croatia); H. Eltousy, A. Farag, N. Saleh, and Z. Tosson (Egypt); M. Guinea- raes and A. Massa (Portugal); A. Abanami and A. Mofadi (Saudi Arabia); P. Procter, N. Rabobee, W. Sinclair, and J. van Heerden (South Africa); J. Faergemann (Sweden); and A. Abu Shareelah (United Arab Emirates).

Corresponding author and reprints: Jan Faergemann, MD, PhD, Department of Dermatology, Sahlgrenska University Hospital, S-413 45 Gothenburg, Sweden (e-mail: jan.faergemann@derm.gu.se).

REFERENCES

5. Van Custem J. Oral and parenteral treatment with itraconazole in various super-

©2002 American Medical Association. All rights reserved.

News and Notes

Richard B. Stoughton Memorial Travel Fellowship applications are invited from US dermatology residents. The fellowship will enable a dermatologist in training to present a poster and attend the British Association of Dermatologists Annual Scientific Meeting in Edinburgh from July 9 to July 12, 2002. The winner will receive free registration and admittance to the president’s reception and annual dinner. Accommodation will also be offered free of charge.

The closing date for completed applications is Friday, February 8, 2002. For further details and application forms please contact the BAD Fellowship Co-ordinator, British Association of Dermatologists, 19 Fitzroy Square, London W1T 6EH, England. Phone: 44-20-7383-0266; Fax: 44-20-7388-5263 (e-mail: admin@bad.org.uk).