# Comparative clinical trial: fluconazole alone or associated with topical ketoconazole in the treatment of pityriasis versicolor.

## Essai clinique comparatif : fluconazole seul ou associé au kétoconazole topique dans le traitement du pityriasis versicolor.

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**RÉSUMÉ**

**Prérequis :** Des études anciennes ont montré que le ketoconazole et le fluconazole sont efficaces dans le traitement du pityriasis versicolor .

**Objectif :** Comparer l'efficacité de 2 doses de fluconazole à une semaine d'intervalle administrée seule ou associée à une application de ketoconazole shampoing.

**Méthodes :** Nous avons inclus tous les patients atteints de pityriasis versicolorayant consulté au service de dermatologie de l'hôpital Habib Thameur de Tunis sur une période de 21 mois. Une distribution aléatoire des médicaments était pratiqué : groupe G1 avaient reçu deux doses de 300 mg de fluconazole à une semaine d'intervalle et groupe G2 avaient appliqué le premier jour du ketoconazole shampoing associé à la même posologie de fluconazole.

**Résultats :** Soixante et onze patients ont été inclus : 35 dans G1 et 36 dans G2. L'âge moyen était de 29,1 ans (extrêmes 16-70 ans). Le pityriasis versicolor se présentait sous forme de : macules (27%), plaques (24%) et de l'association des deux (47%). Les lésions étaient pigmentées (52%), hypochromiques (15%), érythémateuses (6%). Les lésions siégeaient essentiellement à la nuque 67%, au thorax 60% et aux épaules 40%. Concernant le protocole thérapeutique, l'analyse statistique a révélé qu'il n'y a aucune différence statistiquement significative entre les 2 groupes d'étude (p=0,13 à J14, p=0,57 à J28 et p=.0,2 à J56).

**Conclusion :** Une application unique de ketoconazole shampoing ne semble pas renforcer le taux de guérison après prise de deux doses de 300 mg de fluconazole à une semaine d'intervalle.

**Mots-clés**

pityriasis versicolor, kétoconazole, fluconazole, étude comparative

**SUMMARY**

**Background:** The efficacy of ketoconazole and fluconazole in pityriasis versicolor had been proved.

**Aim :** To compare the efficacy and the safety of two doses of fluconazole given 1 week apart alone or associated to ketoconazole shampoo.

**Methods:** Our study included all patients with pityriasis versicolor who attended in dermatology department of Habib Thameur Hospital, Tunis (over a 21-month period). During the considered period, patients were randomly assigned in two study groups: G1 receiving fluconazole two doses 300mg given 1 week apart with G2 taken an association of fluconazole (two doses 300mg given 1 week apart) and ketoconazole shampoo the first day.

**Results:** Seventy one patients were enrolled in our study: 35 in the fluconazole group and 36 in the fluconazole associated to ketoconazole shampoo comparator group. The mean age was 29.1 years [16-70 years]. Concerning the clinical form, 27% had macular lesions, 24% had plaques and 49% had mixed form. Lesions werehyperchromic52%; hypochromic 15% and erythematous 6%. As for main location, 67% had lesions on the neck; 66% on the trunk, 60% on the shoulders. At the end of the study, there was no significant difference in clinical presentation and in improvement rate of pityriasis versicolor between fluconazole and association of fluconazole and ketoconazole shampoo ((p=0.13 at day 14, p=0.57 at day 28 and p=0.2 at day56).

**Conclusion:** In this study, we have shown that the improvement rate of PV treated with two doses of 300 mg of fluconazole with one week interval was similar to those of an association of one application of ketoconazole shampoo and the same dose of fluconazole.

**Key-words**

Pityriasisversicolor, Ketoconazole, Fluconazole, Comparative Study

Pityriasis versicolor is a chronic superficial recurrent mycosis caused by yeasts of the Malassezia spp. genus commensal of the keratinized layers of the skin(1).Under conditions not yet understood, it becomes pathogenic determining the clinical manifestations of the disease. The antifugal treatment should lead to a long-lasting cure, good patient compliance and a low risk of adverse effects. A broad array of effective topical and oral antifungal agents is currently available. The aim of our study was to assess and compare the efficacy and the safety of fluconazole (Funzol® 150 mg, *Saiph Pharmaceutical Ltd, Tunisia*: two doses 300mg given 1 week apart) with those of the association of fluconazole (Funzol® 150 mg, two doses 300mg given 1 week apart) and ketoconazole shampoo (Philazole®, *Saiph Pharmaceutical Ltd*) in the treatment of patients with mycologically proven pityriasis versicolor.

## METHODS

Our study included all patients with pityriasis versicolor who attended in dermatology department of Habib Thameur Hospital, Tunis, Tunisia during a 21-month period. Exclusion criteria included patients under 18 years; pregnant women or nursing mothers; history of hepatic diseases; history of allergy to fluconazole or other azoles; history of treatment within recent 6 months with topical or systemic antifungal drugs (except griseofulvin and terbinafin); concomitant use of interferential drugs such as cisaprid, anticoagulants, hypoglycemic sulfamides, rifampin, isoniazid, diuretics, phenytoin, cyclosporin, tacrolimus, theophyllin, rifabutin and other hepatotoxic drugs.

During the study period, patients were randomly assigned in two study groups, treated with either fluconazole or combination of fluconazole and ketoconazole shampoo. The patients answered questions regarding their personal habits and lifestyle, such as use of oils in the skin, occupation, personal medical history, hammam (or sauna or other dry or wet heat places) attendance, wearing synthetic underwear or towel, underwear or towel exchange, excessive sweating, familial history of pityriasis versicolor, and past history of the disease.

Clinical and mycological evaluation of skin infection was done at baseline, 2, 4 and 8 weeks since the beginning of the treatment. Erythema, scaling, hypopigmentation, hyperpigmentation and pruritis were assessed. The areas involved by pityriasis versicolor were recorded. Patients

**Table 1:** Demographics and duration of disease in both groups at baseline

| 0 | Group I (n=35) | Group 2 (n=36) | p |
|---|---|---|---|
| **Sex (Female/Male)** | 16/19 | 16/20 | 0.91 |
| **Age interval (years)** | | | |
| 16-\| 20 | 8 | 8 | |
| 21-\| 30 | 16 | 14 | |
| 31-\| 40 | 6 | 7 | |
| 41-\| 50 | 2 | 2 | |
| > 50 | 3 | 5 | |
| median and quartile (years) | 27.6 (18-50) | 30.5 (16-70) | 0.32 |
| **Duration of the disease (months) (median and quartile)** | 48.3 (1-240) | 53.9 (1-480) | 0.76 |
| **Duration of the recent episode (months) (median and quartile)** | 8.1 (1-24) | 6.7 (1-36) | 0.44 |
| **Previous therapies** | 12/35 | 13/35 | 0.37 |
| **Familial history of PV (N/Y)** | 19/16 | 16/20 | 0.4 |
| **Drug intake:** | | | 0.3 |
| **Corticotherapy** | | 1/36 | 0.74 |
| Immunosuppressive therapy | 1/36 | 2/36 | 0.37 |
| **Smoking** | 12/35 | 11/36 | 0.55 |
| **Personal habits** | | | |
| Practice of sports | 14/35 | 11/36 | |
| Hammam or sauna attendance | 21/35 | 22/36 | 0.09 |
| Other heat places attendance | 8/35 | 3/36 | 0.54 |
| Use of oils in the skin | 2/35 | 1/36 | 0.41 |
| Wearing synthetic underwear | 16/35 | 13/36 | 0.83 |
| Underwear exchange | 8/35 | 9/36 | 0.56 |
| Towel exchange | 18/35 | 21/36 | |
| **Disease history** | | | |
| Recurrence of PV | 18/35 | 15/36 | 0.41 |
| Seasonal recurrence | 10/35 | 19/36 | 0.04 |
| **History of excessive sweating** | 23/35 | 29/36 | 0.16 |
| **History of hypersebborhea** | 21/35 | 20/36 | 0.70 |
| **History of itching** | 19/35 | 26/36 | 0.12 |

who interrupted the treatment for reasons not related to study medications were considered as drop-outs. At each visit, clinical efficacy was assessed as follows: cure (improvement with negative mycological examination), failure (no change or worsening in baseline signs) and not assessable (no evaluation of clinical response could be made for reasons such as lost to follow-up or protocol violation). Microscopic examination of lesion stripping taken by scotch tape was repeated at baseline, 2, 4 and 8 weeks. In addition, the presence or absence of fluorescence under wood's light was documented. Patients were also evaluated for adverse events at control visit. A statistical analysis between the two groups was performed using Chi-squared test and Fisher's exact test to compare the two study groups and the improvement rate for each treatment group and drug complications. Statistical significance was set at $p<0.05$.

## RESULTS

During the study period, 71 patients were enrolled in our study: the fluconazole group and the fluconazole associated to ketoconazole shampoo comparator group. Table I shows familial history and duration of the PV disease, main habits, activities, use of medication, smoking, individual characteristics of patients diagnosed with pityriasis versicolor and associated signs (hyperseborrhea, itching) in the two study groups. Among the 71 studied patients, 54% were male. The distribution of PV by age showed that the most affected age group was [21-30 years] (42% of patients). The mean age was 29.1 years [16-70 years]. The mean duration of the history of PV disease was 51.1 months [1-480 months]. The mean duration of the clinical manifestations of the recent episode of PV was 7.4 months [1-36 months]. Familial history of PV was reported by 50.7% of patients. Smoking was recorded in 32.4% of cases. Triggering factors possibly associated to the disease were found in the following frequencies: excessive sweating in 73% (52/71); hammam attendance in 60% (43/71); hyperseborrhea in 57% (41/71); towel exchange was recorded in 54% (39/71) of patients; wearing synthetic underwear in 40% (29/71); practice of sport was reported by 35% (25/71); underwear exchange was reported in 24% (17/71) of cases; attendance of heat places other than hammam and sauna in 15% (11/71) of patients and 4% (3/71) applied oil or moisturizers to the skin. Pruritus was observed in 49% (35/71) of cases. Recurrence of the disease was recorded in 46.5% (33/71) of patients. Patients who had been previously treated for the disease accounted for 35% (25/71) of the sample. There were no statistically significant differences regarding age, sex, duration of the disease, habits, triggering factors for patients in the two groups as shown in Table I.

The clinical presentation and the result of mycological examination of PV in the two study groups are presented in Table III. Regarding color, hyperchromic lesions corresponded to 52%; 27% had more than one color; 15% were exclusively hypochromic lesions and 6% were erythematous. Concerning the clinical form, 27% had macular lesions, 24% had plaques and 49% had mixed form. Of patients affected, 30% had more than five body regions involved, 31% had four or five regions involved, 26% had two to three regions involved and 13%, only one site. As for main location, 67% had lesions on the neck; 66%on both the trunk and the back, 60% on the shoulders and40% on the upper limbs. Two patients (3%) of patients had seborrheic dermatitis and 22% presented mycologically proven pityrosporum folliculitis. There were no statistical significant clinical differences between the two groups regarding the diagnostic and clinical evaluation as shown in Table II.

**Table 2 :** Clinical and mycological aspects of pityriasis versicolor in both groups at baseline

| | Group I (n=35) | Group 2 (n=36) | p |
|---|---|---|---|
| **Clinical aspect:** | | | |
| **Color:** | | | |
| Erythematous | 2 | 2 | 0.04 |
| Hypopigmented | 8 | 3 | |
| Hyperpigmented | 15 | 22 | |
| Hypo/Hyperpigmented | 5 | 9 | |
| Erythematous/ Hyperpigmented | 5 | 0 | |
| **Type:** | | | |
| **Macules** | 10 | 8 | 0.74 |
| Plaques | 6 | 10 | |
| Macules and plaques | 17 | 16 | |
| **Squamous:** | | | |
| **Fines scales** | 7 | 20 | 0.02 |
| Scales appearing after curettage | 12 | 7 | |
| **Both (Fines scales or appearing after curettage)** | 12 | 6 | |
| **Non squamous** | 4 | 3 | |
| **Number of sites involved** | | | |
| 1 | 6 | 3 | 0.6 |
| 2 to 3 | 10 | 9 | |
| 4 to 5 | 8 | 14 | |
| >5 | 11 | 10 | |
| **Localization** | | | |
| Face | 4 | 3 | 0.4 |
| Neck | 24 | 24 | |
| Shoulders | 18 | 25 | |
| Trunk | 22 | 25 | |
| Back | 21 | 26 | |
| Abdomen | 2 | 0 | |
| Buttocks | 4 | 2 | |
| Upper limbs | 10 | 19 | |
| Retro-auricular folds | 3 | 5 | |
| Submammary folds | 1 | 0 | |
| Axillae | 3 | 4 | |
| **Hypersebborhea** | 16 | 13 | |
| **Seborrheic Dermatitis** | 1 | 1 | |
| **PityrosporumFollicultis** | 10 | 6 | |
| **Mycological examination** | | | |
| Positive | 34 | 34 | 0.98 |
| Not done | 1 | 2 | |
| **Wood's light** | | | |
| Fluorescence | 5 | 9 | 0.93 |
| No Fluorescence | 3 | 5 | |
| Not done | 27 | 22 | |

**Table 3 :** Clinical and mycological aspects of pityriasis versicolor in both groups at baseline,14 days, 28 days and 56 days

| | Group I (n=35) | | | | | | |
|---|---|---|---|---|---|---|---|
| | **baseline** | 14 days | **28 days** | **baseline** | **14 days** | **28 days** | **56 days** |
| **Clinical aspect:** | | | | | | | |
| **Color:** | | NS | NS | | NS | NS | NS |
| Erythematous | 2/35 | 0/23 | 1/15 | 2/36 | 0/18 | 0/11 | 0/4 |
| Hypopigmented | 8/35 | 11/23 | 8/15 | 3/36 | 9/18 | 3/11 | 1/4 |
| Hyperpigmented | 15/35 | 6/23 | 3/15 | 22/36 | 5/18 | 2/11 | 1/4 |
| Hypo/Hyperpigmented | 5/35 | 3/23 | 1/15 | 9/36 | 4/18 | 1/11 | 1/4 |
| Erythematous/ Hyperpigmented | 5/35 | 1/23 | 0/15 | 0/36 | 0/18 | 0/11 | 0/4 |
| **Clinical cure** | | | | | | | |
| **Lost to follow-up** | | 2/23 | 2/15 | | 0/18 | 5/11 | 1/4 |
| **Type:** | | 12/35 | 8/23 | | 18/36 | 7/18 | 7/11 |
| **Macules** | 10/35 | NS | NS | 8/36 | NS | NS | NS |
| Plaques | 6/35 | 14/23 | 9/15 | 10/36 | 7/18 | 4/11 | 1/4 |
| Macules and plaques | 17/35 | 4/23 | 2/15 | 16/36 | 7/18 | 1/11 | 1/4 |
| **Clinical cure** | | 3/23 | 2/15 | | 4/18 | 1/11 | 1/4 |
| **Lost to follow-up** | | 2/23 | 2/15 | | 0/18 | 5/11 | 1/4 |
| **Squamous:** | | 12/35 | 8/15 | | 18/36 | 7/18 | 7/11 |
| **Fines scales** | 7/35 | NS | NS | 20/36 | NS | NS | NS |
| **Scales appearing after curettage** | 12/35 | 3/23 | 2/15 | 7/36 | 2/18 | 0/11 | 1/4 |
| **Both (Fines scales or after curettage)** | 12/35 | 3/23 | 1/15 | 6/36 | 1/18 | 0/11 | 0/4 |
| **Non squamous** | | | | | | | |
| **Lost to follow-up** | 4/35 | 1/23 | 1/15 | 3/36 | 0/18 | 0/11 | 0/4 |
| | | | | | | | |
| **Number of sites** | | 16/23 | 11/15 | | 15/18 | 11/11 | 1/4 |
| 1 | 6/35 | 12/35 | 8/23 | 3/36 | 18/36 | 7/18 | 7/11 |
| 2 to 3 | 10/35 | | | 9/36 | | | |
| 4 to 5 | 8/35 | 6/23 | 6/15 | 14/36 | 3/18 | 5/11 | 1/4 |
| >5 | 11/35 | 8/23 | 3/15 | 10/36 | 10/18 | 1/11 | 2/4 |
| **Clinical cure** | | 3/23 | 2/15 | | 3/18 | 0/11 | 0/4 |
| **Lost to follow-up** | | 4/23 | 3/15 | | 2/18 | 0/11 | 0/4 |
| **Hyperseborrhea** | 16/35 | 2/23 | 1/15 | 13/36 | 0/18 | 5/11 | 1/4 |
| **Seborrheic Dermatitis** | 1/35 | 12/35 | 8/23 | 1/36 | 18/18 | 7/18 | 7/11 |
| **Pityrosporum Folliculitis** | 10/35 | 4/23 | 3/15 | 6/36 | 5/18 | 3/11 | 0/4 |
| **Mycological examination** | | 1/23 | 0/15 | | 0/18 | 0/11 | 0/4 |
| Positive | 34/35 | 2/23 | 1/15 | 34/36 | 1/18 | 1/11 | 0/4 |
| Negative | 0/35 | NS | NS | 0/36 | NS | NS | NS |
| Not done | 1/35 | 5/23 | 2/15 | 2/36 | 1/18 | 2/11 | 1/4 |
| **Wood's light** | | 16/23 | 13/15 | | 15/18 | 7/11 | 3/4 |
| Fluorescence | 5/35 | 2/23 | 0/15 | 9/36 | 2/18 | 2/11 | 0/4 |
| No Fluorescence | 3/35 | NS | NS | 5/36 | NS | NS | NS |
| Not done | 27/35 | 0/23 | 0/15 | 22/36 | 0/18 | 0/11 | 1/4 |
| **Side Effects** | | 6/23 | 5/15 | | 5/18 | 2/11 | 3/4 |
| Abdominal pain | | 17/23 | 10/15 | | 13/18 | 9/11 | 0/4 |
| Pruritus | | NS | NS | | NS | NS | NS |
| | | 1/23 | 1/15 | | 0/18 | 0/11 | 0/4 |
| | | 3/23 | 0/15 | | 0/18 | 0/11 | 0/4 |

NS: Not significantly different, p>0.05

Patients were re-evaluated 14, 28, 56 days after the first visit clinically and through direct microscopy. As shown in Table III, there was no significant difference in clinical presentation and in improvement rate of pityriasis versicolor between fluconazole and association of fluconazole and ketoconazole shampoo. Mycological response among the treatment groups is summarized in Table IV. Cure rates ranged between 70 and 100% in the first group and between 63 and 63% in the second group (statistically not significant). Adverse reaction to treatments were seen in four patients in fluconazol group (abdominal pain, itching).

The highest rate of reinfection at the follow-up evaluation in our study occurred in the fluconazole group.

**Table 4 :** Mycological cure rate of patients with pityriasis versicolor in both groups at 14 days, 28 days and 56 days

| | Number of patients | | | | | |
|---|---|---|---|---|---|---|
| | 14 days | | 28 days | | 56 days | |
| | Examined | Showing clinical /mycological cure | Examined | Showing clinical/ mycological cure | Examined | Showing clinical/ mycological cure |
| G1 | 23 | 16 (70%) NS | 15 | 13 (86%) NS | 6 | 6 (100%) NS |
| G2 | 18 | 15 (83%) NS | 11 | 7 (63%) NS | 4 | 3 (75%) NS |

NS: Not significantly different, p>0.05

## DISCUSSION

Treatment with topically applied antifungal agents is still recommended as initial therapy for most patients with PV. Nevertheless this approach had some disadvantages such as need for regular application over large areas of the body for prolonged periods of time, short term efficacy and a high rate of relapse. Systemic therapy has generally been reserved for the management of extensive or recalcitrant cases. To our knowledge, no studies compared systemic treatment of PV to association of topical and systemic treatments. Previous studies have shown that fluconazole (400 mg single dose), fluconazole (two 300 mg doses with 1 week interval), fluconazole 300mg once weekly for two weeks was effective in 74% and 100%, 98% of patients respectively (2). Fluconazole is rapidly and almost completely absorbed after oral administration. Next, it is distributed extensively throughout body tissues and eliminated slowly from plasma. Fluconazole appears also to accumulate in the stratum corneum. Oral fluconazole given at 300mg once weekly for two weeks seems to be the best treatment regimen (3,4). It is associated to high cure rate, a low incidence of side effects, a short treatment duration and an increased adaptation of the patients. Nevertheless, resistance to treatment or relapses had been reported (5). Ketoconazole 2% shampoo used as a single application had been proved to be more effective than placebo in the clinical and mycological response of PV. No statistical difference was noted between single application of ketoconazole shampoo and daily application for three consecutive days (6). In the present study, we choose to apply ketoconazole shampoo as a single dose. The aim of our study was to attest if association of topical and systemic treatment may enhance clinical cure, decrease rate of recurrence compared to systemic treatment alone. We conclude that the improvement rate of PV treated with two doses of 300 mg of fluconazole with one week interval was similar to those of an association of one application of ketoconazole shampoo and two doses of 300 mg of fluconazole with one week interval. No significant differences in safety and tolerability between the two drugs were observed.

## CONCLUSION

In conclusion, association of topical ketoconazole and oral fluconazole demonstrated to be as effective as oral fluconazole alone. Therefore, it seems useless and not economic to associate topical and systemic route for the treatment tinea versicolor.

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