A comparative efficacy of fluconazole to itraconazole in treatment of pityriasis versicolor

Nasruddin E. El-Reyani[1*], Huda D. Abuhjar[1], Huwaida D. Abuhjar[1], Mahran J. Tarabi[2] and Bashir M. Al-Zandah[2]

[1]Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, University of Tripoli and

[2]Department of Dermatology, Tripoli Medical Centre, Tripoli, Libya

[*]*Correspondence to N.ElReyani@uot.edu.ly*

Abstract: Pityriasis versicolor is a benign superficial fungal infection. Topical drugs are often effective in treatment of limited lesions while in extensive case systemic drugs are more suitable. The new oral antifungal drugs triazole, itraconazole and fluconazole showed remarkable promising results at different dose schedules. This study was aimed to compare the efficacy and safety of two oral antifungal drugs; fluconazole and itraconazole on the progression of Pityriasis Versicolor after two and four week's interval. Sixty patients with extensive Pityriasis Versicolor were assigned for treatment with either two doses of 300 mg fluconazole once weekly for two weeks (FTP), a single dose of 400 mg of itraconazole (ITP 1) and two doses of 400 mg itraconazole with one week interval for two weeks (ITP 2, n = 20 patients each group). All patients were clinically investigated by wood's lamp and mycologically by 10% potassium hydroxide. Four weeks after treatment the improvement rate and side effects were evaluated. Our results showed that 83.3%, 41.2%, and 52.6% of respectively pretreated FTP, ITP1 and ITP2 groups were significantly became wood's lamp and potassium hydroxide negative at the end of four weeks. In addition, fluconazole was found more complied by Pityriasis Versicolor infected patients compared to itraconazole treated patients. The present findings showed that fluconazole is clinically preferred than itraconazole in cure of Pityriasis Versicolor.

Keywords: Pityriasis Versicolor, fluconazole, itraconazole, wood's lamp

Introduction

Skin disorders are worldwide health problem that represent a group of exhausted diseases with different causes. A fungal infection, in particular Pityriasis Versicolor (PV), is one of these disorders that have a special concern on patient's satisfaction. In the tropics and temperate climates, it representing a common superficial fungal skin infection caused by lipophilic fungi of the *Malassezia* type. The three kinds most commonly related to this disease are: *M. furfur, M. globosa* and *M. sympodialis* (1- 3). It has been reported that PV infected all age groups with peak age-specific prevalence is among young adults of 20 - 40 years old (4). PV disease usually appears as hypopigmented or hyper-pigmented slightly scaling macules limited to the upper trunk and neck (5, 6). Studies have indicated that PV treatment is sought only for cosmetic reasons. As spontaneous improvement is mostly uncommon the majority of patients require further treatment. In general, treatment is simple but relapse is a common problem. Clinical studies have indicated that topical treatment, ranging from selenium sulphide to imidazoles,

were effective in managing PV but found time consuming, messy and inadequate especially for large areas (7). Orally, ketoconazole was the first antifungal drug used in treatment of PV, but its use was limited due to its hepatic toxicity and possible endocrine effects. Newer triazoles like itraconazole and fluconazole have improved the treatment of PV. The advantages are their safety, better cure rate and infrequent relapses (8). Furthermore, itraconazole solution form and capsule permits its usage in various regimens and dosage (9, 10). As the drug achieves higher concentrations in the stratum corneum and persists for 3 - 4 weeks after discontinuation of therapy single-dose regimen was found remarkably effective (11, 12). In addition, in plasma itraconazole was found with an approximately equal concentration of its biologically active metabolite hydroxyl itraconazole (10, 13). Whereas, fluconazole concentration was 10 times higher than the concentration in the stratum corneum and persists for about two weeks. So it is expected to be effective in similar fashion with a single dose (14). Moreover, it is readily diffuses into body fluids with significant first pass metabolism (15). Therefore, the present study was aimed to clinically compare the efficacy and safety of fluconazole versus itraconazole, administered orally, in the treatment of PV.

Materials and methods

Patients: a multicenter designed study for PV patients was performed. Three main hospitals, at Tripoli city, were selected to incorporate patients with confirmed diagnosis of PV and only those patients with extensive lesions of PV were eligible in the study. Accordingly, sixty patients of either sex and with an average age of 29.1 ± 8.3 years were randomly recruited. Patients were requested to follow-up for four weeks. The main point of the study was to measure the drug effectiveness at different dose regimens. The patients were divided into three groups (n = 20 patients per group). The first served for fluconazole and represented fluconazole treated patients (FTP), the second served for itraconazole with a single dose and represented itraconazole treated patients (ITP1), and the third group was served the itraconazole with two dose-regimens, itraconazole treated patients (ITP2).

Dose regimen: after a verbal consent of the enrolled patients in this study the following regimen was designed. For FTP group, the patients were asked to take their medication in a range of two doses of 300 mg/week for two consecutive weeks. ITP1 participants were asked to take their medication as a single dose of 400 mg for one week. ITP2 were treated by two doses of 400 mg of itraconazole once weekly for two weeks. None of the regimens designed for these patients was set for pulse therapy.

Exclusion criteria: patients were excluded from the study if were on multiple therapies for more than one disease, those with systemic mycosis, those with history of hepatic and renal diseases, pregnant and lactating mother and those patients on systemic steroids, anti-mitotic and immunosuppressive drugs. Moreover, patients are excluded if had receive any topical or systemic antifungal therapy for at least two months prior to the study. Consequently, two patients from FTP group (10%), three patients from ITP1 group (15%) and one patient (5%) from ITP2 group were excluded from the study.

Patient examination: after detailed history was taken from each patient, clinical examination and investigation using wood's lamp were done

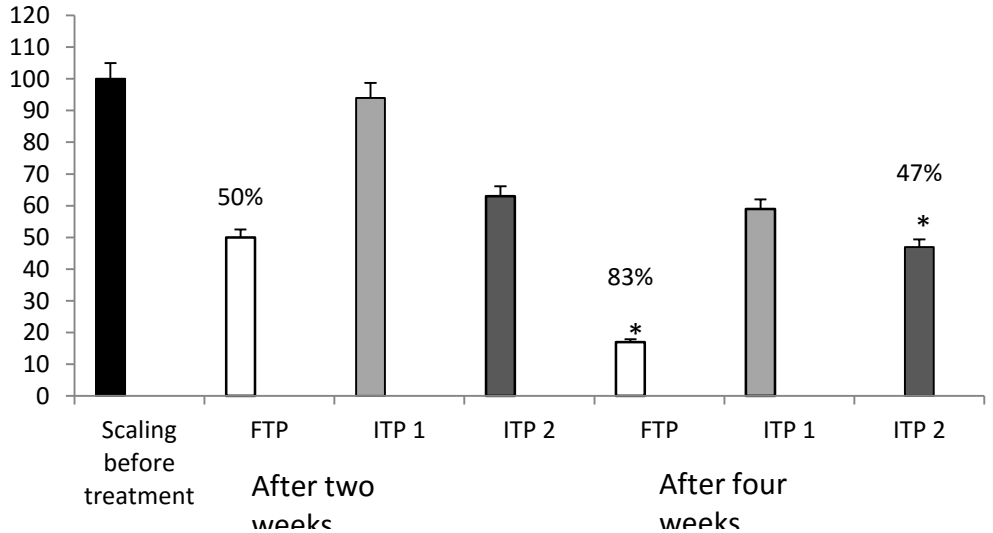
at first visit and rechecked weekly for four consecutive weeks. At baseline investigation, skin scraping for potassium hydroxide (10%) examination was taken from the lesions to confirm the diagnosis and continued to be reinvestigated to the end of the study. Routin investigation on baseline haemogram parameters including complete blood picture and liver and renal function tests were done in all patients and repeated weekly throughout the study. Variable parameters for clinical evaluation were presence of itching, scaling and over pigmentation and drug side-effects if any were noted. Irrespective to residual dyschromia patients who became KOH negative were considered to be cured.

Statistical analysis: The differences between and within treatment groups were analyzed by means of analysis of variance ANOVA followed by *post hoc* Tukey's test. Values are presented as mean (±SD). All analyses were performed with SPSS for Windows version 20.0 (IBM SPSS Inc., Chicago, IL, USA). Differences were considered to be significant at $P < 0.05$.

Results

Four weeks before starting treatments all patients (100%) were arrived to hospitals with skin scaling. Among patients treated with fluconazole, nine patients showed 50% reduction in scaling compared to basline observation (Fig. 1). After four weeks of fluconazole therapy 15 patients displayed significant disappearance in scaling by 83.3% ($P < 0.05$) compared to day zero. ITP groups, ITP1 (eight patients) and ITP2 (seven patints), showed remarkable reduction in scaling by respectively 41.2% and 37% compared to baseline remarks. After four weeks 10 patients (52.6%) showed significant reduction in scaling compared to baseline records ($P < 0.05$, Fig. 1).

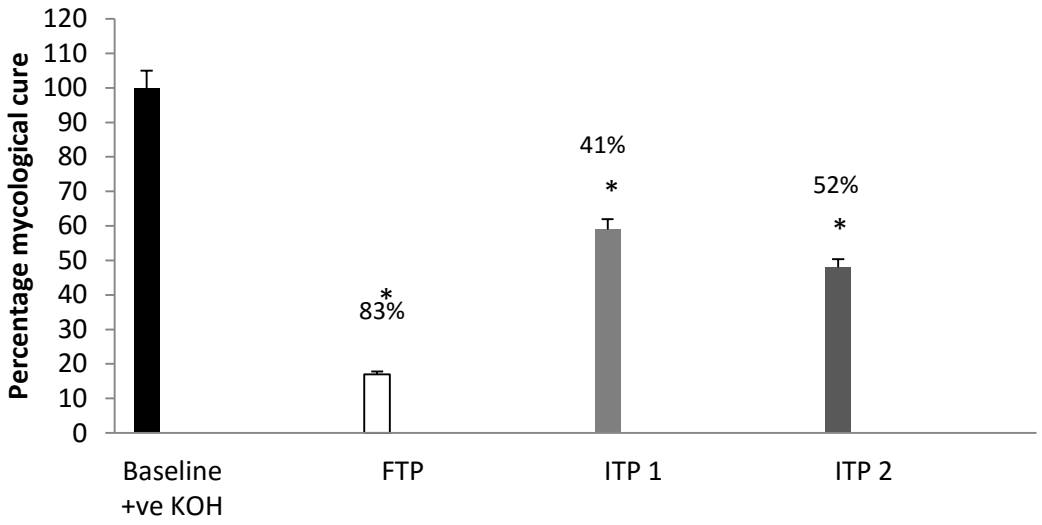
Figure 1: Effects of fluconazole and itraconazole treatment (single dose or two doses) in reduction of scales. Numbers indicates percentage reduction, *P < 0.05.



FTP = Fluconazole treated patients (300 mg), **ITP 1** = Itraconazole treated patients (group 1, single dose 400 mg), **ITP 2** = Itraconazole treated patients (group 2, two doses 400 mg).

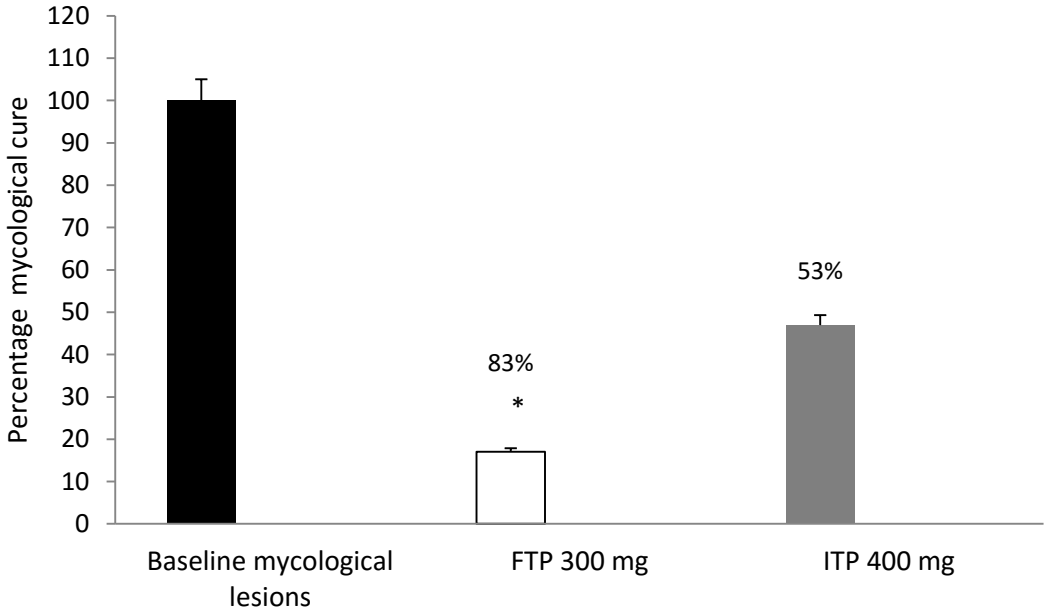
In addition, all patients displayed entire relieve of itching irrespective to while color that remained without significant changes. The mycological assessment, at the end of the four weeks, developed negative KOH results in all treated patients. The differences among these groups were statisticaly significant compared to their correspondent baseline values. Fiveteen FTP showed 83.3% in mycological reduction, seven ITP1 showed 41.2% reduction in mycological assessment and ten of ITP2 showed 52.6% reduction in mycological evaluation ($P < 0.05$, Fig. 2). Moreover, two weeks floconazole therapy has resulted in more significant improvement compared to four weeks itraconazole therapy ($P < 0.05$, Figs. 2 and 3). The presnt study showed that there is no significant changes in the haematological and biochemical data among all treated patients. In spite of this, one patient treated by floconazole showed gradual elevation in liver enzyme (ALT) activity that returned to normal value after two months.

Figure 2: Effects of fluconazole and itraconazole on the progress of mycological cure. Numbers indicates percentage reduction, *P< 0.05.



FTP = Fluconazole treated patients (300 mg), **ITP 1** = Itraconazole treated patients (group 1, single dose 400 mg), **ITP 2**= Itraconazole treated patients (group 2, two doses 400 mg).

Figure 3: Effects of fluconazole and itraconazole on fate of mycological cure after four weeks treatment. Numbers indicates percentage reduction, * P <0.05.



FTP = Fluconazole treated patients, **ITP** = Itraconazole treated patients

Discussion

Pityriasis Versicolor is a benign super facial fungal infection more commonly caused by *M. furfur*. In some studies *M. globosa and M. sympodialis* were the most common isolates from patients with PV (6-8). PV can be effectively treated by topical medication, but has a very high propensity for recurrence. Systemic therapy has a definite role in such cases (16). Itraconazole and fluconazole have been successfully used in the treatment of extensive and recurrent PV. Both these drugs have been tried in different dosages for varying periods. Several studies have indicated that itraconazole is recommended at a dose of 200 mg/day for 7 days (17). Recently two doses of 300 mg of fluconazole with one week interval for two weeks has also been tried in different studies (18, 19), and it has been found to be as effective as other treatment given for longer duration. Since itraconazole is known to achieve higher concentration in the stratum cornum which persists for 3-4 weeks even after discontinuation of drug. This coincides with our results which showed that single dose of 400 mg itraconazole once a week has significantly resulted in mycological cure compared to its baseline parameter. Despite that two doses of 400 mg itraconazole for two weeks have reached significant differences however, when compared to one dose regimen the drug was devoid from such effect. Moreover, despite that the significances have been reached by fluconazole and itraconazole in the two doses regimens, fluconazole had higher significancy effect than itraconazole.

The most other distressing symptom in patients with PV is cosmetically unacceptable pigmentation (mostly hypopigmentation), scaling and itching. Itching was the first symptom disappeared in most patients. Next to be controlled was scaling which cleared earlier and in a higher number of patients after fluconazole than itraconazole.

Residual dyschromia even after successful treatment is a well-known problem (1, 20-21). So in the present study the complete normalization of the color was not observed, because skin color alterations usually resolve within a few months of treatment. Fluconazole has shown to be significantly better than itraconazole regarding the mycological cure in the treated patients. Our findings coincide with others studies that reported mycological cure in patients treated for two weeks with fluconazole (17, 22). In itraconazole groups, the observed mycological cure was comparable with their baseline parameters. The safety of both drugs are well documented in the literature (21, 23 - 24). Moreover, the short term influence of fluconazole on the mycological as well as scaling disappearance placed the drug on the top promising agents in controlling early and late symptoms. Most common side effects noted with these drugs are mild gastrointestinal disturbances (10, 16, 23-26).

In this study, only one patient in the fluconazole group showed gradual elevation in liver enzyme (ALT) which then returned to the normal level after two months of treatment. On the other hand, patients' compliance with short term treatment compared with long one has contributed largely on the early cure of the symptoms. This is true with fluconazole but not with itraconazole. It has been postulated that one dose fluconazole therapy for two weeks has resulted in

significant mycological cure (21). Moreover, one week of one dose itraconazole has also reached significant cure. However, many studies have conflict results on short term and long-term effectiveness of both drugs. In this study, single dose fluconazole produced higher efficacy than itraconazole. Our findings confirmed the efficacy of single short term effectiveness of fluconazole and it significantly reduces the expenditure of costs regarding long drug use.

In conclusion: This study concluded that despite the diversity in their actions, fluconazole at 300 mg once weekly for two weeks was found more effective and complied by patients compared to itraconazole. In addition, both drugs were safe in regard to their lab investigation.

Acknowledgments: The authors appreciates the financial contribution of The National Center for Medical and Pharmaceutical Research and the stock supply of fluconazole from S. A. I. Ph. Company for Pharmaceuticals. The authors would also like to thank the nursing and medical staff members at Tripoli Medical Center for their valuable contribution.

References

1. Crespo-Erchiga V and Florencio VD (2006) Malassezia yeasts and pityriasis versicolor. Curr Opin Infect Dis. 19(2): 139-147.
2. Ramadán S, Sortino M, Bulacio L, Marozzi ML, López C and Ramos L (2012) Prevalence of Malassezia species in patients with pityriasis versicolor in Rosario, Argentina. Rev Iberoam Micol. 29(1): 14-19.
3. Aspiroz C, Ara M, Varea M, Rezusta A and Rubio C (2002) Sympodialis from patients with pityriasis versicolor in Spain. Mycopathologia. 154(3): 111-117.
4. Kyriakis KP, Terzoudi S, Palamaras I, Pagana G, Michailides C and Emmanuelides S (2006) Pityriasis versicolor prevalence by age and gender. Mycoses. 49(6): 517-518.
5. Salah SB, Makni F, Marrakchi S, and *et al*. (2005) Identification of Malassezia species from Tunisian patients with pityriasis versicolor and normal subjects. Mycoses. 48(4): 242-245.
6. Prohic A and Ozegovic L (2007) Malassezia species isolated from lesional and non-lesional skin in patients with pityriasis versicolor. Mycoses. 50(1): 58-63.
7. Bita T and *et al*. (2004) Study of the distribution of *Malassezia* species in patients with pityriasis versicolor and healthy individuals in Tehran, Iran**.** BMC Dermatol. 1: 4-5.
8. Rasi A, Naderi R, Behzadi AH and *et al*. (2010) Malassezia yeast species isolated from Iranian patients with pityriasis versicolor in a prospective study. Mycoses. 53 (4): 350-355.
9. Doncker PD, Gupta AK, Marynissen G, Stoffels P and Heremans A (1997) Itracon-azole pulse therapy for onychomycosis dermatomycoses: an overview. J Am Acad Dermatol. 37(6): 969-974.
10. Bennett JE (2006) Antimicrobial agents: antifungal agents In: Goodman and Gilman's the pharmacological basis of therapeutics, (11th ed., chapter 48), 802-804.
11. Crespo Erchiga V, Ojeda Martos A, Vera Casaño A, Crespo Erchiga A and Sanchez Fajardo F (2000) Malassezia globosa as the causative agent of pityriasis versicolor. Br J Dermatol. 143(4): 799-803.
12. Ashbee HR and Evans EG (2002) Immunology of disease associated with malassezea species. Clin Microbiol Rev. 15(1): 21-57.
13. Uetrecht J and Walmsley SL (1998) Anti microbial agents and antifungal agents that act on cell membrane. Principles of medical pharmacolog (6th ed., Chapter 54), 681-683.
14. Faergemann J (2000) Management of seborrheic dermatitis and pityriasis versicolor. Am J Clin Dermatol. 1 (2): 75-80.
15. Muhammad N, Kamal M, Islam T, Islam N and Shafiquzzaman M (2009) A study to evaluate the efficacy and safety of oral fluconazole in the treatment of tinea versicolor. Mymensingh Med J. 18(1): 31-35.
16. Partap R, Kaur I, Chakrabarti A and Kumar B (2004) Single-dose fluconazole versus itraconazole in pityriasis versicolor. Dermatology. 208(1): 55-59.
17. Montero-Gei F, Robles ME and Suchil P (1999) Fluconazole vs. itraconazole in the treatment of tinea versicolor. Int J Dermatol. 38(8): 601-603.
18. Yazdanpanah MJ, Azizi H and Suizi B (2007) Comparison between fluconazole and and ketoconazole effectivity in the treatment of pityriasis versicolor. Mycoses. 50(4): 311-313.
19. Gupta AK, Bluhm R and Summerbell R (2002) Pityriasis versicolor. J Eur Acad Dermatol Venereol. 16(1): 19-33.
20. Zampino MR, Osti F, Corazza M and Virgili A (2007) Prevalence of pityriasis versicolor in a group of Italian pregnant women. J Eur Acad Dermatol Venereol. 21: 1249-1252.
21. Partap R, Kaur I, Chakrabarti A and Kumar B (2004) Single-dose fluconazole versus itraconazole in pityriasis versicolor. Dermatol. 208(1): 55-59.

22. Karakaş M, Durdu M and Memişoğlu HR (2005) Oral fluconazole in the treatment of tinea versicolor. J Dermatol. 32 (1):19-21.
23. Jaswal R, Thami GP and Kanwar AJ (1999) Fluconazole and itraconazole in pityr-iasis versicolor. Indian J Dermatol Venereol Leprol. 65(5): 216-218.
24. Tucker RM, Haq Y, Denning DW and Stevens DA (1990) Adverse events associate with itraconazole in189 patients on chronic therapy. J Antimicrob Chemother. 26 (4): 561-566.
25. Faergemann J, Gupta AK, Al Mofadi A, Abanami A, Shareaah AA and Marynissen G (2002) Efficacy of itraconazole in the prophylactic treatment of pityriasis (tinea) versicolor. Arch Dermatol. 138(1): 69-73.
26. Sheppard D and Lampiris H (1998) Antifungal agents In: basic and clinical pharmacology, chapter 48, 783-785.