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The Treatment Of Onychomycosis By Oral Terbinafine: The Efficacy And Adverse Evevnts

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Abstract

Onychomycosis contributes to approximately half of all nail disorders and appears to be increasing in frequency. The main aim of this study was to access efficacy and adverse events of oral terbinafine in the treatment of adult patients with onychomycosis of the fingernails and toenails. Forty patients with onychomycosis, aged 22-48 years were enrolled in this study. The patients were divided into two groups; group I, consisted of 20 patients with fingernail onychomycosis and group II, 20 patients with toenail onychomycosis. The two groups (I-II) of patients were received, freely, oral terbinafine in a dose of 250 mg/day for 6 and 12 weeks, respectively. The patients were examined clinically and mycologically before start of the treatment, at end of the treatment and after a follow up period of 18 weeks from the treatment in both groups. The results of the study showed marked clinical (75.0%) and mycological (85.0%) cure rates in the total patient group. The clinical and mycological cure rates in group I were 80.0% and 90.0%, respectively. While, in group II the clinical and mycological cure rates were 70.0% and 80.0%, respectively. Also, 17.5% of the total patient group had adverse events, 71.4% of these events were mild and 42.9% were drug related. Lastly, complete cure rate at follow up at 18 weeks from the treatment was 87.5% of the total patients group. It could be concluded that terbinafine appears to be safe and effective in the treatment of fungal infections of the fingernails and toenails.

Introduction

Onychomycosis contributes to 40.0%-50.0% of all nail disorders and appears to be increasing in frequency (Baran *et al*., 1997; Tom & Kane, 1999 and Vinod, 2000). In the United Kingdom 2.7% of the population suffers from onychomycosis (Heikkila, 1995). Also, in the United Stats an increase in the number of patients with onychomycosis has been reported (De Cuyper, 1996).

Mycotic nail infections are usually caused by dermatophytes, yeasts and nondermatophyte moulds. Most cases of the toenail onychomycosis are caused by dermatophytes (Tom & Kane, 1999 and Veer *et al.*, 2007). Also, it is predominantly caused by Trichophyton rubrum (T. rubrum) (Heikkila, 1995 and Veer *et al*., 2007).

Mycotic nail infections are a therapeutic challenge and do not always resolve spontaneously. Dermatophyte infections of the nail have been difficult to treat, requiring long courses of therapy and having high recurrence rates (De Backer *et al.*, 1998 and Tom & Kane, 1999). Also, it may have a substantial impact on the patient's quality of life (Tom & Kane, 1999 and Drake *et al*., 1999).

Previously, griseofulvin was the drug of choice for onychomycosis. This drug cures about 70.0% of the fingernail onychomycosis but less than 40.0% of the toenail onychomycosis (Blafour and faulds, 1992; Faergeman *et al*., 1995 and Hotman *et al*., 1995). But recently, terbinafine (lamasil) that is active orally as well as topically has been used in the treatment of onychomycosis. Its mode of action is inhibition of fungal squalene epoxidase. This enzyme is active in the synthesis of ergosterol, an essential lipid component of the fungal cell wall. The accumulation of

squalene following inactivation of squalene epoxidase seems to be fatal for the fungus, thus accounting for the in vitro fungicidal action of terbinafine (Finaly, 1992a and Darkes *et al*., 2003). The drug is effective in both adults and elderly patients. There is a high compliance with the regimen. So, terbinafine therapy is effective and safe (Gupta *et al.*, 2001 and Tavakkol *et al*., 2006). It's effective in onychomycosis, 70.0%-100.0% mycological cure rates and 42.0%-100.0% clinical cure rates after 3-6 months of treatment (Zaias, 1990; Goodfield, 1992; Baudarz-rosselet *et al*., 1992; Drake *et al.*, 1995; Shear & Gupta, 1995; Waston *et al.*, 1995; Gupta *et al*., 2001 and Jansen *et al*., 2001). The drug is generally well tolerated and has a low potential for drug interactions. So, terbinafine is the treatment of choice for dermatophyte onychomycosis (*Darkes et al.*, 2003). Aggressive debridement, as an adjunct therapy with oral terbinafine, impr-oved treatment satisfaction and reduced symptom frequency (Potter *et al.*, 2007).

In vitro terbinafine is active against a wide range of fungi, including dermato-phytes, dimorphic and dermatiaceous moulds and yeasts. The most susceptible fungal species are the dermatophytes. It is also active against aspergillus species and other pathogenic filamentous fungi infecting the skin, nails and cornea. Clinical studies have primarily dealt with dermato-phytosis (Roberts, 1992; Williams, 1993 and Darkes *et al*., 2003). Pharmacokinetic studies have shown that terbinafine, following oral administration, is rapidly absorbed and widely distributed to body tissues including the poorly perfused nail matrix. Its full concentration in the nail is detected within 1 week after starting therapy and persists for at least 30 weeks after the completion of the treatment (Darkes *et al*., 2003). Also, it can be detected in the distal part of the nail 3-18 weeks after the initiation of the therapy (Finlay, 1992b; Munro & Shuster, 1992 and Faergeman *et al*., 1993).

The aim of the present study is to determine characteristics of the studied patients with onychomycosis, to determine the most common causative organism for onychomycosis and to assess efficacy and adverse events of oral terbinafine in the treatment of adult patients with onychomycosis.

Material and Methods

This study was carried out in the Dermatology Out-patient Clinic, Al-Hussein Hospital, Al-Azhar University. A total number of 40 adult patients with onychomycosis were enrolled in this study. A clinic based, therapeutic trial study design was chosen to carry out this research. The patients with onychomycosis were adults, their age was ≥22 years. The purpose of the study was explained to the patients. The patients group was subjected to scrapings from the affected nails. A verbal consent to participate in the study was given. Also, a questionnaire was designed to contain data relevant to the topic of the study.

Inclusion criteria are an adult patient with chronic onychomycosis, a definite history, and confirmed by a positive mycological results in this study.

Exclusion criteria included a patient sample negative by microscopy or culture, using systemic and/or topical antifungal therapy (one month prior to the study), pregnant or breast feeding women, and any systemic disease or condition that might affect the outcome of the study.

The forty patients enrolled in the study were divided into 2 equal groups; group (I), consisted of 20 patients with fingernails onychomycosis, and group (II), 20 patients with toenails onychomycosis.

We suggested a clinical score, for signs and symptoms, to determine disease severity; mild =1, moderate =2, and severe =3. These symptoms and signs included disfiguring, pain (paronychial inflamma-tion), hyperkeratosis and/or onycholysis.

Mycological examinations: specim-ens (scrapings) were placed on a slide with a drop of 10.0% potassium hydroxide (KOH) and examined imme-diately and after 24 hours by microscope for hyphae and spores. Also, specimens were inocul-ated into Sabouraud's agar plates. Further examinations were done on blood dextrose agar and corn meal agar for subcultures.

Patients were supplied, freely, by lamasil tablets (250 mg, 7 tablets each week). They instructed to take one tablet in

the evening after a meal each day, for 6 weeks in the first group and for 12 weeks in the second group. They were also instructed not to apply any topical therapies; creams, ointments or lotions to their lesions during the course of the study and till the end of the follow up period, which extends to 18 weeks in both groups after treatment initiation.

In both groups, patients were examined clinically and mycologically before the start of therapy and end of treatment. In addition a final examination was planned 18 weeks in both groups after treatment initiation to assess complete cure of the patients. The criterion for mycological cure was that samples should be negative by both microscopy and culture. The subjective clinical criteria were considered improvements in the appearance of the nails with a marked reduction in the signs and symptoms of infection. Cure was evaluated by clinical cure (≥87.5% nail clearing), mycologic cure (negative microscopy of KOH samples and negative culture) and complete cure at follow up (mycologic cure and complete nail clearing) (Potter *et al.*, 2006).

Safety and tolerability were assessed by adverse event (AE) rates based on patient information, answers to investigator questions, and physical examinations.

Lastly, descriptive statistics; frequency, percent distribution and arithmetic mean ± standard deviation (SD) and analytical statistical tests; chi-square (χ^2) and Fisher exact (FE) were used. The significance level for χ^2 and FE were accepted if the P-value ≤0.05.

Results

Table (1) shows characteristics of the studied onychomycosis patients, it is apparent from the table that 50.0% of the patients were in the 31-39 year age group. At the same time, 55.0% of the patients were males. More than half (55.0%) of the patients had a moderate form of the disease and 30% had a severe form. The mean duration of onychomycosis ± SD was 9.3 ± 1.1 year. Also, the mean of onychomycosis nail number ± SD was 3.2 ± 0.4. As respect the main presenting symptom; disfiguring was the most common, 75.0%, while; the most common presenting sign was hyperkeratosis, 70.0%.

Table (2) clears distribution of the studied two onychomycosis patient groups according to the laboratory and clinical aspects. As regard the causative organism, we found that T. rubrum and T. mentagrophyte were the most common organisms; 30.0% and 30.0% of our patients were infected by them, respectively. In details, the most common (40.0%) causative organism in group I was T. rubrum. While, the most common (60.0%) causative organism in group II was T. mentagrophyte. At the same time, 40.0% and 0.0 % of the patients in groups I and II, respectively their lesions were caused by a mixed infection (T. mentagrophyte and C. albicans). As regard drug adverse events, 17.5% of the total patient group had AEs, and most of them had mild AEs, 71.4%. In details, 15.0% and 20.0% of the patients in groups I and II, respectively had drug AEs. All AEs disappeared rapidly after cessation of the treatment. These AEs were gastrointestinal complaints, (as diarrhea), urticaria, erythema multiform, and disturbance of the sense of taste and smell. Most of the AEs in group I and II were mild, 66.7% and 75.0%, respectively. Respecting investigator opinion in the relation between AEs and drug usage, 50.0% of AEs were drug related. Regarding clinical cure, 75.0% of the total patient group had clinical cure at end of the treatment period. In details, 80.0% and 70.0% of the patients in groups I and II, respectively had clinical cure. Respecting mycological cure, 85.0% of the total patient group had mycological cure at end of the treatment period. In details, 90.0% and 80.0% of the patients in groups I and II, respectively had mycological cure. Lastly, complete cure rate at follow up at 18 weeks from the treatment was 87.5% of the total patients group.

Table (1): Characteristics of the studied onychomycosis patients.

Characteristics	N=40	Percent
Age (years):		
22-30	12	30.0
31-39	20	50.0
40-48	8	20.0
Sex:		
Male	22	55.0
Female	18	45.0
Severity of onychomycosis:		
Mild	6	15.0
Moderate	22	55.0
Severe	12	30.0
Duration of onychomycosis (in years, mean ± SD):	9.3 ± 1.1	
Number of nails involved (mean ± SD):	3.2 ± 0.4	
Main presenting symptoms/signs:		
Disfiguring	30	75.0
Pain	10	25.0
Hyperkeratosis	28	70.0
Onycholysis	12	30.0

Table (2): Distribution of the studied two onychomycosis patient groups according to the causative organism, drug adverse events, and clinical and mycological cure.

Variables	Group I		Croup II		Total		χ^2 FE	P-Value*
	No.	%	No.	%	No.	%		
Causative organism:								
T. rubrum	0	0.0	12	60.0	12	30.0	14.40	0.0001*
T. mentagrophyte#	8	40.0	4	20.0	12	30.0	1.07	0.3006
C. albicans~	4	20.0	2	10.0	6	15.0	FE	0.6614
T. tonsurans	0	0.0	2	10.0	2	5.0	FE	0.4871
Mixed infection (#+~)	8	40.0	0	0.0	8	20.0	FE	0.0032*
Drug adverse events (AEs):								
Absent	17	85.0	16	80.0	33	82.5	FE	1.0000
Present:	3	15.0	4	20.0	7	17.5		
Mild	2	66.7	3	75.0	5	71.4	FE	1.0000
Moderate	1	33.3	0	0.0	1	14.3	FE	0.4285
Severe	0	0.0	1	25.0	1	14.3	FE	1.0000
Investigator opinion: Is AEs drug related?	(n=3)		(n=4)		(n=7)			
Yes	1	33.3	2	50.0	3	42.9	FE	1.0000
No	2	66.7	2	50.0	4	57.1		
Clinical cure at end of ttt.:								
Yes	16	80.0	14	70.0	30	75.0	0.13	0.7150
No	4	20.0	6	30.0	10	25.0		
Mycological cure at end of ttt.:								
Yes	18	90.0	16	80.0	34	85.0	FE	0.6614
No	2	10.0	4	20.0	6	15.0		
Complete cure at follow up:								
Yes	18	90.0	17	85.0	35	87.5	FE	1.0000
No	2	10.0	3	15.0	5	12.5		

* Significant

Discussion

Fungal infections are a major cause of morbidity allover the world and appears to be increasing in frequency (Baran *et al*., 1997 and Tom & Kane, 1999). Skin and its adnexae (hair and nail) can be suitable targets for fungal infections that producing a wide range in clinical expression and duration, even among organisms, which are closely related (Tosti *et al*., 1996a; Tom & Kane, 1999 and Veer *et al*., 2007).

Onychomycosis is a common infection of the nails in adults and its incidence increases with age (Vinod, 2000). In this study, onychomycosis was found to be commonest in the age group 31-39 years in accordance with most of the studies of Vinod (2000); Madhuri (2002) and Nelson *et al*. (2004). Also, the disease is more frequent among men than women (55.0% vs. 45.0%) in agreement with Nelson *et al*. (2004). This observed sex differences warrant further investigation (Potter *et al*., 2007).

The laboratory offers the clinicians the opportunity to confirm their clinical diagnosis and assessment of treatment results (Goodfield & Evans, 1992 and Veer *et al.*, 2007). We reported that 30.0% of our patients their disease was caused by T. rubrum and 30.0% their disease was caused by T. mentagrophyte. Organisms blamed to cause these infections are dermatophytes, moulds and yeasts (Heikkila, 1995; Baran *et al*., 1996; Tosti *et al*., 1996a; Tom & Kane, 1999 and Veer *et al*., 2007).

Current treatment modalities for onychomycosis include surgery, topical antifungals and oral antifungals. Surgery is generally not recommended as first-line therapy. Broad-spectrum topical and oral antifungal agents are the most frequently used treatments. Topical treatment is well tolerated but is usually not effective because of poor patient compliance and inadequate penetration of the nail. Oral antifungals are more successful but carry greater risks (Tom and Kane, 1999). Drug adverse events were present in 17.5% of the total patient group, and most of them had mild AEs, 71.4%. Oral therapy carries greater risks and requires close monitoring. Intermittent oral antifungal therapy may reduce the risk of systemic adverse effects and the cost of therapy, but more study of this approach is recommended (Munro & Shuster, 1992 and Tom & Kane, 1999). Also, tolerability was good in almost 90.0% of patients, and all reported AEs were known for this drug (De Backer *et al*., 1998). The drug appeared safe with no significant AEs or clinically significant laboratory abnormalities; all the AEs were mild and transient. There is a high compliance with regimen (Gupta *et al*., 2001). Clinical trials revealed that oral terbinafine had a better tolerability profile than griseofulvin and it is comparable to that of itraconazole or fluconazole. AEs were experienced by 10.5% of the patients, gastrointestinal complaints being the most common. Moreover, terbinafine has a low potential for drug-drug interactions (Darkes *et al*., 2003). Terbinafine is well tolerated and efficacious in treating adult patients with onychomycosis. There were no reported clinical signs of drug interactions. Incidence of AEs reported during the treatment period or within 30 days after its discontinuation and treatment-emergent AEs (TEAEs) was 23.0%. Most TEAEs were mild (73.7%) to moderate (23.7%) in severity (Tavakkol *et al*., 2006).

Respecting investigator opinion in the relation between AEs and drug usage, 50.0% of AEs were drug related. Tavakkol *et al*. (2006) cleared that 86.8% of AEs were not suspected to be related to the studied treatment.

The traditionally used oral antifungals for onychomycosis were griseofulvin and ketoconazole. But these classical treatments of onychomycosis are associated with relatively low cure rates, 40.0% for fingernail infections and 20.0% for toenail infections and high recurrence rates (Munro and Shuster, 1992). Recently, itraconazole and terbinafine are safe and effective first-line agents; reported cure rates were 50.0%-90.0% for dermatophyte onychomycosis (Munro & Shuster, 1992 and Tom & Kane, 1999). However, review of several recent studies of terbinafine orally in dose of 125 mg twice/ day or 250 mg once/day showed the high efficacy of this new antifungal,

especially in treating chronic cases of dermatophytosis (Gupta *et al*., 1994; Roberts, 1994; Tosti *et al.,* 1996b; Gupta *et al*., 1997; De Backer *et al*., 1998; Gupta *et al*., 2001 and Jansen *et al*., 2001). In cases of dermatophytosis such as tinea pedis (planter type) and onychomycosis, the clinical and mycological cure rates are 91.0% and 95.0%, respectively in those patients with fingernail infection and 72.0% and 82.0%, respectively for those patients with toenail infections (Gupta et al., 1994 and Roberts, 1994). The response of various organisms to oral treatment with terbinafine is high; including T. rubrum, T. mentagrophytes, T. violaceum, T. verrucosum, Epidermophyphyton floccosum and Microsporum canis (Goodfield and Evans, 1992; Gupta *et al*., 1994; Roberts, 1994; Tosti *et al.,* 1996b and Gupta *et al*., 1997).

De Backer *et al*. (1998) used a 12 weeks oral treatment with terbinafine 250 mg/day for confirmed toenail dermatophyte onychomycosis. At week 48, 73.0% of the patients showed negative mycology and 76.2% showed clinical cure or had only minimal symptoms. Also, Gupta *et al*. (2001) evaluated the efficacy of terbinafine in the treatment of dermatophyte onychomycosis. The patients received terbinafine 250 mg/day for 12 weeks. At month 6 from the start of therapy, if there was less than 50.0% reduction in the affected nail plate area compared with baseline, or if there was less than 3 mm outgrowth of unaffected nail plate as measured in midline, then these patients (26.0% of the patients) were given an extra 4 weeks of the drug. The mycological cure rate at 18 months from the start of therapy was 64.0%. Recently, Darkes *et al*. (2003) found that mycological cure rates were 76.0% for patients after 12 weeks' treatment and 81.0% for recipients after 16 weeks' therapy in patients with toenail mycosis. Also, they showed that terbinafine is clinically effective at 5-year follow-up. It produced a complete cure rate (35.0%), mycological cure rate (46.0%) and clinical cure rate (42.0%). The mycological and clinical relapse rates were 23.0% and 21.0%, respectively. More recently, Tavakkol *et al*. (2006) illustrated that mycological cure had occurred in 64.0% of their older subgroup, clinical cure in 41.3% and complete cure in 28.0%.

It could be concluded that terbinafine (lamasil) appears to be safe and effective in a dose of 250 mg/day for 6 weeks and for 12 weeks in the treatment of fungal infections of the fingernails and toenails, respectively.

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علاج فطريات الأظافر بواسطة تعاطى عقار التيربينافين: الكفاءة والأعراض الغير مرغوبة

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الجلدية و التناسلية – الميكروبيولوجى المناعة* ـ طب المجتمع**

تمثل الاصابة الفطرية لأظافر اليد والقدم تقريباً النصف من كل الأمراض التى تصيب الأظافر واالتى تبدو أنها آخذة قى الزيادة. و كان الهدف الأساسى لهذه الدراسة تحديد كفاءة علاج فطريات الأظافر بعقار التيربينافين عن طريق الفم و كذلك تحديد الأعراض الغير مرغوبة لهذا العقار.

وقد أُجرى هذا البحث على 40 مريض من المصابين بفطريات الأظافر تتراوح أعمارهم بين 22 – 48 عاماً. وقد تم تقسيم المرضى إلى مجموعتين: الأولى وتتكون من 20 مريض من المصابين بفطريات أظافر اليد والثانية تتكون من 20 مريضً مصابين بفطريات أظافر القدم. وقد تم علاج المجموعتين مجاناً بعقار التيربينافين بجرعة 250 مجم /اليوم لمدة 6 و 12 أسبوع و ذلك للمجوعة الأولى والثانية على الترتيب.

وقد تم فحص المرضى من الناحية الاكلينيكية والمعملية (الفطرية) فى بداية العلاج وبعد الانتهاء من العلاج، وكذلك عند المتابعة بعد 18 أسبوع من بداية تعاطى العقار وذلك فى كلا المجموعتين.

وقد بينت نتائج الدراسة تحسناً إكلينيكياً (75.0%) ومعملياً (85.0%) ملموساً فى معدلات الشفاء لمجموعة المرضى و أن نسبة الشفاء فى المجموعة الأولى بلغت 80.0% إكلينيكياً و 90.0% فطرياً، وفى المجموعة الثانية 70.0% إكلينيكياً و 80.0% فطرياً. وكذلك عانى 17.5% من المرضى من أعراض غير مرغوبة للعقار والتى كان 71.4% منها بسيطاً و 42.9% منها لة علاقة بتعاطى العقار. وأخيراً كان معدل الشفاء الكامل عند المتابعة بعد الأسبوع 18 من بدء العلاج هو 87.5%.

وبذلك يعتبر تعاطى عقار التيربينافين لعلاج إصابة الفطريات للأظافر دواء ذو تأثير فعال فى الشفاء من هذه الإصابة.