Treatment of Dermatophytic Onychomycosis with Intermittent and Continuous Terbinafine Regimens

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The treatment of onychomycosis is a difficult and long-standing course because of the relatively low success and high recurrence rates and the necessity of laboratory monitoring for the traditional oral antifungal agents. The introduction of newer systemic antifungal drugs such as triazoles (itraconazole and fluconazole) and allylamines (terbinafine) offer an increased cure rate, a broader spectrum of activity, shortening of the treatment period, and increased safety, compared with the traditional systemic antifungal drugs (griseofulvin and ketoconazole). Preliminary results suggest that terbinafine is promising in the treatment of onychomycosis, although its spectrum of activity is not as broad as that of itraconazole. Terbinafine persists in the nails at effective concentrations for a long time even after discontinuation of treatment. An open randomized study was planned to compare the efficacy of intermittent and continuous terbinafine regimens. The clinical and microscopic cure rates were higher in the continuous group than in the intermittent group, but the differences between two groups were not statistically significant. It is suggested that continuous terbinafine regimen should be preferred in the treatment of dermatophytic onychomycosis. [Journal of Turgut Özal Medical Center 1997;4(2):135-138]

***Key Words**: Onychomycosis, terbinafine, intermittent therapy*

Dermatofitik onikomikozlarda aralıklı ve devamlı terbinafin tedavisi

Tırnak mantar enfeksiyonlarının tedavisi; oldukça zor, başarı oranları nispeten düşük, tekrarlama ihtimali yüksek, uzun ve kullanılan ilaçların yan etkileri sebebiyle sık laboratuar kontrolleri gerektiren bir süreçtir. Triazoller (itrakonazol ve flukonazol) ve allilaminler (terbinafin) gibi yeni ilaçların kullanıma girmesi; tam iyileşme oranlarını yükseltmiş, etki spektrumunu genişletmiş, tedavi sürelerini kısaltmış ve yan etkileri kısmen azaltmıştır. Elde edilen ilk sonuçlar terbinafin'in, itrakonazol kadar geniş spektrumlu olmamakla beraber, onikomikoz tedavisinde oldukça etkili olduğunu göstermektedir. Terbinafin, tedavi kesildikten sonra da uzunca bir süre tırnaklarda etkili bir konsantrasyonu korumaktadır. Onikomikoz tedavisinde aralıklı ve devamlı terbinafin kullanımının etkinliğini karşılaştırmak amacıyla yaptığımız bu çalışmada, devamlı tedavi grubunda klinik ve mikroskopik iyileşme oranlarının aralıklı tedavi grubuna göre daha yüksek olduğunu fakat aradaki farkın istatistik açıdan anlamlı olmadığını gördük. Dermatofitik onikomikozların tedavisinde devamlı terbinafin uygulamasının tercih edilmesi gerektiği sonucuna vardık. [Turgut Özal Tıp Merkezi Dergisi 1997;4(2):135-138]

***Anahtar Kelimeler**: Onikomikoz, terbinafin, aralıklı tedavi*

Onychomycosis (tinea ungium), the infection of the nails by any kind of fungus, far from being just a cosmetic problem, has also significant psychological, physical, social, and economical considerations. Further, its incidence is growing dramatically in recent years. Because the fungi

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involved in this disorder are difficult to eradicate from the public bathing facilities and the crowded areas, where the infection is often spread by contagion, an effective treatment is likely to have a significant importance on the prevalence of the disease (1-3).

Until recently, the treatment of onychomycosis was fairly discouraging because of the relatively low cure rates, the need for prolonged therapy, and the laboratory monitoring necessary with the traditional systemic antifungal agents (griseofulvin and ketoconazole). The advent of new generations of oral antifungal drugs, including two triazoles (itraconazole and fluconazole) and an allylamine (terbinafine), has greatly improved the outlook for patients with fungal nail infections, particularly those with toenail onychomycosis (2).

Terbinafine is highly effective and has partly solved the well-known problems in the treatment of dermatophytic nail infections. It persists in the nail plate at effective concentrations for several weeks after discontinuation of treatment (4). Its pharmacologic and pharmacokinetic properties suggested that intermittent treatment courses may be equally effective to continuous regimens in the management of onychomycosis (3-6).

In this study, it was aimed to verify whether intermittent terbinafine therapy is effective in dermatophytic onychomycosis and to compare the efficacy of continuous and intermittent regimens for the treatment of tinea ungium.

MATERIALS AND METHODS

Fifty patients with clinically and microscopically proven dermatophytic tinea ungium of toenails were the subjects of this study. Patients were randomly and equally divided to two treatment groups. Group 1 was given 250 mg of terbinafine daily during consequent 4 months, whereas 500 mg of terbinafine daily was given to group 2 in the first week of each month during consequent 4 months. Nails were examined clinically and microscopically at every months. The most affected nail was accepted as reference. The lenght of affected part of the reference nail was measured in milimeters. Dystrophy scores for every patients were calculated according to the existences and severities (0=absent, 1=slight, 2=mild, and 3=severe) of onycholysis, subungual hyperkeratosis, fragility, and paronychia. Routine laboratory studies were performed at the beginning and at the ends of second and fourth monhs. All patients were followed up for 6 months after starting the treatment. At the end of the follow-up period, clinical and microscopic improvements were evaluated. A fifty percent improvement in dystrophy score and up was accepted as cure, 10 to 50 percent improvement as partial cure, and 10% or less improvement as failure. Side effects such as skin eruptions, gastrointestinal discomfort, headache, and disturbances in laboratuary evaluations were noted. The results were compared statistically by Student's t- and Chi-square tests.

RESULTS

The demographic features of the groups were shown on Table 1. Both groups were similar in age, sex, and history of onychomycosis. There was no significant difference between two groups according to the means of age and duration of the disease ($p>0.05$). Most of the patients were men.

Clinical findings and the therapeutic results in continuous (group 1) and intermittent (group 2) treatment groups were outlined in Table 2. The means of diseased nails were similar in both groups affecting predominantly the first toenail. In group 1, we observed cure in 19 (76%) patients, partial cure in 4 (16%) patients, and failure in 2 (8%) patients. In group 2, these values were 17 (68%) patients, 4 (16%) patients, and 4 (16%) patients, respectively. Both of two treatment regimens were highly effective ($p<0.001$) and differences between two groups were not significant ($p>0.05$).

Side effects observed in two groups were seen on Table 3. The rate of adverse events was 36% in the continuous group and 40% in the intermittent group. No serious side effects that resulted in the cessation of therapy were not noted.

Table 1. Demographic features of the patients

	Group 1 (n=25)	Group 2 (n=25)
Male/Female	19 / 6	20 / 5
Mean age (year)	41.3 10.1	39.8 11.2
Range	25-72	21-76
Mean duration of the disease (year)	7.8 6.2	8.6 8.3*

*: $p>0.05$

Table 2. Clinical findings and the therapeutic results in two groups

Mean	**Group 1** (n=25)	**Group 2** (n=25)
Affected nails	4.43	3.79
Dystrophy score		
Before treatment	6.9±1.6	6.1±1.9
After treatment	2.8±1.2*	2.4±2.1*
Results		
Cure	19 (76%)	17 (68%)
Partial cure	4 (16%)	4 (16%)
Failure	2 (8%)	4 (16%)**

*: p<0.001
**: p>0.05

Table 3. Side effects observed in two groups

Side effect	**Group 1** (n=25)	**Group 2** (n=25)
Rush	2 (8%)	2 (8%)
GI discomfort	3 (12%)	2 (8%)
Dizziness and headache	3 (12%)	4 (16%)
Liver toxicity (slight)	1 (4%)	2 (8%)
Total	9 (36%)	10 (40%)*

*: p>0.05

DISCUSSION

Onychomycoses are among the most frequent diseases that affect the nails, especially toenails, accounting for roughly 30% of all cutaneous fungal infections. The principal etiologic agents are dermatophytes. Onychomycosis may be due to secondary infection from tinea pedis that invades the healthy nail plate and secondary invasion in nails with preexisting disease (7).

Current treatment of onychomycosis of the toenail is poor and relapse is common. The introduction of newer systemic antifungal drugs (itraconazole, fluconazole, and terbinafine) offer an increased cure rate, a broader spectrum of activity, shortening of the treatment period, and increased safety, compared with the traditional systemic antifungal drugs (griseofulvin and ketoconazole) (1).

Terbinafine, an allylamine drug, is an effective antimycotic agent that may be used systemically and topically. Previous experimental and clinical trials have shown that treatment with effective concentrations for 3 months cause drug deposits in nail plates and fungicidal concentrations persist in plasma and peripheral tissue samples for prolonged periods (weeks to months) after administration of the last dose. Available studies have shown that the efficacy of terbinafine appears to be greater than those of griseofulvin, ketoconazole, and fluconazole in patients with dermatophyte onychomycosis or cutaneous fungal infections, but activity spectrum of itraconazole seems to be broader than those of fluconazole and terbinafine. Terbinafine is also effective on *Candida* species (2,5,8-12).

In the treatment of onychomycosis, oral therapies have generally been given as a continuous-dosing regimen. Based on the advances in our understanding of the pharmacokinetics of terbinafine, we investigated the efficacy of intermittent pulse-dosing and continuous therapy with oral terbinafine in patients who were suffering from onychomycosis. We found both of therapy courses as highly effective, but the continuous regimen was more effective. These results were parallel in some previous studies (3,4,6,9). Alpsoy E, et al have found that intermittent therapy with terbinafine was as effective as 3-month continuous treatment in dermatophytic toenail-onychomycosis (3). In another study, the percentage of patients who were cured was higher in the continuous terbinafine group than in the intermittent terbinafine and group, but statistical analysis did not reveal any significant difference between these cure rates (4). Albanese G, et al have reported that terbinafine has proved to be effective and well tolerated in the very short-term treatment of dermatophyte nail infections (6).

We observed no serious side effects that required the cessation of therapy. Gastrointestinal disturbances, skin rush, dizziness, and headache can occur most commonly; liver toxicity has been rarely described (1,2,7). We observed such kind of unimportant side effects in 36 percent of group 1 and 40 percent of group 2 patients. It has been suggested that liver enzyme values should be determined during the first month of treatment (7). In some recent studies, it has been reported that terbinafine can cause toxic epidermal necrolysis (13).

As conclusion, although both treatment regimens are highly effective, we suggest that continuous therapy should be preferred in the management of dermatophytic tinea ungium.

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