The Long Term Efficacy and Relapse Rate of Itraconazole Pulse Therapy Versus Terbinafine Continuous Therapy for Toenail Onychomycosis
- a 96-week follow-up study -

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발톱 조갑 진균증에서 Itraconazole 주기 요법과 Terbinafine 연속 요법의 치료 효과에 대한 비교 연구
-96주간의 관찰-

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연구 배경: 조갑 진균증의 치료에서 itraconazole 주기 요법과 terbinafine 연속 요법의 치료 효과와 안전성은 여러 연구에서 이미 밝혀진 바 있지만 한국인을 대상으로 한 장기적인 치료 효과와 재발율에 대한 연구는 부족하였다.

연구의 목적: 이 연구의 목적은 경증 내지는 중증도의 발톱 조갑 진균증에 이환된 한국인 환자를 대상으로 itraconazole 주기 요법과 terbinafine 연속 요법의 치료 효과를 장기간 (96주)에 걸친 관찰로 평가하는 것이다.

연구 수행 방법: 총 72명의 발톱 조갑 진균증 환자가 무작위로 두 군으로 나뉘어져 한 군은 12주 동안 itraconazole (400 mg/d)을 4주마다 1주일씩 복용하였고 다른 군은 terbinafine (250 mg/d)을 매일 복용하였다. 환자들은 연구 시작시점과 치료 4, 8, 12, 24, 48, 72, 96주에 방문하여 임상적 평가 및 진균학적 검사를 받았다. 일차 치료평가 항목은 이환된 조갑의 직접도말검사와 진균배양검사 결과였고, 이차 치료평가 항목은 이환된 조갑의 침범된 범위와 근위 조갑 추벽 (proximal nail fold)에서부터 이환되지 않은 부분까지의 수직 거리였다.

결 과: 경증 내지는 중증도의 발톱 조갑 진균증에 이환된 총 49명의 환자에서 96주 이상의 장기간

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의 관찰평가가 이루어졌고 이중 진균학적 검사상 음성을 나타낸 환자의 비율은 itraconazole 치료군이 28명 중 22명 (78.6%)이었고 terbinafine 치료군이 21명 중 18명 (85.7%)이었다. 재발율은 itraconazole 치료군이 21.4%이었고 terbinafine 치료군이 14.3%이었다. 심각한 부작용은 두 치료군 모두에서 관찰되지 않았고 부작용 발생율은 두 치료군에서 비슷하였다.

결 론: 경증 및 중증도의 조갑 진균증에서 itraconazole 주기 요법과 terbinafine 연속 요법은 장기간 (96주)에 걸친 관찰결과 치료 효과와 안전성에서 유의한 차이가 없이 동등하였다.

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Key Words: Itraconazole, Terbinafine, Onychomycosis

INTRODUCTION

Onychomycosis is a common nail disorder that may be caused by several fungi, e.g., dermatophytes, yeasts, and molds[1]. Currently itraconazole and terbinafine are the mainstay treatments for onychomycosis[2,3]. The pharmacokinetic and pharmacodynamic profiles of itraconazole and terbinafine have been previously studied with regard to onychomycosis treatment[4,5].

Several studies have compared the safety and efficacy of itraconazole pulse therapy with terbinafine continuous therapy for toenail onychomycosis [6~13]. Both itraconazole and terbinafine have proven to be effective against onychomycosis[3,6~15]. However, the results of these studies are inconsistent, so a study to compare the long-term cure rates and relapse rates of itraconazole and terbinafine therapy was needed. The objectives of this study were to evaluate the long-term mycological and clinical cure rates for terbinafine and itraconazole for toenail onychomycosis. The other aim was to provide, for the first time, long-term data on cure maintenance and the relapse rates of these medications in a Korean cohort.

MATERIALS AND METHODS

1. Patients and methods

A total of 72 patients (ages 17~70) who visited two research centers in Seoul, Korea, and were diagnosed with toenail onychomycosis, were enrolled in this study. Patients eligible for inclusion were those with a clinical diagnosis of distal or distolateral subungual toenail onychomycosis, not more than 75% involvement of the nail plate in the most severely affected nail, limited involvement of the proximal region of nail plate (maximum 2 mm or the proximal region was unaffected at screening), confirmation by microscopy (potassium hydroxide examination and/or a positive mycological culture for dermatophytes, yeasts, or molds). We excluded patients with the followings; subjects who had received topical antifungal therapies or topical steroids within the previous month or had received systemic antifungal therapy within the previous 2 months at a screening visit or subjects with any systemic disease. The study protocol was approved by an institutional review board from Seoul National University hospital and written informed consent was obtained from all patients.

2. Methods

Patients were randomly selected to receive either itraconazole (400 mg/d) for 1 week in every 4 for 12 weeks (3 cycles) or terbinafine (250 mg/d) for 12 weeks. Medications were dispensed on visit 2, 3, and 4. A second intervention was made in patients who showed insufficient response, i.e., <50% reduction in the affected nail plate area compared with baseline or <3 mm outgrowth of

the unaffected nail plate (measured at midline) at 6 months (24 weeks). An additional cycle of itraconazole or 4 weeks treatment with terbinafine was administered to those showing insufficient response according to their prior corresponding therapy. Patients were checked clinically and mycologically at the baseline, and on weeks 4, 8, 12, 24, 36, and 48. Subsequent follow-ups were made every 6 months up to 96 weeks. Laboratory testing was done during visits 1 (baseline) and 5 (after the medication was dispensed, excluding the additional treatment given to non-responders). The target nail, which was the most severely affected toenail, on each patient was photographed at the baseline and on weeks 12, 36, and 96.

3. Primary and secondary efficacy parameters

The primary efficacy parameter was the proportion of patients who remained mycologically cured at the end of follow-up. A mycological cure is defined as negativity by both a direct smear and a culture of samples taken from the target toenail. The method for the mycological examination was as follows. Each specimen was collected after the collection site was cleaned and decontaminated with a 75% alcohol swab, and it was obtained by scraping the proximal and subungual surface of the target nail determined to be the most severely affected nail. A fifteen-percent potassium hydroxide (KOH) preparation of the nail material was examined by direct microscopy. When a specimen was negative according to microscopic examination, KOH preparation was made again and examined by the other investigator. The primary isolation media for the fungus culture included 2 sets of Rubrum slanted media and 2 sets of Sabouraud's dextrose agar (SDA) media with cycloheximide and chloramphenicol. All cultures were incubated at 30℃ for up to 4 weeks. Fungal species were identified by colony morphology and color with the naked eye and microscope. All recovered yeasts were identified using API20C AUX kit (bio-Merieux, Inc, Durham, NC, U.S.A.). The determination of pathogens was based on the criteria of the previous literatures[16,17]. Dermatophytes were considered to be pathogens if isolated, and non-dermatophyte molds and yeasts isolates were also considered as pathogens only if they have been reported as causative agents for onychomycosis and the isolates were found in serial culture.

The secondary efficacy parameter was clinical effectiveness on the target nail. The most severely affected toenail was selected as the target nail, and nail growth was evaluated in the area involved and the length of the unaffected part of the target nail (from the border of the proximal nail fold to the most proximal point of infection). Evolutions of signs such as onycholysis, hyperkeratosis, discoloration and paronychia were assessed using a 4-point scale (0~3).

Treatment failure was defined as a failure to achieve mycological cure and included re-infection (i.e., when a patient who had achieved mycological cure at some stage was found to be infected by another fungal species on subsequent visit) and relapse (defined as being infected by the same species after mycological cure). We did not differentiate re-infection from relapse in the final statistical analysis.

Clinical global evaluations were performed at weeks 12, 24, 36, 48, and 96, which were rated into 5 grades as follows: (0) cured: defined as >90% clear nail, with or without nail malformation compared to baseline, (1) marked improvement: defined as >50% and <90% clear nail, (2) moderate improvement: defined as <50%, (3) unchanged, and (4) deteriorated (defined as more nail involve-

Table 1. Baseline demographics of patients treated with terbinafine and itraconazole therapies (n=50)

Characteristics	Itraconazole (n=28)	Terbinafine (n=21)	Total (n=50)	*p*-value*
Mean age (yr)	44.8±7.9	47.1±12.3	45.8±10.0	0.4405
Sex				
No. (%) of Male	12 (42.9%)	13 (59.1%)	25 (50.0%)	0.2545
No. (%) of Female	16 (57.1%)	9 (40.9%)	25 (50.0%)	
Duration (mo)	90.4±70.4 (7 yr 6 mo)	148.4±93.3 (12 yr 4 mo)	−	0.0157†
Involved area (%)	43.9±15.5	50.9±16.5	−	0.1309
Unaffected length (mm)	3.1±1.6	2.8±1.2	−	0.4855

* *p*-values represent inter-treatment group comparisons. T-test was performed.
† $p<0.05$

ment than at baseline).

RESULTS

A total of 72 patients were recruited and studied from March, 2002 to February, 2005 and followed up prospectively up to week 96. They were randomly selected to receive either itraconazole or terbinafine. Of these 72 patients, 68 were followed up to 96 weeks and completed the study. Two groups of the patients were discovered to be statistically different in terms of the involved area at the baseline level. To correct this sampling bias, we included only the patients who had 20 to 70 percentage nail area involved at the baseline in the further analyses of efficacy. Secondary intervention (the additional administration of antifungal agents) was done in 3 patients in each treatment group, respectively. Treatment efficacies were evaluated in 49 patients (28 patients with itraconazole and 21 patients with terbinafine) at the end of the study. And adverse events were evaluated in 70 patients (All patients who were followed for 96 weeks). The two treatment groups were compared with regard to demographics, the percentage area of the involved nails, unaffected length of nails and duration of toenail onychomycosis at the screening visit (Table 1).

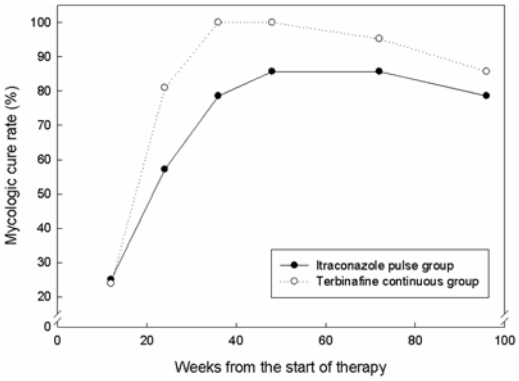

Fig. 1. Comparison of the mycological cure rates after itraconazole pulse therapy and terbinafine continuous therapy. Although the terbinafine group showed an increased mycological cure rate, no significant differences were observed between the two groups at the end of the study ($p>0.05$).

1. Identification of the causative fungus

The positive culture rate in positive direct smear specimens was 57.2% at baseline. The species identified at screening were *Trichophyton rubrum* (30 patients, 76%), *Trichophyton mentagrophytes* (3 patients, 8%), *Trichospon beigelli* (3 patients, 8%), and *Candida parapsilosis* (3 patients, 8%).

2. Mycological and clinical cure rates

The mycological cure rates are shown in Fig. 1.

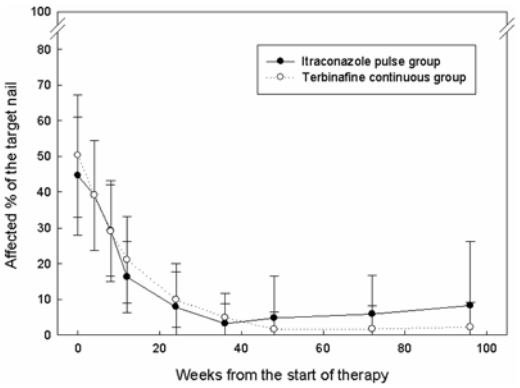

Fig. 2. Comparison of the mean % affected area of target nail during the study. At the end of the study both groups showed a reduction in the affected areas, compared to the baseline. No significant differences were observed between the two groups at the end of the study (p>0.05).

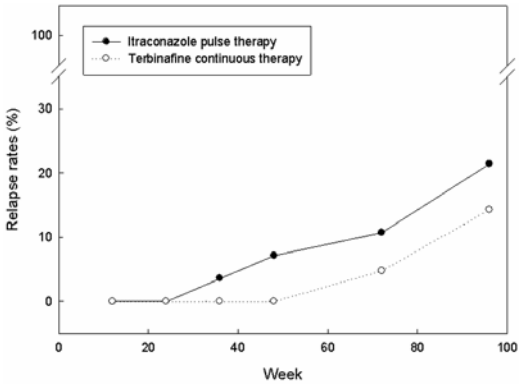

Fig. 3. Comparison of relapse rates after itraconazole pulse therapy and terbinafine continuous therapy. No significant differences were observed between the two groups at the end of the study (p>0.05).

Although the subjects treated with terbinafine showed more rapid mycological cure than the subjects treated with itraconazole, 22 (78.6%) of the 28 patients who were treated with itraconazole and 18 (85.7%) of the 21 patients who were treated with terbinafine had mycologically negative results at 2-year follow up. The mycological cure rate of itraconazole was not different statistically from that of terbinafine (p>0.05, Fisher's exact test). The mean % affected area of the target nail was 43.9±15.5 (mean ± SD) % in the itraconazole group and 50.9±18.5% in the terbinafine treated group at baseline (Fig. 2). At the end of the study, the mean % affected areas of target nails decreased to 8.3±17.9% in the itraconazole group and 2.2± 6.9% in the terbinafine group. The mean length (mm) of the unaffected part in the target nails was 3.1±1.6 in the itraconazole group and 2.7±1.1 in the terbinafine group at baseline, and these increased to 11.4±4.6, and 12.6±4.3 at the end of the study, respectively. No significant difference was observed between two groups with respect to clinical cure rates at the end of the study.

3. Relapse rates

Relapse rates are shown in Fig. 3. Two of the 28 patients in the itraconazole group relapsed, whereas none of 21 in the terbinafine group did at the 48 weeks' visit. At the end of the follow up, 6 of the 28 patients (21.4%) in the itraconazole group and 3 of the 21 (14.3%) in the terbinafine group were found to have relapsed. No significant difference was observed between the two treatment groups with respect to relapse rate (p>0.05).

4. The analysis of the clinical global evaluation

Table 2 compares the clinical global evaluation and mycological cures (primary efficacy parameter) between the two groups. The average rating in the clinical global evaluation was 0.68±1.49 in the itraconazole group and 0.12±0.49 in the terbinafine group at the end of the study, and there were no significant statistical differences. According to clinical global evaluations, 3 of 19 subjects who had achieved mycological cure with itraconazole showed clinical deterioration, and none of the 17 subjects who had achieved mycological cure by terbinafine showed clinical deterioration at the

Table 2. A comparison between clinical global evaluations and mycological cures at week 96

Clinical global evaluation	Mycological evaluation					
	Itraconazole			Terbinafine		
	Cure N=19	Relapse N=5	Tx. failure N=1	Cure N=17	Relapse N=3	Tx.‡failure N=0
Cured	15 (79.0%)	3 (60.0%)		16 (94.1%)	2 (66.7%)	
Marked	1 (5.3%)				1 (33.3%)	
Moderate		1 (20.0%)		1 (5.9%)		
Unchanged						
Deterioration	3 (15.8%)	1 (20.0%)	1 (100%)			
Average†	0.68±1.49‡			0.12±0.49‡		

* Values are number (%).
† Average represents the average score of clinical global evaluations using a 4-point scale
‡ Tx. means treatment
p=0.1788 for Wilcoxon's rank sum test
The grading system used is defined as follows; (0) cured: defined as >90% clear nail, with or without nail malformation compared to baseline, (1) marked improvement: defined as >50% and <90% clear nail, (2) moderate improvement: defined as <50% clear nail, (3) unchanged, and (4) deteriorated: defined as more extensive nail involvement than baseline status

end of the study.

5. The assessment of the clinical features

For the assessment of the clinical parameters including onycholysis, hyperkeratosis, discoloration and paronychia, we evaluated both treatment groups using a 4-point scale. The mean values of these parameters were compared in the two treatment groups at baseline and at the end of the study. All parameters improved with both treatments, and no significant difference between the two treatment groups was observed (data not shown).

6. Subject acceptance

After finishing 12 - week - treatment, subjects were asked "Would you take this medication again?" The answer was selected from the following choices; Yes, definitely, Yes, No opinion, Would rather not, and Would never take the medication again. Acceptance in the itraconazole group was greater than that of the terbinafine group. The percentages of patients who answered 'Yes, definitely' were 88% in the itraconazole group and 79% in the terbinafine group, which was without statistical significance.

7. Adverse events

The frequency of adverse events was similar in the two groups. The most common adverse event was gastrointestinal discomfort. Eight patients in the itraconazole group and 6 patients in the terbinafine group complained of gastrointestinal discomfort. However, the symptom was not severe and disappeared spontaneously. No patient dropped out of the study because of an adverse event. Moderate degrees of elevation (more than twice the norm) were observed in aspartate aminotransferase and alanine aminotransferase levels in one patient after itraconazole and in 2 patients after terbinafine (at the 24-week visit). Isolated mild elevation of gamma-glutamyl transpeptidase was observed in 5 patients on terbinafine and 1 patient on itraconazole.

DISCUSSION

A number of studies have compared the efficacies of oral antifungal treatments for fungal infection of toenails[6~13]. But there were few studies that lasted more than 18 months, which show relapse rates after treatment with itraconazole or terbinafine[12]. Comparative analyses of the clinical cure rates reported by these studies were difficult because of the different definitions that have been used to evaluate therapeutic effectiveness[15].

We conducted this randomized, prospective, comparative trial to compare the efficacy and the relapse rates of itraconazole pulse therapy with terbinafine continuous therapy for the treatment of onychomycosis. We evaluated the mycological and clinical cures in terms of involved target nail areas, and changes in the clinical parameters of onychomycosis, i.e., onycholysis, hyperkeratosis, discoloration, and paronychia, during treatment.

Based on mycological cure rates, the two therapies were equally effective for treating toenail onychomycosis at the 96-week follow up. The overall mycological cure rates in this study were relatively higher than those reported by other studies[6~13]. A recent meta-analysis on the antifungal agents for the randomized controlled trials reported that itraconazole pulse therapy and terbinafine continuous therapy have 75±10% to 63±7% and 78±6% to 76±3% mycological cure rates, respectively[15]. It is known that the predisposing factors to a poor response to antifungal therapy are the extensive involvement of the nail unit (more than 75% area), dermatophytoma, total nail dystrophy, yellow spike and onychomycosis in the immunologically challenged patients[18]. We excluded the patients with severe nail plate disease and limited the extent of proximal involvement of nail plate according to the criteria mentioned. These limitations may enhance the overall cure rates in our trial. Several studies showed significantly superior cure rates for terbinafine continuous treatment to itraconazole pulse therapy[9~12]. We also believe that the small sample size used in the present study may have influenced the determined cure rates. Moreover, other studies in which secondary intervention (the additional administration of antifungal agents) was performed showed better cure responses[10,12,13]. In the present study, 6 patients received additional treatment and achieved mycological cure at the end of the study, and secondary additional intervention probably contributed to our higher cure rate than that of others without subsequent treatment.

Many trials separately included separate parameters for mycological and clinical assessment and did not correlate individual results[19]. We compared the mycological cure rate and clinical global evaluation (Table 2). There were some patients who showed clinical deterioration in spite of mycological cure in week 96. This discordance may be due to the false negative results of mycological examinations. Otherwise, it was reported that 5~10% of nail surface remained clinically abnormal even when mycological evaluations showed a full cure, particularly after severe fungal toenail infection[19]. The subjects treated with terbinafine showed more consistent cure rates in terms of mycological and clinical evaluations than those treated with itraconazole. However, no significant difference was observed between the two treatment groups (Table 2).

As shown in Fig. 2 the maximum therapeutic effect of each treatment occurred at 48 weeks in the terbinafine group and at 36 weeks in the itraconazole group. The affected areas of target nails increased in some patients after maximal effect.

We assume that it would be due to relapse or re-infection when no treatments were done. In this context, it is suggested that additional antifungal treatments would be beneficial to prevent relapse.

Adverse events were similar in both treatment groups, and no serious adverse events occurred. With regard to patient acceptability, we found a preference for itraconazole pulse therapy, but results were not significantly different. We believe that the reason for this preference was dues to the ease of administration, but further confirmation is necessary.

CONCLUSION

In conclusion, itraconazole pulse therapy appears to be equivalent to terbinafine continuous therapy in terms of efficacy and safety in patients with mild to moderate toenail onychomycosis after a long-term follow up.

REFERENCES

1. Roberts DT. Prevalence of dermatophyte onychomycosis in the United Kingdom: results of an omnibus survey. Br J Dermatol 1992; 126(suppl 39): 23-27.
2. Gupta AK, Scher RK. Oral antifungal agents for onychomycosis. Lancet 1998; 351: 541-542.
3. Roberts DT, Taylor WD, Boyle J, et al. Guidelines for treatment of onychomycosis. Br J Dermatol 2003; 148: 402-410
4. De Doncker P, Decroix J, Pierard GE, et al. Antifungal pulse therapy for onychomycosis: a pharmacokinetic and pharmacodynamic investigation of monthly cycles of 1-week pulse therapy with itraconazole. Arch Dermatol 1996; 132: 34-41
5. Finlay AY. Pharmacokinetics of terbinafine in the nail. Br J Dermatol 1992; 126(suppl 39): 28-32
6. Tosti A, Piraccini BM, Stinchi C, et al. Treatment of dermatophyte nail infections: an open randomized study comparing intermittent terbinafine therapy with continuous terbinafine treatment and intermittent itraconazole therapy. J Am Acad Dermatol 1996; 34: 595-600
7. Negroni R, Avechvala A, Bonvehi P. Treatment of onychomycosis due to mycelial fungi. Revista Argentina de Micologica 1998; 21: 8-14
8. Kejda J. Itraconazole pulse therapy vs continuous terbinafine dosing for toenail onychomycosis. Postgrad Med 1999; Spec No: 12-5
9. Sigurgeirsson B, Billstein S, Rantanen T, et al. The L.I.ON. Study: efficacy and tolerability of continuous terbinafine (Lamisil) compared to intermittent itraconazole in the treatment of toenail onychomycosis: Lamisil vs itraconazole in onychomycosis. Br J Dermatol 1999; 141(suppl 56): 5-14
10. Evans EG, Sigurgeirsson B. Double blind, randomised study of continuous terbinafine compared with intermittent itraconazole in treatment of toenail onychomycosis. The LION Study Group BMJ 1999; 318: 1031-1035
11. Heikkila H, Stubb S. Long-term results in patients with onychomycosis treated with terbinafine or itraconazole. Br J Dermatol 2002; 146: 250-253
12. Sigurgeirsson B, Olafsson JH, Steinsson JB, et al. Long-term effectiveness of treatment with terbinafine vs itraconazole in onychomycosis: a 5-year blinded prospective follow-up study. Arch Dermatol 2002; 138: 353-357
13. Gupta AK, Konnikov N, Lynde CW. Single-blind, randomized, prospective study on terbinafine and itraconazole for treatment of dermatophyte toenail onychomycosis in the elderly. J Am Acad Dermatol 2001; 44: 479-484
14. Crawford F, Young P, Godfrey C, et al. Oral treatments for toenail onychomycosis: a systematic review. Arch Dermatol 2002; 138: 811-816.
15. Gupta AK, Ryder JE, Johnson AM. Cumulative meta-analysis of systemic antifungal agents for the treatment of onychomycosis. Br J Dermatol 2004;

150: 537-544

16. Ghannoum MA, Hajjeh RA, Scher R, et al. A large-scale North American study of fungal isolates from nails: the frequency of onychomycosis, fungal distribution, and antifungal susceptibility patterns. J Am Acad Dermatol 2000; 43: 641-648
17. Lim SW, Suh MK, Ha GY. Clinical Features and Identification of Etiologic Agents in Onychomycosis (1999-2002). Korean J Dermatol 2004; 42: 53-60
18. Scher RK, Baran R. Onychomycosis in clinical practice: factors contributing to recurrence. Br J Dermatol 2003; 149 Suppl 65: 5-9
19. Hay RJ. The future of onychomycosis therapy may involve a combination of approaches. Br J Dermatol 2001; 145 Suppl 60: 3-8