대한이식학회지 : 제 9 권 제 1 호
Vol. 9, No. 1, November, 1995

The Study of the Efficacy and Tolerability of Oral Terbinafine in the Treatment of Onychomycosis in Renal Transplant Patients

Kwang Hoon Lee, M.D.*, **Yu Seun Kim**, M.D., **Myoung Soo Kim**, M.D.
Hae-Shin Chung, M.D.* and **Kiil Park**, M.D.

Departments of Surgery and Dermatology*, Yonsei University College of Medicine, Seoul, Korea

=국문초록=

신장이식환자에서 발생한 조갑진균증 환자에서 경구용 Terbinafine의 치료효과에 관한 연구

연세대학교 의과대학 장기이식연구소, 외과학교실 및 피부과학교실*

이광훈* · **김유선** · **김명수** · **정혜신*** · **박기일**

본원에서 신이식을 시행한 환자중 임상적 및 진균학적 검사상 조갑진균증으로 진단된 20명의 환자를 대상으로 terbinafine(Lamisil®) 250mg 을 1일 1회 썩 손톱진균증에는 6주간, 발톱진균증에는 12주간 경구투여하고, 치료 종료후 모든환자를 12주간 추적 관찰하였으며, 임상적, 진균학적 소견을 관찰하여 다음과같은 결론을 얻었다.

1) 첫 내원시 진균배양 검사상 30명의 환자에서 21주의 원인 균주를 분리하였으며, *T.rubrum*이 13주로 가장 많았다.

2) 대상 표적 조갑상 정상부분의 조갑 길이 측정결과, 투약종료후 12주째 손톱은 9.6 mm, 발톱은 10.4 mm로 현저히 증가 되었다.

3) 조갑박리, 조갑하 과각화증, 조갑주위염 등 임상증상이 치료종료후 현저한 호전을 보였으며, 최종 투약후 12주 추적관찰시에는 대부분 환자에서 모든증상이 거의소실 되었다.

4) 진균학적 검사에서 손톱의경우 치료 종료시 71.4%, 추적관찰시 85.7% 의 완치율을 보였으며, 발톱의경우 각각 56.5%, 85.7%의 완치율을 보였다.

5) 치료도중 현저한 간기능 이상이나, 신기능 이상은 전혀 관찰 되지 않았으며, 현저한 Cs 의 혈중농도 변화도 관찰되지 않았다.

이상의 연구결과로 보아 신이식 환자의 조갑 진균증의 치료에 terbinafine(Lamisil®)은 단기간 경구요법으로도 효과적이고 안전하게 사용할수 있는 약제로 사료된다.

핵심어: Terbinafine, Onychomycosis, Renal transplantation, Cyclosporin

Onychomycosis is a fungal infection of the nail. In patients with HIV infection, those receiving immunosuppressants or organ transplantation, the incidence of onychomycosis is more prevalent and more serious. Cyclosporin is largely metabolized by hepatic cytochrome P-450 enzymes, and the metabolism of cyclosporin has been shown to be inhibited by azole antifungal drugs, both in vivo and in vitro[1,2]. Terbinafine is an allylamine antifungal agent showing a fungicidal action by producing ergosterol deficiency and causing accumulation of squalene[3]. Terbinafine does not have a general inhibitory

*본 논문은 1994년도 연세대학교 의과대학 임상연구비 (승인번호 1994022) 지원으로 이루어졌음.

effect on cytochrome P-450 isoenzymes unlike azole compounds[4]. The aim of this study was to determine whether oral terbinafine alters the serum concentration of oral cyclosporin in vivo and to assess the efficacy of terbinafine in the treatment of onychomycosis in renal transplant patients.

PATIENTS AND METHODS

Patients

Thirty patients(23 toenail mycoses and 7 fingernail mycoses) ages from 26 to 61 years with clinically and mycologically diagnosed onychomycosis who received renal transplantations were entered into this open trial. Ethical committee approval was obtained for the trial and all participants gave their informed consent.

Drug administration

The terbinafine 250 mg in tablets was administered once a day orally to the patient with finger nail onychomycosis for 6 weeks and the patient with toenail infection for 12 weeks.

Assessment of clinical efficacy

The clinical efficacy were assessed at baseline and at 4, 8, 12 weeks and followed up every 4 weeks for 12 weeks for the toenail group; assessed at baseline and at 4, 6 weeks and followed up at 12, 16, 20 weeks for the fingernail group. Clinical signs and symptoms including onycholysis, hyperkeratosis and paronychial inflammation were to be allocated scores as follows: absent=0, mild=1, moderate=2, severe=3. The length of unaffected nail were also measured.

Assessment of mycological efficacy

Mycological evaluation were performed with microscopic examination of a specimen of infected nail after treatment with potassium hydroxide and with a culture of infected tissue at the same time with the evaluation of clinical efficacy.

Measurement of cyclosporin levels

Samples of blood were collected into glass tubes and further blood samples were taken at 2, 6, and 12 week. Whole blood cyclosporin was measured by radioimmunoassay using monoclonal antibody.

Safety assessment

Every 4 weeks, adverse events were recorded and biochemical tests including SGOT, SGPT, LDH, gamma GT, alkaline phosphatase, bilirubin, and creatinine were performed.

RESULTS

Cyclosporin assay

The mean concentration of cyclosporin was 164.70± 47.73 ng/ml at baseline. The concentration of cyclosporin

Table 1. Blood concentration of cyclosporin after treatment of terbinafine

Time of terbinafine treatment	Cyclosporin concentration (ng/ml)	Cyclosporin dose (mg/kg/day)
Baseline	163.70±47.73*	3.65±1.16
2 weeks	153.48±54.31	3.64±1.19
6 weeks	158.48±42.07	3.63±1.21
12 weeks	147.33±38.36	3.63±1.20

*: mean±SD

Table 2. Mycological data for study patients

Organisms isolated	Study target nails		
	Fingernails	Toenails	Total
T. rubrum	3	10	13
T. mentagrophytes	1	2	3
Candida spp.	2	1	3
Mould	0	1	1
Total	6	14	20

at 2, 6, 12weeks after oral terbinafine treatment were 153.48±54.31 ng/ml, 158.48±42.07 ng/ml, 147.33±38.36 ng/ml, respectively(Table 1). All patients had no changes in dosage and regimen of cyclosporin from 2 months prior to entering the study to the end of the treatment.

Mycological assay

All patients showed positive findings on KOH examination. On culture, 21 causative fungi(70%) were isolated and Trichophyton rubrum was most common organism(76.2%)(Table 2).

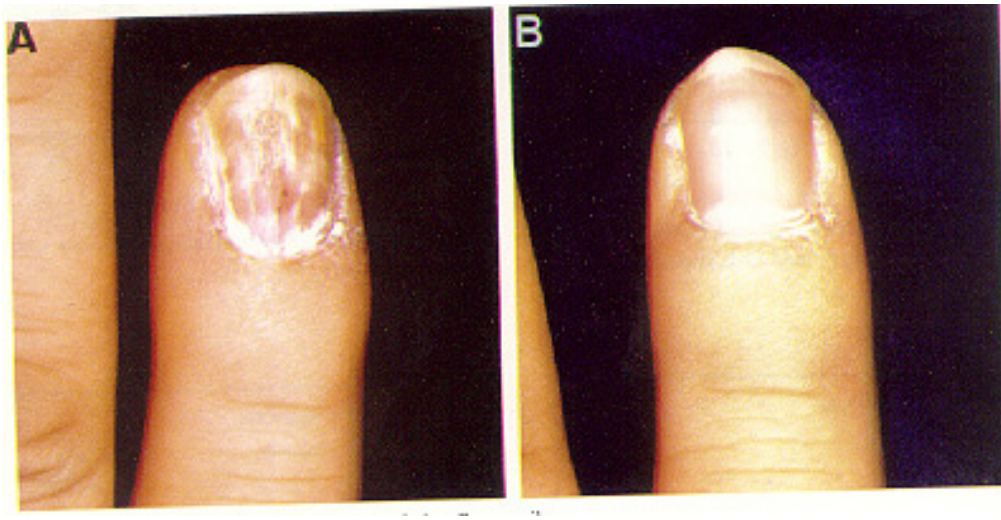

Fig. 1. Onychomycosis of the fingernail.
A. before terbinafine treatment, B. after 20 weeks(last follow-up).

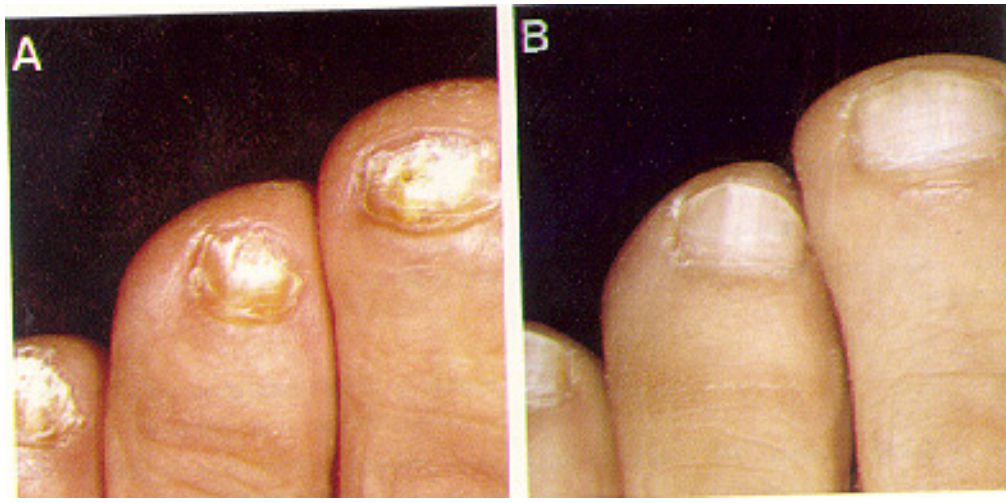

Fig. 2. Onychomycosis of the toenail.
A. before terbinafine treatment, B. after 24 weeks(last follow-up).

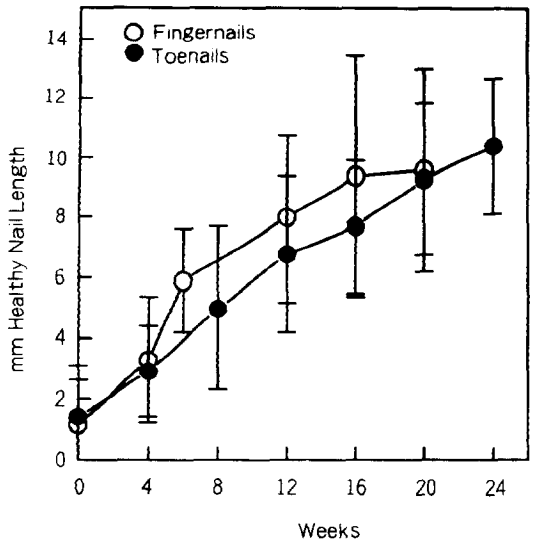

Fig. 3. Length of the unaffected nail during terbinafine treatment of finger nails and toenails.

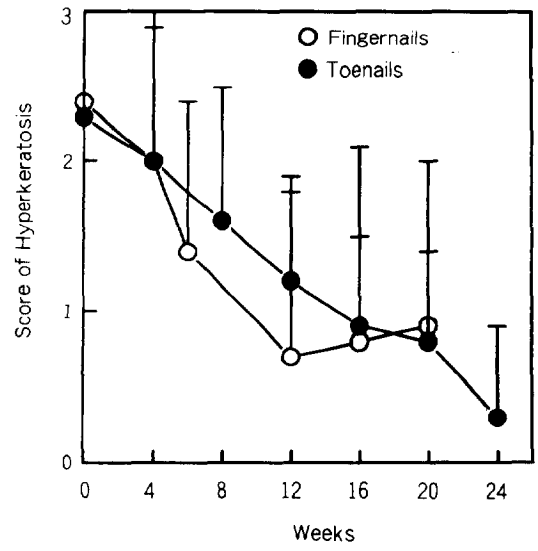

Fig. 5. Mean score of hyperkeratosis in patients with onychomycosis.

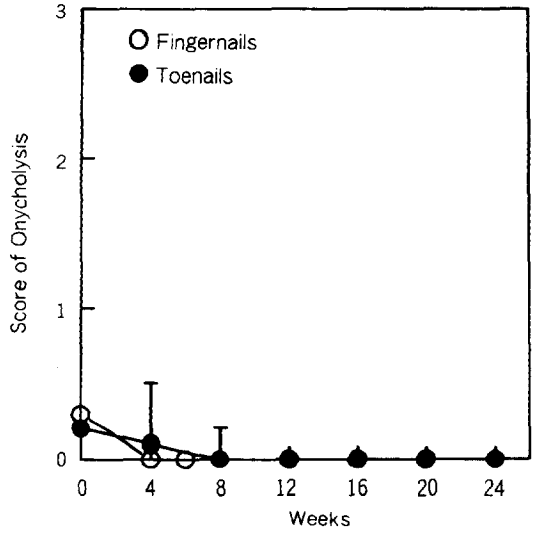

Fig. 4. Mean score of onycholysis in patients with onychomycosis.

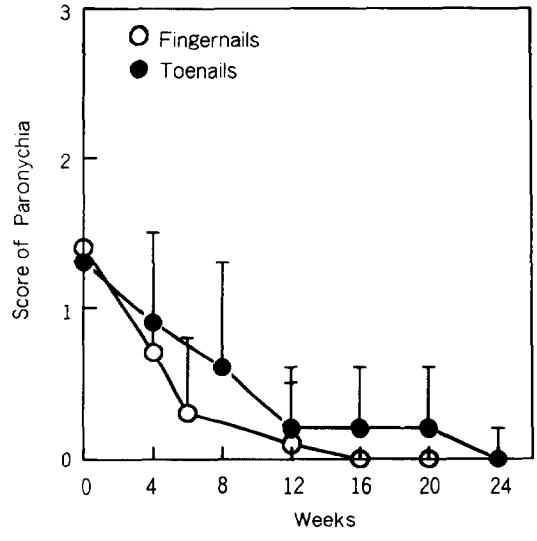

Fig. 6. Mean score of paronychia in patients with onychomycosis.

Efficacy

The length of healthy, unaffected nail were increased significantly from 1.4mm at baseline to 6.8, 10.4 mm at the end of treatment, and at the end of follow-up, respectively in the toenail group and 1.1 mm at baseline to 5.9 mm, 9.6 mm at the end of treatment, and at the end of follow-up, respectively in the fingernail group(Fig. 3). The mean scores of onycholysis on entry diminished significantly from 0.2 at baseline to 0, 0 at the end of

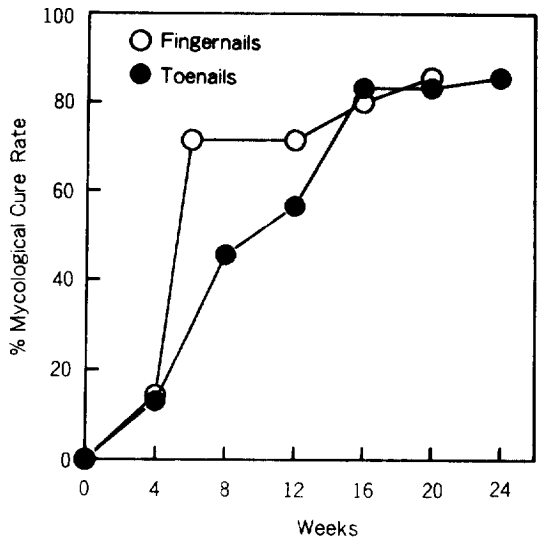

Fig. 7. Mycological cure rates(negative microscopy and negative culture) with terbinafine treatment.

treatment, and at the end of follow-up, respectively(Fig. 4). The mean scores of hyperkeratosis(Fig. 5) and paronychial inflammation(Fig. 6) also diminished significantly from 2.3, 1.3 at baseline, to 1.2, 0.2 at the end of treatment, to 0.3, 0 at the end of follow-up, respectively. The mean scores of all clinical symptoms were also significantly reduced in the fingernail group after both the end of treatment and at the end of follow-up. The total mean scores of each clinical symptoms were also significantly diminished. The mycological cure rates showing negative microscopy and negative culture findings in fungus study was 56.5%, at the end of treatment for toenail infection. The number of patients with fingernail infection was small, but 71.4% of those were mycologically cured at the end of treatment. At the end of follow-up 85.7% of evaluable patients with toenail infections and 85.7% of those with fingernail infection who had received terbinafine were mycologically cured (Fig. 7).

Safety

No clinically important adverse events were seen in all patients received terbinafine. There were no significant changes in the laboratory test including hematological, hepatic, renal blood test and urinalysis both at the end of treatment and at the end of follow-up.

DISCUSSION

Individuals with many types of immunodeficient states are at an increased risk for fungal infections. They include those with organ transplant, those who take immunosuppressants, and those with primary immunodeficiency. Onychomycosis is more prevalent in transplant patients than in normal controls. Because of development of new broad-spectrum antifungal agents-itraconazole, fluconazole, and terbinafine, the treatment of onychomycosis is generally satisfactory today. However, the choice of antifungal agents in the case of organ transplant is relatively difficult due to more common resistant causative organisms and interactions with cyclosporin. Cyclosporin is mainly metabolized by cytochrome P-450 enzymes. Drugs that are metabolized by these enzymes may interfere with the metabolism of cyclosporin. Both increased and decreased blood levels of cyclosporin may lead to undesired side effects. It has been shown that azole antifungal agents inhibited the metabolism of cyclosporin, both in vivo and in vitro[1,2].

Terbinafine is an allylamine antifungal agent which has a broad-spectrum in vitro activity and a unique fungicidal action. Terbinafine is effective in the treatment of cutaneous fungal infections[3], and do not interfere with cytochrome P-450 enzyme unlike azole agents. So terbinafine have no effect upon the metabolism of cyclosporin both in vivo and vitro[2,4,5]. The results of this study support the results of those investigations. Furthermore, the results suggest that long-term treatment of terbinafine for patients with onychomycosis would not induce an increase in the blood concentration of cyclosporin. Previous investigations demonstrated that the short course treatment of terbinafine for patients with onychomycosis was very successful and safe[6]. The cure rates achieved with 6 weeks and 12 weeks for patients with onychomycosis of fingernail, toenail, respectively were comparable to those

found in patients with onychomycosis in normal healthy persons. Delayed clinical cure was reconfirmed here. Adverse events were reported by about 5～10% of the patients receiving oral terbinafine; the major side effect is gastrointestinal discomfort even though they develop transiently in the first 6 weeks of treatment[7]. In this study, no adverse effects were seen in contrast to the results in earlier studies. Encouragingly, there were no important changes in the laboratory studies.

Our results suggest that terbinafine is an effective and safe systemic antifungal treatment for patients with onychomycosis who has received renal transplantation and whom are taking cyclosporin.

REFERENCES

1) Freeman DJ: Clin Biochem 24: 9, 1991
2) Kramar MR, Marshall SE, Denning DW, et al: Ann Intern Med 113: 327, 1990
3) Petranyi G, Ryder NS, Stutz A: Science 224: 1239, 1984
4) Back DJ, Tjia JF: Br J Clin Pharmac 32:624, 1991
5) Long CC, Hill SA, Thomas RC, et al: J Invest Dermatol 102: 740, 1994
6) Goodfield MJD, Andrew L, Evans EGV: Br Med J 304: 1151, 1992
7) Villars V, Jones TC: J Dermatol Treat 1: 33, 1990