

Long-term Results of Patients with Onychomycosis Treated with Itraconazole

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We studied the long-term results of 88 patients treated with itraconazole either with continuous or pulse therapy. No differences were noted in the treatment results between these two groups. Thirty-six weeks after cessation of a 12-week drug therapy total clinical cure was achieved in 35% of these patients with 93% negative culture. At a follow-up at week 104 the total clinical cure was 39%, with negative culture in 57%. **Key words:** dermatophyte; continuous therapy; pulse therapy; mycological cure.

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The prevalence of onychomycosis varies between 2.2 and 8.4% in different studies (1,2). In recent years more effective medications for the treatment of onychomycosis have been developed. In contrast to griseofulvin, which reaches the nail only through the matrix, the new drugs terbinafine and itraconazole also reach the nail plate directly from the nail bed (3, 4).

In onychomycosis of the toenails treatment results with 250 mg/day terbinafine and 200 mg/day itraconazole for 3-6 months or with 150 mg fluconazole once weekly for 5-12 months vary between 42 and 92% (4-6). Intermittent therapy with itraconazole 400 mg/day, 3-4 one-week cycles once monthly, has been found to be as effective as 3-month continuous therapy with 200 mg/day (4, 7-9).

Although treatment of onychomycosis with the new antifungals is effective, follow-up studies of the duration of results have been carried out only up to 1 year (5, 7-10). In order to get a view of the long-term treatment results in onychomycosis of the toenails, we reexamined patients treated with itraconazole 2 years after cessation of drug therapy.

PATIENTS AND METHODS

A multicentre study of 129 patients with onychomycosis was made in Finland during 1993-1994. At the beginning of the study all the patients had clinical suspicion of onychomycosis of at least one toenail, with the affected part of the nail comprising more than 50% of the whole nail surface or at least 25% of the nail surface when the lunula was also affected. The diagnosis was confirmed with direct microscopy and mycological culture. All the patients included in the study had positive culture for dermatophytes (*Tr. rubrum* or *Tr. mentagrophytes*). In this study the efficacy of 200 mg/day itraconazole for 12 weeks was compared with itraconazole pulse therapy (three 1-week pulses with 400 mg/day once monthly for 12 weeks). Both groups of patients were followed up for an additional 36 weeks.

Our secondary follow-up study was performed at week 104 after the end of drug intake. For administrative reasons only 5/6 centres could participate in our reexamination study. The total number of the patients at these five centres was 91, of which one could not be located and 2 were unwilling to participate, thus bringing the actual number of patients to 88, 44 men and 44 women, age range 21-61 years. We reviewed patient histories for mycological treatments and examined the patients: in all suspected cases we took nail specimens. All specimens were examined by direct microscopy (20% KOH) and culture. Fungal culture was performed in three different media: brain-heart infusion agar (Difco agar 0418-17-7 from Difco Laboratories, Detroit, MI, USA) with 0.05 g/l chloramphenicol, selective agar for pathogenic fungi (Merck 5467) and Sabouraud's maltose agar with 0.026 g/l streptomycin and 0.006 g/l penicillin.

RESULTS

We first divided the patients treated with itraconazole into two groups: those receiving continuous therapy and those receiving pulse therapy. When we found that the clinical cure was equally good and that there were no marked differences between the mycological results of these two groups, we combined the patients into one group. As can be seen in Table I, 36 weeks after cessation of drug therapy total clinical cure was observed in 31/88 patients (35%). In 6/88 patients

Table I. Clinical and mycological results of patients with onychomycosis treated with itraconazole

Number of patients	36 weeks after therapy				104 weeks after therapy		
	Clinical cure	Mycologic cure		Clinical cure	Mycologic cure		
		Microscopy	Culture		Microscopy	Culture	
No additional therapy	65	29 (45%)	54 (83%)	62 (95%)	24 (37%)	32 (49%)	36 (55%)
Additional therapy	23*	2 (9%)	12 (52%)	20 (87%)	10 (43%)	14 (61%)	14 (61%)
Total	88	31 (35%)	66 (75%)	82 (93%)	34 (39%)	46 (52%)	50 (57%)

* During weeks 36 and 104 all these patients had received additional systemic antifungal therapy (6 itraconazole, 12 terbinafine, 4 fluconazole, 1 itraconazole + terbinafine).

(7%) the culture was positive and in 22/88 (25%) the microscopy. After the primary study 23/88 patients had received additional systemic therapy for onychomycosis from their private doctors. Two out of 23 were cured clinically but in both of them the microscopy and in one of them the culture was positive.

At week 104 clinical cure was observed in 34, mycological cure in microscopy in 46 and in culture in 50 out of the 88 cases studied.

There were no statistically significant differences in the treatment results between men and women or between light and heavy subgroups. Younger patients exhibited distinctly better clinical cure (22/43) than older patients (9/45) at week 36, but at week 104 the differences (19/43 and 15/45) were not significant. The mycological results were equal in both age groups.

DISCUSSION

To obtain a view of the long-term results of itraconazole therapy we reexamined the patients 2 years after cessation of medication. At week 36 and 104 the clinical situation was almost identical: 35 and 39% of the patients were totally cured. In contrast, great differences were apparent in the mycological results, especially in culture at weeks 36 and 104. These results can be explained as follows: At week 36 the itraconazole had killed the fungi, thus making culture negative but the clinical picture of onychomycosis and hyphae of dermatophytes were still found in the nails of many patients. At week 104 the old infection had reactivated or the patients had become reinfected and viable organisms could be cultured. Younger patients showed significantly better clinical cure rates at week 36 than older patients, which could be due to the faster nail growth in young people (11). An interesting finding is that body weight did not influence the cure rates of the patients. The poor results were probably not attributable to too low doses of medication; otherwise lighter patients would have shown better cure rates than heavy patients.

Published treatment results of onychomycosis with itraconazole, terbinafine and fluconazole have often been too optimistic, because in many studies the improvement rather than the cure was estimated. In our 2-year follow-up study only 39% of patients were clinically and 52–57% mycologically cured. Twenty-one out of 23 of those patients who later got additional therapy had clinical onychomycosis at week 36 and the remaining 2 were mycologically positive. We can assume with all probability that those 23 patients would have had onychomycosis at week 104 without additional treatment, so the long-term clinical cure rate of all 88 patients would be only 27%.

If we examine those 31 patients who were totally clinically cured at week 36, we find out that at week 104 24 of them were still clinically symptomless (2 of them had got additional systemic antimycotic therapy) and only 7 had clinical onychomycosis. On the other hand, if we look at those 24 patients whose worst nail was only 0–20% affected at week 36 we find that at week 104 15 of them had worsened clinical onychomycosis. Seven of them had got additional treatment and only 2 were clinically cured without additional treatment. So if the patients were totally cured at week 36, it is probable that they are symptomless at week 104, but if they have the very smallest amount of clinical onychomycosis left at week 36 it is probable that they have onychomycosis also at week 104.

In conclusion our study shows that the long-term treatment results of onychomycosis with itraconazole are not very encouraging. To get a better view of the long-term prognosis, total cure of all nails rather than improvement should be used as a criterion.

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