ARTICLE

Itraconazole Pulse Therapy for Dermatophyte Onychomycosis in Children

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Background: Onychomycosis, or fungal infection of the nail, can occur in prepubertal children. However, its diagnosis is often missed or the condition is inappropriately treated with topical medication. Griseofulvin has been the therapy of choice, but even long-term treatment is associated with a poor cure rate and high rate of relapse. Trials with adult patients have shown that itraconazole pulse therapy for onychomycosis requires a shorter duration of total therapy than griseofulvin treatment and is rarely associated with adverse reactions, suggesting that it may be the treatment of choice for pediatric patients with onychomycosis.

Design: We retrospectively reviewed the courses of prepubertal patients with dermatophyte onychomycosis who initiated treatment with itraconazole pulse therapy between January 1995 and June 1998.

Setting: Urban and suburban pediatric dermatology clinics of a children's hospital.

Patients: Seventeen prepubertal patients met the enrollment and follow-up criteria. These included fungal infection of the nail(s), documented by fungal culture and/or positive potassium hydroxide mounts of nail scrapings; at least 1 follow-up visit; and contact by telephone or clinic visit within 2 months prior to compilation of data. In 59% of patients, a relative living at the home had onychomycosis at the time of diagnosis.

Intervention: Patients were treated with daily to twice-daily pulses of itraconazole, administered for 1 week of each of 3 to 5 months.

Main Outcome Measures: Clinical cure after itraconazole therapy in patients with documented onychomycosis and clinical and mycologic relapse after initial cure. Fungal cultures were not repeated if clinical cure was noted.

Results: All but 1 patient responded fully to therapy, showing improvement within a few months and subsequently clearance (94% clinical cure rate). No patients experienced any clinical adverse reactions. No relapses occurred after clinical cure during a follow-up period of 1 to 4.25 years after initiation of therapy.

Conclusions: Itraconazole pulse therapy is effective and safe for the treatment of onychomycosis in children. The relapse rate in pediatric patients is lower than in adults, although the high frequency of onychomycosis in nonpediatric family members suggests that the recurrence risk is increased if other family members are not treated concomitantly.

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ONYCHOMYCOSIS, or dermatophyte fungal infection of the nail, has traditionally required treatment with systemic antifungal therapy for clinical improvement and cure. Griseofulvin has been the therapy of choice, but requires daily administration until the nail has been fully replaced, generally for 6 to 12 months. In addition, the cure rate after griseofulvin therapy is poor and the relapse rate is high. Newer oral antifungal agents, such as itraconazole, terbinafine, and fluconazole, accumulate and persist in the underlying stratum corneum and the nail, allowing them to be administered in a pulsed regimen and/or for a shorter overall duration than griseofulvin.[1]

Studies in adults suggest that itraconazole pulse therapy is highly efficacious and has a low relapse rate compared with griseofulvin.[2,3] The use of itraconazole pulse therapy for dermatophyte onychomycosis has only been described in 7 pediatric patients (up to age 17 years).[4-6] Yet itraconazole pulse therapy is theoretically far superior to griseofulvin administration for pediatric patients because the fewer total days of administration increases tolerability and compliance and minimizes the risk of any adverse events. We retrospectively evaluated

PATIENTS AND METHODS

A retrospective analysis of prepubertal pediatric patients with onychomycosis treated with pulse itraconazole therapy was undertaken. Patients with underlying skin disease that could affect the nail, such as psoriasis, were excluded because of the difficulty with clinical assessment of improvement. To meet inclusion criteria, patients had their infection confirmed by culture and/or potassium hydroxide analysis. All patients had at least 1 follow-up visit during the first 3 months after initiation of therapy, and most were seen again at approximately 6 months after initiation. Contact was made within the 2 months prior to data compilation by telephone or clinic visit to assess long-term course. Clinical cure was defined as clinically normal nails after itraconazole therapy. Clinical relapse was defined as recurrence of signs of onychomycosis and positive fungal culture after initial clinical cure. Nails were not routinely cultured again after clinical clearance, because clinical clearance correlates well with a mycologic cure, although mycologic cure may not be associated with normalization of nail appearance.

our experience in treating pediatric onychomycosis with pulse itraconazole therapy during a 2½-year period in patients with at least 1 year of observation after initiation of therapy to determine the efficacy, adverse events, and relapse rate.

RESULTS

Seventeen patients with onychomycosis of the toenails and/or fingernails who met inclusion criteria were evaluated initially in the pediatric dermatology clinics at Children's Memorial Hospital, Chicago, Ill, between January 1995 and June 1998 (**Table**). Eight were girls and 9 were boys. The patients ranged in age from 3 to 14 years (mean age, 8.5 years). Only 8 of the 17 patients had no other medical problems, consistent with the referral base at the hospital. Asthma was the most common medical problem (29% of patients), although no affected patients had been receiving long-term systemic corticosteroid therapy. One patient each had idiopathic thrombocytopenic purpura, Down syndrome, and acute lymphoblastic leukemia in remission. Patients and parents had reported the presence of nail changes for 2 months to 5 years before diagnosis (mean, 10.8 months). One patient had been treated for 6 months with griseofulvin without effect. A topical antifungal had been prescribed for 10 of the 17 patients at some time before evaluation, and had not shown any effect on the nail changes in any of the patients. Eight of the patients had concurrent tinea pedis or a history of tinea pedis. Six of these 8 were boys. At least 1 first-degree relative reportedly had similar nail changes in 10 of the 17 patients; in 9 of these 10 cases, a male relative was affected, usually the father. All parents were advised to seek systemic therapy for the onychomycosis of the other affected individual(s). Six of these relatives were examined by us, and pulse itraconazole therapy was initiated.

Clinical examination showed thickened discolored nails in all patients (**Figure**). The medical records provided insufficient detail to determine the type of onychomycosis; eg, distal subungual onychomycosis, proximal subungual onychomycosis, or white superficial onychomycosis. Only toenails were involved in 83% of patients. Both toenails and fingernails were affected in 2 of the 17 patients. Only 2 of the patients had a single nail involved; no patient had all 20 nails involved. The diagnosis of onychomycosis was based on a potassium hydroxide mount that showed septate hyphae (positive in 47% of patients tested [8/17]) and confirmed in all patients by isolation of the dermatophyte on Sabouraud culture medium or dermatophyte test medium (positive in all cases cultured). One patient (patient 12) had classic onychomycosis clinically, with a positive potassium hydroxide mount, but a culture was not performed. Subspeciation was not routinely performed to confirm that the dermatophyte was *Trichophyton rubrum*, as has been described in the majority of children with onychomycosis.[7-9]

The dosage of itraconazole was approximately 5 mg/kg per day and, with the use of 100-mg capsules, was determined as follows: weight 10 to 15 kg, 100 mg every other day; 16 to 20 kg, 100 mg daily; 21 to 40 kg, 100 mg twice daily; more than 40 kg, 200 mg twice daily. All patients were administered capsules to open into food, unless the patient was able to swallow the capsule, and the medication was taken with meals. Eight patients received a 3-month course of therapy, 6 patients received 4 months of treatment, and 3 patients received 5 months of treatment. All patients who received a 5-month course had hallucal nail onychomycosis.

Patients were followed up initially after 1 or 2 months of therapy. By that time, clearance of the nail base was seen in all patients. Fifteen of the 17 patients were also seen in follow-up at approximately 6 months after initiation of therapy to determine if full clinical clearance had been achieved. All patients were contacted by telephone to determine if recurrence had occurred during the subsequent years. Parents were asked to examine carefully all fingernails and toenails. Three of the patients were seen in follow-up beyond 6 months when they came to the clinic for dermatologic conditions that did not involve the nails. Follow-up cultures were not performed to verify mycologic cure, but mycologic cure was suggested by the clinically normal appearance of nails and failure to recur.

All patients but 1 experienced clinical cure. Seven of the 16 patients with clinical cure were administered 3 pulses (patients 2-5, 8, 9, and 13). None have shown evidence of relapse during a minimum follow-up of 2 years. The 1 patient who did not respond fully (patient 1) was a 13-year-old boy with dystrophy and discoloration of the entire right hallucal nail. He was administered itraconazole for a 3-month pulse. He was examined at 1 month, but did not return for follow-up as advised. In telephone follow-up 4 years later, he reportedly had had partial clearance at the base after a few months, but denied further improvement despite completion of his 3-month course of medication. The entire nail report-

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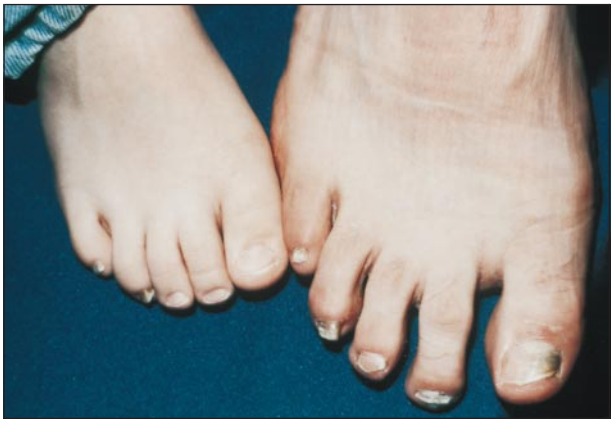
Patient No./ Age, y/Sex	Family Affected	Previous Therapy	Nails Affected	Tinea Pedis	Course	Follow-up, y	Time to Relapse
1/13/M	None	TAF	TNs	No	Clear at base of nail	4.25	1 y, full nail
2/11/F	Brother	TAF	TNs	Yes	Cured	4.25	None
3/11/M	Father	TAF	RTNs	Yes	Cured	4.25	None
4/7/F	Father, grandfather	GF, 6 mo	LTNs: R5	No	Cured	4.00	None
5/7/M	Sister	TAF	TNs	No	Cured	3.25	None
6/8/F	None	None	TN: L2, R2, R3	No	Cured	3.25	None
7/3/F	None	None	TN: R3, R4	No	Cured	3.00	None
8/14/M	Father	TAF	TN: R	Yes	Cured	2.75	None
9/6/M	Father	TAF	TN: L1; FN: R1	Yes	Cured	2.25	None
10/6/M	Father	None	TN: R4, R5	No	Cured	2.25	None
11/14/M	None	TAF	TN: R4, R5	Yes	Cured	2.00	None
12/11/M	None	None	TN: R1, L3	Yes	Cured	2.00	None
13/5/M	Father	TAF	TN: R	Yes	Cured	1.75	None
14/6/F	Father, mother	TAF	TN: L5, R1, R3, R5	Yes	Cured	1.75	None
15/5/F	None	TAF	TN: R2	No	Cured	1.25	None
16/9/F	Grandfather, grandmother	None	TN: R4, R5	No	Cured	1.00	None
17/8/F	None	None	FN, TN	No	Cured	1.00	None

*TAF indicates topical antifungal; GF, griseofulvin; TN, toenail; R, right; L, left; and FN; fingernail.



Distal and lateral subungual onychomycosis in patient 10 and his affected father.

edly became dystrophic during the subsequent year. During the past month, fungal culture was obtained and showed *T rubrum* infection. Pulse itraconazole therapy was initiated for a planned 3-month course. No patient had any known adverse reactions, although laboratory testing was not performed. Patients were followed up for up to 4.25 years after initiation of therapy (range, 12 months to 4.25 years; mean follow-up period, 2.5 years). Fifteen patients were followed up for more than a year after completion of therapy. To date, no patient has experienced relapse after clinical cure.

COMMENT

Onychomycosis in the general pediatric patient population is considered unusual, with a prevalence of 0.2%[10] to 0.44%[4] in most studies, in contrast to its prevalence in 2.7% to 13% of the adult population.[10,11] The low occurrence has been attributed to the faster nail growth in children, smaller surface area for invasion, reduced likelihood of trauma to the nails, a lower incidence of tinea pedis, and less time spent in environments with infective spores and hyphae, such as locker rooms. *Trichophyton rubrum* is the predominant causative dermatophyte in children.[7,12] Onychomycosis can be characterized as distal and lateral subungual onychomycosis (the most common type in both adults and children),[12] proximal subungual onychomycosis, or white superficial onychomycosis, which appears as tiny white spots that eventually merge to form a rough-surfaced, well-demarcated white plaque on the dorsal surface. As in our patients, involvement of toenails is far more common than involvement of fingernails.

Asymptomatic tinea pedis has been found to be more common than onychomycosis in children, occurring in 2.2% to 8.2% of screened healthy children aged 7 to 10 and 11 to 14 years, respectively.[13] Similarly, another study of schoolchildren between the ages of 10 and 14 years found 2.7% of the children to have dermatophyte infections of the feet through fungal culture confirmation. In the most recent prospective study, 14% of 50 Mexican children aged 2 to 12 years with clinically normal feet showed fungi by potassium hydroxide mounts or positive cultures.[14] Foot dermatitis, presumed to be related to the irritant effects of hyperhidrosis, is the common misdiagnosis of prepubertal children with scaling due to tinea pedis. Kearse and Miller[15] found evidence of dermatophyte infection, in each case caused by *T rubrum*, in 8 of 15 cultured prepubertal patients with a previous diagnosis of foot dermatitis. Becerril-Chihu et al[14] similarly found evidence of dermatophyte infection, usually caused by *T rubrum*, in 21 of 50 children with scaly feet. Associated tinea pedis, verified by fungal culture or potassium hydroxide mounts, occurred overall in 47% of our patients, with a significant skewing toward male patients (67% of boys, 25% of girls). This skewing may reflect exposure to dermatophyte infection through sports and locker rooms, and is consistent with the skewing toward male adult family members affected by onychomycosis in our study.

Because of its unusual occurrence, onychomycosis is underrecognized in children. In fact, onychomycosis may be difficult to distinguish clinically from noninfectious nail dystrophy as a feature of trauma, psoriasis, atopic dermatitis, and alopecia areata. In some cases the clinical characteristics on the nails and particularly elsewhere allow diagnosis, but in all cases potassium hydroxide mounts and/or fungal cultures are necessary to confirm diagnosis. Many patients have reported that they were told that nail fungus did not occur in children by their primary care physician, which delayed diagnosis and proper therapy. The fact that almost 60% of our patients were administered topical antifungal therapy before the itraconazole therapy suggests that primary care physicians are not familiar with the need for systemic therapy or are concerned about safety. Topical therapy tends to be ineffective for onychomycosis because of the inability of the topical agents to penetrate the nail plate deeply and reach therapeutic drug levels locally. Although the nail plate in children is thinner than in adults, response to topical agents is poor. In contrast, topical antifungal agents work well to clear and prevent tinea pedis, and may lower the relapse rate of children with onychomycosis who continue to be exposed to tinea pedis and onychomycosis.

In the past, oral griseofulvin therapy has been the treatment of choice for onychomycosis. In adults, its cure rate has been 20% to 60% and its relapse rate 40% to 70%, even with 9 to 12 months of continuing therapy.[16,17] Itraconazole, terbinafine, and fluconazole are newer oral antifungal agents that are highly lipophilic and keratinophilic, so that they accumulate in the stratum corneum.[1] Itraconazole accumulates in the stratum corneum for 3 to 4 weeks, and the concentration tends to increase with successive pulses.[18] Levels of itraconazole in the nail are detectable for up to 13 months after discontinuation of pulse therapy,[2] and are detectable at therapeutic levels for 6 to 9 months.[19] This persistence allows a shorter duration of therapy and pulse dosing for 1 week out of each 4 weeks. For pediatric patients, the shorter duration improves compliance.

In contrast to the persistence in nail, the plasma levels of drug decrease during 7 to 10 days.[19] The decreased overall concentration of drug lowers the risk of adverse effects. Both continuous and pulse itraconazole therapy have been found to be safe and well tolerated in children.[4-6,20,21] None of our patients experienced any adverse effects, although adults have complained of gastrointestinal disorders, fatigue, rash, pruritus, and headache. In double-blind trials, these complaints have not occurred at increased frequency compared with patients receiving placebo.[3] In a series of 82 children receiving continuous or pulse itraconazole for fungal infections (particularly tinea capitis), 3 children had an asymptomatic, reversible increase of liver function test results to less than twice normal levels; 1 of the 3 children had received pulse therapy.[22] At this time, routine laboratory testing is not recommended for patients receiving pulse itraconazole therapy.[18] It should also be noted, however, that itraconazole interacts with a variety of medications, which may result in increased plasma concentrations of the interacting medication (such as cyclosporin and methylprednisolone) or decreased itraconazole plasma concentration (such as when anticonvulsants or antimycobacterial agents are administered concurrently).

Gupta et al[4] first described the efficacy of itraconazole pulse therapy for prepubertal children with onychomycosis in 1997. All 4 treated patients had clinical and mycologic cures. Similarly, we found a clinical cure rate of 94% with pulse itraconazole therapy in our 17 children. In our trials, the duration of therapy varied from 3 to 5 months. It should be stressed that this report retrospectively reviews the courses of our patients, at least half of whom initiated therapy before guidelines of duration of therapy in adults were available. More recent reports in adults have not shown any advantage in increasing the duration of therapy for onychomycosis beyond 3 months,[3,18] suggesting that 3 months should be adequate therapy in children for toenail dermatophyte infection. Pulse therapy for 2 months has been advocated for fingernails. However, hallucal toenails grow more slowly than other nails and longer trials have been advocated. It is currently suggested that a fourth pulse of itraconazole be administered if clinically indicated at 6 to 12 months after initiation of therapy. In view of the partial response in our 1 treatment failure with hallucal nail involvement, it is possible that a longer course of treatment may have been curative. Alternatively, the untreated onychomycosis in this patient's father and grandfather may have led to reinfection.

In addition to the higher clinical cure rate of pulse itraconazole therapy, the relapse rate is much lower than with long-term griseofulvin therapy. In contrast to the 40% to 70% relapse rate of griseofulvin in adults,[16,17] the risk of relapse of toenail onychomycosis in adults within 1 year after starting therapy is 10.4% after 3 pulses of therapy and the relapse rate of fingernail onychomycosis is 4.9% after 2 pulses.[18] This relapse rate in adults with onychomycosis is similar to the 11% relapse rate of patients treated with terbinafine 18 to 21 months after cessation of therapy.[19] In a recent study by Gupta et al,[4] 1 of the 4 pediatric patients treated with pulse itraconazole experienced relapse. None of our 16 patients with clinical cure from itraconazole pulse therapy showed a relapse with a follow-up period of at least a year after initiation of treatment. Familial infection with onychomycosis seems to be the leading risk factor for the development of onychomycosis in prepubertal children, as was the case in almost 60% of our patients. This high rate of familial infection is consistent with other studies, in which parents were the source in 46% to 100%.[3,6,12] It is thus likely that our efforts to diagnose onychomycosis in family members and initiate concomitant therapy lowered the risk of recurrence from reinfection and relapse in our patients. Because we cannot identify and completely eradicate sources of infection in the immediate environment of the patients, however, a low rate of relapse through reinfection will be inevitable.

In this report, the very high clinical cure rate, clinical safety, and low risk of relapse at 1 to 2 years after pulse itraconazole therapy provide strong evidence that itraconazole pulse therapy is far preferable to long-term griseofulvin therapy in prepubertal patients. Recent

studies have also shown the high efficacy and low relapse rate of the allylamine antifungal agent, terbinafine, which has been described in continuous dosing for up to 12 weeks in 19 pediatric patients (up to age 17 years).[23,24] Terbinafine theoretically offers the advantage of fewer potential drug interactions, but a recent report noted that terbinafine affects CYP2D6, a cytochrome P450 that metabolizes more than 35 drugs.[25] Although a course of terbinafine is less expensive than that of itraconazole, the recommendation for continuous dosing for up to 12 weeks is more difficult for families. Although there has been even more limited experience with fluconazole, the triazole has been used effectively in a 16-year-old patient administered on alternate days[4] and in 11- and 17-year-old patients administered the currently recommended weekly pulsing regimen for several months.[26]

Onychomycosis should be considered in the evaluation of prepubertal patients with nail discoloration, thickening, or abnormal texture, and a fungal culture and/or potassium hydroxide mount performed. The current availability of highly effective oral antifungal drugs dictates that this dermatophyte infection be recognized in children and treated appropriately.

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