ABSTRACT Currently approved options for the treatment of onychomycosis include systemic therapy (the antifungal agents fluconazole, itraconazole, and terbinafine), topical agents (ciclopirox, which has been available since 1996, efinaconazole, currently pending approval), and laser systems. Phase III studies on another topical, tavaborole, have been completed and this medication also shows promise. Mechanical modalities are sometimes used but are seldom necessary. Recurrence of infection is common; the risk for recurrence may be reduced by adherence to preventive measures, especially avoiding (if possible) or promptly treating tinea pedis infections.

The goal of onychomycosis treatment is to eradicate the causative organism. Elimination of the fungus generally restores the appearance of the nail in most cases. However, patients should not expect to see normal-appearing nails until after the fungi are eliminated and until the damaged nail has grown out—a process that, for fingernails, may take 6 months or more from the time effective treatment is initiated and, for toenails, 12 to 18 months. Toenails grow at the rate of about 1 to 2 mm per month and fingernails grow faster, at the rate of 2 to 3 mm per month; however, nail growth rate peaks during the teenage years and decreases with advancing age. (1) Some onychomycosis infections, especially those involving the nail matrix, may produce permanent scarring of the matrix, and, thus, the nail may never appear normal even after the infection is completely eradicated (Figure 1). The definition of "complete cure," as defined by the US Food and Drug Administration (FDA) for the evaluation of clinical trial results, is negative results on potassium hydroxide (KOH) preparation and on fungal culture, as well as a completely normal appearance of the nail. In clinical practice—and for practical purposes—most cures will be defined by the absence of fungus on KOH preparation and possibly, but not always, by a completely normal nail (Figure 2). Realistically, patients who have had long-standing infections or chronic onychomycosis are likely to have sustained damage to the nail matrix or subungual area so that, despite the clearance of infectious organisms, new nail growth may be permanently discolored and/or dystrophic, and some onycholysis (lifting of the nail plate) may persist. Furthermore, nails may be thickened, discolored, and dystrophic for reasons other than mycotic infection—as is common, for example, in elderly patients who have age-related changes in the nails or onychogryphosis, or even in patients with inflammatory disorders such as psoriasis.

Systemic Therapy

Systemic antifungal therapy options currently include itraconazole, terbinafine, and fluconazole. A summary of systemic antifungal agents and cure rates can be found in Tables 1 and 2. A meta-analysis of studies involving these medications demonstrated low risk for side effects in immunocompetent patients. (2) Fluconazole is not approved by the FDA for this indication, although it is approved for fingernail and toenail onychomycosis in other countries. It was originally tested in dosages of 150 mg/week, 300 mg/week, and 450 mg/week for up to 9 months or until clearance of the nail. (3) In an FDA study, clinical cures were seen in 48% of patients who received 450 mg/week, 46% of those who received...
300 mg/week, and 37% of those who received 150 mg/week. However, probably a dosage of 200 mg or 400 mg once weekly is effective, and once-weekly dosing is convenient for patients on multiple medications and the elderly. Fluconazole can be taken with or without food; the drug must be avoided in pregnant women. Drug interactions are via CYP2C9.

[FIGURE 2 OMITTED]

Itraconazole can be used to treat fingernail or toenail onychomycosis. It may be given according to either of two dosing schedules, for a duration of 2 to 3 months for fingernail infections and 3 to 4 months for toenail infections. Regimen 1 is 400 mg/day for 7 days for 1 week out of each month for 4 months. Regimen 2 is 200 mg/day continuously for 3 months. Regimen 1 (pulsed dosage) is not approved for treating toenail onychomycosis. The cure rate for Regimen 2 (continuous dosage) per the package insert is 14%. Evans and colleagues (5) reported higher cure rates for pulsed (intermittent) dosing in the Lamisil vs Itraconazole in Onychomycosis (LION) study: 25% complete cure in three cycles; 28% complete cure in four cycles.

Itraconazole is a potent inhibitor of CYP3A4 and may result in serious cardiovascular events if used simultaneously with cisapride, pimozine, quinidine, or levomethadyl. It must be used with caution when treating onychomycosis in patients with congestive heart failure or other ventricular dysfunction. Ahmad and colleagues (6) reported that itraconazole has a negative inotropic effect on the heart in healthy individuals.

Terbinafine is used at a dosage of 250 mg/day for 6 weeks for fingernails and for 12 weeks for toenails. Drake and colleagues (8) reported a complete cure rate of 38% with 250 mg/day for 3 months and no significant difference in response between 12-week and 24-week treatment courses. In the LION study, Evans and colleagues (5) found that terbinafine produced a 49% complete cure with a 12-week course and a 54% complete cure with a 16-week course.

Pulsed-dose therapy with terbinafine is not FDA approved. Tosti and colleagues (9) noted that most studies show that continuous therapy of daily 250-mg dosing was more efficacious than 500 mg daily for 1 week followed by 3 weeks of no treatment.

Topical Therapy

Assuming reasonable efficacy could be assured, topical therapy would be the preferred methodology for onychomycosis to avoid systemic side effects and the need for laboratory monitoring. In addition, if adverse reactions occur from topical agents, the effect is site-specific and, as such, generally is more acceptable to patients. However, no topical treatment has been approved as monotherapy to date. A summary of topical antifungal agents and cure rates can be found in Tables 1 and 2.

The development of topical therapy for onychomycosis presents unique challenges. First, to be effective, the drug must penetrate through the nail plate and reach the nail bed in sufficient quantities. This requires overcoming the unique properties of the nail plate--its thickness and relatively compact structure. The factors involved probably include the proper molecular weight, lipophilicity, and keratin-binding properties.

Ciclopirox 8% lacquer, which was approved by the FDA in 1999, is associated with a complete cure rate ranging from 5.5% to 8.5% but requires frequent nail debridement.

In clinical studies, fewer than 12% of patients were able to achieve a clear or almost-clear nail. (10)

New and Investigational Topical Agents
A new topical agent, efinaconazole, currently pending approval by the FDA, will be the first topical triazole to become available for dermatologic use and the first new antifungal for onychomycosis to be introduced in more than a decade. Unlike ciclopirox, no debridement of nails is required.

Efinaconazole is a solution, not a lacquer, so, unlike ciclopirox, efinaconazole does not need to be removed each week. The solution is applied on, under, and around the nail. In the pivotal clinical trials, efinaconazole yielded a mycologic cure in the range of 50%. Complete cure was seen in 15% of patients in one study and 18% of patients in the second phase III study. Cure classified as "almost complete" exceeded 20%. (11)

Currently in the research pipeline is topical tavaborole 5% solution. In the first of two phase III clinical trials recently completed, the primary end point of complete cure (both mycologic cure and a completely clear nail) was seen in 6.5% of patients versus 0.5% of patients treated with vehicle alone (P=0.001). In addition, a negative fungal culture was reported after 52 weeks of treatment in 87% of patients on tavaborole versus 47.9% of those in the vehicle group (P<0.001); at the same time point, a negative nail culture and "completely clear" or "almost clear" nail was seen in 24.6% of patients in the tavaborole group versus 5.7% in the vehicle group (P<0.001). (12)

Over-the-Counter (OTC) Treatments

A mention of nonspecific topical OTC and "folk" remedies is appropriate here. Many such remedies have been used--usually self-prescribed by patients--as monotherapy or in the belief that these agents will enhance the efficacy of prescription medications. Currently popular are tea tree oil and a camphor-containing ointment marketed as a chest rub. Many other substances have been used, including foot soaks with hydrogen peroxide or household chlorine bleach and applications of salicylic acid, as well as OTC solutions, creams, and ointments.

Evidence-based studies have not been done demonstrating that these agents are helpful, but there is some theoretical scientific basis for anecdotal claims of efficacy by patients--and by some clinicians--when these remedies have been used diligently. Although they cannot be recommended on the basis of evidence of efficacy, most of these methods are neither harmful nor costly. Patients who choose to forgo prescription therapy for whatever reason should not be discouraged from trying these remedies for a time and told to reconsider definitive treatment if the infection does not clear or worsens.

Mechanical Modalities

Nail avulsion and matrixectomy are seldom needed. These techniques may be appropriate if only one nail is affected and the infection does not respond to other treatments, as well as in cases of infections with nondermatophyte mold organisms. However, most patients have involvement of more than one nail. Occasionally, patients develop thickened dystrophic nails that are painful or interfere with proper ambulation. Such circumstances also may constitute an indication for surgical intervention.

Lasers, photodynamic therapy (PDT), and other methods have been used with varying degrees of success in treating onychomycosis. The laser devices approved by the U.S. FDA to date are the short-pulse neodymium-doped yttrium aluminum garnet (Nd:Yag) type, although other types currently are being studied; these include carbon dioxide, near infrared diode, and femtosecond infrared laser systems.

The exact mechanism of action of laser systems in onychomycosis has not been established. One early proposed mechanism was the direct action of heat on the infecting organisms, (13) but recent in vitro studies show that laser-generated heat to a level required to kill Trichophyton rubrum is much higher than what would be tolerable; experiments with direct lasering of fungi have not
affected the growth of fungal organisms. Others have suggested that the use of lasers may enhance the efficacy of other modalities. (14,15) More likely mechanisms of action are the triggering of an immunologic effect or laser-induced denaturization of enzymes essential to fungal activity.

As the results of ongoing research provide additional insights regarding treatment regimens and patient selection along with longer-term evidence of efficacy, laser systems may become more widely used for treating onychomycosis.

The mechanism of action of PDT in dermatophytic onychomycosis has been established and involves eradication of the organism. (16-18) No PDT system has been approved by the FDA for the treatment of onychomycosis, and it is not a practical therapeutic option. However, PDT may be useful in chronic cases that are refractory to other modalities, particularly when the causative organism is uncommon, such as a nondermatophyte mold. (19)

Other devices and modalities continue to be developed and investigated, including the use of iontophoresis to enhance penetration of a topical medication through the nail plate. (20)

Preventing Recurrence

Reinfection with dermatophytic onychomycosis is common. (21,22) It is difficult to know whether subsequent infection is a new infection or whether the original infection was not cleared completely and recurred after weeks, months, or years of dormancy. In either case, patients must understand that it is unlikely that one course of treatment will be all that is required over the long term.

However, it is important to emphasize that the risk for reinfection can be reduced by avoiding practices that expose the nails to infectious organisms and that create a milieu that encourages fungal colonization. (See the patient handout in the article in this supplement by Pariser et al. (23))

Conclusion

Onychomycosis is a common problem that increases in prevalence with increasing age. Simple techniques are readily available for making an accurate diagnosis in all patients. The only prescription topical agent available has been ciclopirox 8% lacquer. A new topical agent, efinaconazole, currently pending approval by the PDA, provides better efficacy. Another topical agent, tavaborole, has shown good results in phase III studies to date. Systemic agents are highly effective for many patients but are contraindicated or otherwise inadvisable for some because of the potential for drug interactions or the presence of certain comorbidities.

Caption: Figure 1. Persistence of dystrophia after mycologic cure. In some cases, permanent scarring of the nail matrix may occur, so a normal appearance may not be restored even after the infection is eradicated. Photo courtesy of Phoebe Rich, MD.

Caption: Figure 2. Before and after successful systemic therapy. This patient presented with distal subungual onychomycosis. Note the distortion of the nail before treatment (left) and the resolution of onycholysis and discoloration after 4 months of systemic therapy (right). Photo courtesy of Phoebe Rich, MD.

References


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Richard K. Scher, MD, is an advisor/consultant to Valeant.
Table 1. Summary of Treatment Options for Onychomycosis

A. Topical Therapy

Fingernails and Toenails

Ciclopirox 8% Apply daily, up to 48 weeks (10)
Efinaconazole Phase III clinical trials studied daily application for 48 weeks (11)
Tavaborole Phase III clinical trial (data available on first of two recently completed) studied daily application for 52 weeks (12)

B. Systemic Therapy

Fingernails

Fluconazole (3) * 3 to 8 mg/kg pulsed-dose weekly for 6 weeks OR 200 mg/week for 8 to 16 weeks
Itraconazole (4) 400 mg/day for 1 week/month, repeated for 2 or 3 months ([dagger])
Terbinafine (7) 250 mg/day for 6 weeks

Toenails

Fluconazole (3) 200 mg/week for 12 to 24 weeks
Itraconazole (5) 400 mg/day for 1 week/month, repeated for 3 or 4 months ([double dagger])
Terbinafine (7) 250 mg/day for 12 weeks

* Although it is commonly used for onychomycosis, this is not an FDA-approved indication for fluconazole.

([dagger]) Note that the dosage recommended in the prescribing information for fingernails is 400 mg/day (two 200-mg capsules twice daily) for 1 week, followed by a 3-week period of no treatment, then a second treatment pulse of 400 mg/day/1 week.

([double dagger]) Note that the dosage recommended in the prescribing information for toenails, with or without fingernail involvement, is 200 mg (2 capsules) once daily for 12 consecutive weeks.

Table 2. Complete Cure Rates in Onychomycosis Reported in Clinical Studies *

http://go.galegroup.com.liboff.ohsu.edu/ps/retrieve.do?sort=RELEVANCE&docType=Arti...
### A. Topical Therapy

**Medication and Regimen (Once-daily Application)**  
**Complete Cure Rates**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Complete Cure Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciclopirox 8% (10)</td>
<td>5.5% to 8.5%</td>
</tr>
<tr>
<td>Efinaconazole (11)</td>
<td>15% and 18% ([dagger])</td>
</tr>
<tr>
<td>Tavaborole (12)</td>
<td>6.5% ([double dagger])</td>
</tr>
</tbody>
</table>

### B. Systemic Therapy

**Medication (Regimen)**  
**Complete Cure Rates**

| Medication   | Complete Cure Rates (
<table>
<thead>
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<tbody>
<tr>
<td>Fluconazole (3)</td>
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</tr>
<tr>
<td>150 mg/week</td>
<td>37%</td>
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<tr>
<td>300 mg/week</td>
<td>46%</td>
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<tr>
<td>450 mg/week</td>
<td>48%</td>
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<tr>
<td>Itraconazole</td>
<td></td>
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<tr>
<td>200 mg/day for 12 weeks (4)</td>
<td>14%</td>
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<tr>
<td>400 mg/day for 1 week/month (5)</td>
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</tr>
<tr>
<td>Repeated for 3 pulses</td>
<td>25%</td>
</tr>
<tr>
<td>Repeated for 4 pulses</td>
<td>28%</td>
</tr>
<tr>
<td>Terbinafine</td>
<td></td>
</tr>
<tr>
<td>250 mg/day for 12 weeks (8)</td>
<td>38%</td>
</tr>
<tr>
<td>250 mg/day for 1 week/months (5)</td>
<td></td>
</tr>
<tr>
<td>Repeated for 3 pulses</td>
<td>49%</td>
</tr>
<tr>
<td>Repeated for 4 pulses</td>
<td>54%</td>
</tr>
</tbody>
</table>

* The dosages shown above are not necessarily those approved by the US Food and Drug Administration.

([dagger]) Data from two phase III, double-blind studies.

([double dagger]) Data from the first of two phase III clinical trials recently completed.

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