Rediscovering Topical Antifungal Therapy for Onychomycosis

A number of potential topical therapies for onychomycosis have failed clinical investigation. Do we at last have a viable alternative to oral treatment options?

BY JOSEPH BIKOWSKI, MD

Toenail onychomycosis is a common diagnosis for dermatologists and its incidence continues to rise worldwide. Despite onychomycosis accounting for approximately half of all nail disorders and one third of cutaneous fungal infections, treatment options remain limited and it continues to be notoriously difficult to manage. In addition, treatment failures and relapses are common, exacerbating the problem. The lengthy period the nail takes to grow, the hardness of the nail plate, and location of the infection between the nail bed and plate are major contributing factors. Nail fungal infections are more than just a cosmetic problem. They cause physical discomfort and are associated with social and emotional consequences. As a result, comprehensive treatment of onychomycosis is critical not only for the prevention of secondary dermatomycoses and complications of existing health conditions, but also to improve quality of life.

Many patients would prefer a topical treatment for onychomycosis, but results so far have been disappointing. Poor nail penetration is the main factor limiting the use of topical antifungal agents in the treatment of onychomycosis, and directly relates to the nail plate’s unique properties: its thickness and relatively compact structure.

Oral treatment is generally recommended but may be limited in some patients by drug-drug interactions that are of particular note given the high incidence of onychomycosis in the elderly who are frequently on other concomitant medications, and other safety concerns, most notably hepatotoxicity.

FAMILIAR AGENTS
Toenail onychomycosis is recognized to be a difficult condition to treat, and most of the patients studied in clinical trials had long-standing and widespread disease as shown by the duration of disease and number of nails involved.

Oral antifungal agents are considered the most effective agents among the various treatment options currently available for the management of onychomycosis. They have been shown to be more effective than lacquer-based topical antifungal formulations. However, before starting therapy, always consider any concomitant medications and patient’s preferences, especially when treating those who have diabetes mellitus, liver disease, or are immunocompromised.

Currently, only itraconazole and terbinafine are indicated for the treatment of onychomycosis in the US. Mycologic cure (i.e., the eradication of the causative organism proven by negative culture) is the only consistently defined efficacy parameter in toenail onychomycosis trials, and it is widely accepted that mycologic cure is the main treatment goal, with complete clinical clearing occurring after this stage has been achieved. Reported mycologic cure rates in the pivotal phase III studies for oral itraconazole and terbinafine were 54 percent and 70 percent, respectively.

Relapse rates range from three to 20 percent for terbinafine, depending on follow-up, and from 21 to 27 percent for itraconazole. Relapse has been attributed to chronic or recurrent tinea pedis, genetic predisposition, and T rubrum infections. One study followed up patients treated with oral therapy and...
found that after five years, only 46 percent of patients treated with terbinafine remained disease free compared with just 13 percent of those treated with itraconazole.20

Efficacy must be balanced against the risk of side effects. In a meta-analysis, 3.4 percent of patients who received terbinafine, 2.6 percent who received pulsed itraconazole, and 4.2 percent who received continuous itraconazole discontinued therapy due to side effects.21 Common side effects of terbinafine include gastrointestinal upset, headache, and minor rashes. Serious side effects are reported in less than one percent of patients,22 but include serious or even fatal liver toxicity. Thus, systemic therapy is not recommended in patients with chronic or active liver disease, and liver-function testing is advisable. Monitoring liver function at four to six weeks is recommended by several experts.23 The side effects of itraconazole are similar to those of terbinafine but also include congestive heart failure, which represents a contraindication.

**TOPICAL OPTIONS**

Several studies investigated the usefulness of topical lacquers for the management of onychomycosis and demonstrated mycologic cure and clinical improvement.12,25,26 Compared to systemic therapy, results have been disappointing. Current topical treatment options are only advocated for the management of superficial white onychomycosis and in very early cases of distal subungual onychomycosis (DSO), where the infection is limited to the distal edge of the nail plate or in cases where patients are restricted from using oral antifungal medications.27

Ciclopirox 8% nail lacquer is the only topical treatment approved by the FDA for the treatment of onychomycosis in the US. Mycologic cure rates ranging from 29 to 36 percent have been reported.28,29 In these pivotal trials, nine percent of patients treated with ciclopirox nail lacquer and eight percent of patients receiving vehicle experienced adverse events considered by the investigator to be related to the study medication.29,30 These included mild rash localized to application site (periungual erythema and erythema of the proximal nail fold) and infrequent nail alterations.

**VEHICLES DRIVE NEW TOPICAL THERAPIES**

Newer antifungal topical agents have been formulated to deliver better penetration into the nail unit, increasing their therapeutic effectiveness. Yet, the development of effective topical antifungals for onychomycosis has been challenging. For example, a topical formulation of terbinafine demonstrated mycological and clinical efficacy in vitro and was superior to ciclopirox in a Phase II study.31 However, two Phase III studies failed to demonstrate efficacy in mild to moderate DSO.32

Hopefully, all this is about to change. Efinaconazole 10% solution is the first triazole antifungal specifically developed for the topical treatment of mild to moderate DSO. Efinaconazole inhibits ergosterol biosynthesis and has been shown to exhibit similar or more potent in vitro antifungal activity compared to existing antifungal agents.34,35 It is believed that low surface tension of the alcohol-based formulation helps efinaconazole to first penetrate through the nail plate, then access the nail bed by wicking into the air gap and spreading over the site of infection.36

In two large pivotal trials involving 1,655 patients, mycologic cure was 56 percent, and significantly greater than vehicle (Figure 1, P<.001). Clinical treatment success (0 percent to ≤10 percent area disease involvement of the affected toenail) was achieved in 43 percent of patients. Given that the majority of patients had ≥40 percent affected area involvement of the great toenail at baseline, this represents a meaningful improvement for the onychomycosis patients in the studies.

As expected for a topical agent, efinaconazole 10% solution was found to be safe, with mild, transient irritation at the site of application reported as the most common adverse event in two percent of patients.36

**INVOLVE THE PATIENT**

It is essential that clinicians take time to discuss therapy selection with patients. Choice of treatment depends on many factors including patient’s age and preference, etiologic agent, number of nails affected, degree of nail involvement, whether toenails or fingernails are infected, and whether other drugs are taken.

Patient education and involvement is paramount in preventing recurrence. In most onychomycoses, prolonged therapy is needed to achieve resolution. Indeed, continued improvement in cure rates within onychomycosis studies over time has been noted by earlier investigators, leading to longer-term studies.37 It was noted in the pivotal studies with efinaconazole that complete cure rates seen at completion of therapy (week 48)
continued to rise throughout the short four-week follow-up period.³⁹

Efinaconazole 10% solution provides the first viable alternative to oral therapy for onychomycosis. Mycologic cure rates are comparable to those seen with itraconazole. Managing patient expectations, especially with such a chronic, often long-suffering condition is important, and again the data from the pivotal studies with efinaconazole 10% solution provide important landmarks to encourage compliance. For example, almost 20 percent of patients were judged as clinical treatment successes as early as week 24. These data give us the confidence to anticipate that many of our onychomycosis patients will see clinically meaningful results at this time.³⁶

Of course, complete cure can never be promised because the potential for treatment failures exists with all antifungals. Despite successful elimination of fungus from the nails, patients undertaking treatments for toenail onychomycosis should be advised that successful eradication of fungus from the nail may not necessarily restore a toenail to a normal appearance, as it may have been damaged and dystrophic before the infection occurred.

Checking the foot for early signs of re-infection is key so that topical treatment can be instigated at an early stage. Although formally untested, the prophylactic use of topical antifungal agents such as efinaconazole 10% solution should be considered for those with recurrent fungal foot infection, particularly in those with diabetes, poor peripheral circulation, or a history of recurrent lower limb cellulitis.

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Joseph Bikowski, MD, FAAD is Clinical Assistant Professor of Dermatology, Ohio State University, Columbus, OH and Director of Bikowski Skin Care Center in Sewickley, PA.

References