THERAPEUTIC UPDATE


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Onychomycosis

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"Doc, is there anything I can do about these toenails?"

A question we hear very often, yet do not often have a great answer for. A painfully common and seemingly mundane condition, the management of onychomycosis can actually be quite difficult with frequent treatment failures and post treatment relapses. Onychomycosis affects 10% of all American adults and 48% of people aged 70 years.[1] Americans will spend approximately $1.26 billion annually on oral and topical prescriptions for onychomycosis, which speaks to the fact that patients are motivated to seek out remedies to improve the appearance of their nails.[2] Although often considered a cosmetic ailment, a recent survey of 1017 residents of Hong Kong dubbed the "Fungal Nail Perception Survey" found that those who suffer from onychomycosis are perceived as less likely to form good social relationships, more likely to be excluded from social activities, and less able to perform well in their chosen career than those not affected.[3] As physicians we are limited in our ability to treat onychomycosis by variable efficacy and poor penetration of topical agents, long courses of treatment, and of course the ever-looming threat of rare but life-threatening side effects of systemic agents.

General Treatment Guidelines

Onychomycosis is most commonly caused by *Trichophyton rubrum* but can also result from infection with other dermatophytes as well as yeast. There are four subtypes: distal subungual onychomycosis typically caused by *T. rubrum*; white superficial onychomycosis usually due to *T. mentagrophytes* (unless that patient is HIV positive in which case *T. rubrum* is more common); proximal subungual onychomycosis, which is usually due to *T. rubrum* and can be a sign of HIV infection; and candidal onychomycosis with results in severe destruction of the nail plate in patients who often also have mucocutaneous disease. There are two primary endpoints to consider when treating onychomycosis: mycologic cure and a clinically normal appearing nail. Patients should be followed for 6 months after discontinuation of treatment to adequately assess for clinical cure. Prior to initiating treatment, appropriate cultures or diagnostic studies should be obtained to distinguish true fungal infection from other causes of nail dystrophy such as trauma.

Topical Therapy

For patients with mild disease and for those who are not candidates for systemic therapies, topical treatment still plays a role in the management of onychomycosis. Treatment success with topical agents, however, is generally considered to be less than 10%.[4] One of the most commonly utilized topical treatments is ciclopirox (Loprox, Penlac), which is manufactured as a cream, gel, suspension, solution, or nail lacquer and is indicated for *Trichophyton rubrum* onychomycosis without lunula involvement. Ciclopirox has a high affinity for trivalent metal cations and thus exerts its antimicrobial activity by inhibiting metal-dependent enzymes that are responsible for the degradation of peroxides within the fungal cell.[5] When applied daily for 6 to 12 months with concomitant nail debridement, the complete cure rate at 48 weeks is only 6-9%.[6] Chemical avulsion of the nail plate with urea under occlusion may improve efficacy slightly.

Efinaconazole 10% solution (Jublia, Valeant, Montreal, Canada) is a new triazole antifungal that recently completed Phase III clinical trials. A pooled analysis of two Phase III clinical trials that included 1436 subjects showed eficonazole to be superior to the placebo in attaining both mycologic cure (negative KOH and fungal culture) and complete cure (0% clinical involvement and mycologic cure).[7] Specifically, the complete cure rate in the eficonazole group was 18.5% compared to 4.7% in the placebo at 48 weeks ($P<0.001$).[7] Notably, approximately 20% of subjects began to achieve <10% nail involvement by week 24.[7] In contrast to the studies of ciclopirox, efficacy was not contingent upon daily nail debridement. Authors concluded that eficonazole may become the preferred first line agent for topical therapy. It may also be a useful adjunct to existing therapies either as dual therapy or to prevent recurrence after treatment with systemic therapy.

Oral Therapy

The two main options for oral therapy are terbinafine (Lamisil) and itraconazole (Sporonox, Omnel). Terbinafine is taken daily for 12 weeks in the treatment of onychomycosis. Although effective, the use of terbinafine is limited by concerns regarding rare yet potentially severe side effects. The overall adverse event rate for terbinafine is about 10%, with gastrointestinal (GI) upset and nausea being most common. "Very rare" events which occur in <0.01% of patients include liver failure resulting in transplant or death, severe neutropenia, cutaneous and systemic lupus, prolonged taste loss, and toxic epidermal necrolysis (TEN). Temporary loss or disturbance in taste is considered "uncommon" occurring in 0.1 to 1% of patients.[8] These side effects should be discussed with the patient, and the diagnosis must be confirmed with fungal culture prior to initiating treatment. Baseline laboratory testing including complete blood count and liver function tests should be performed with most practitioners repeating the liver function tests monthly during treatment.

Itraconazole is an alternative to terbinafine that is sometimes more cost effective yet not without its own limitations. It is a fungistatic, triazole antifungal that blocks ergosterol synthesis by inhibiting 14α-demethylase. Itraconazole carries a black box warning for both congestive heart failure and drug interactions. It is a potent inhibitor of the cytochrome P3A4 enzyme and thus can lead to dangerously high levels of many medications when administered together. It is strictly contraindicated for co-administration with at least 25 medications including statins. Other adverse effects include elevated liver functions tests, decreased white blood cell count, elevated triglycerides, and nephrotoxicity. For young healthy patients, however, who are not on many other medications it remains a viable alternative. Omnel (Merz Aesthetics, Greensboro, NC) is a relatively new formulation of itraconazole that utilizes a proprietary melt-extrusion or Meltrex technology designed to improve bioavailability and allow for steady and consistent GI absorption. It is administered 200mg a day for 12 weeks in the treatment of onychomycosis. Itraconazole can also be administered in a pulsed fashion, most commonly 200mg twice daily for 7 days, off for 21 days, repeated for 2 or 3 months. It is important to note, however, that the pulsed regimen is not FDA approved.

Laser Treatment

The use of lasers in the treatment onychomycosis has gained popularity as an answer to the need for a treatment with better efficacy than topicals but without the potential side effects of oral therapy. One such laser is the Pinpointe® Foot Laser (Cynosure, Westford, MA), which is a patented 0.65ms 1064 Nd:YAG marketed for the treatment of onychomycosis. It is a fiber optic device that directs a matrix of 1mm spots that covers the nail plate and surrounding 2mm of epidermis. In a small study of 8 patients, 7 of 8 obtained a negative culture after 2 to 3 sessions.[9] Another study of the 1064 Nd:YAG (6mm spot size, 5 J/cm^2 fluence, 0.3 ms pulse duration) yielded less impressive results with only 9.3% of the nails treated achieving a complete cure.[10]

Fractional CO2 combined with topical therapy has also been utilized with a reasonable degree of success. A study of 24 subjects treated with fractional CO2 laser three times at 4 week intervals in conjunction with topical amorolfine showed a 50% complete response rate with negative microscopic result.[11] The protocol consisted of 30 minutes of topical anesthesia on periungual skin followed by 2-3 passes at 160mJ with a density of 150 spots/cm^2 using static operating mode over the affected nail and surrounding 1mm of normal nail or skin. Topical therapy was initiated immediately post treatment.[11] As of yet, there is no data available regarding recurrence rates after laser therapy.

Photodynamic therapy (PDT) has also been utilized in the treatment of onychomycosis as it has been shown that *T. rubrum* can metabolize aminolevulinic acid (ALA) to protoporphyrin IX with a subsequent growth reduction of 50% after ALA PDT.[12] A study published in the *Archives of Dermatology* described the successful treatment of onychomycosis using 5-ALA and the excimer laser.[13] In this case report of 2 patients, the application of 20% urea under occlusion was followed by 20% 5-ALA under foil for 5 hours. Affected nails were then treated with horizontal and vertical passes of the 630nmexcimer laser. A total of 6 to 7 treatments were required to obtain a cure.

Conclusion

Currently available treatments for onychomycosis remain suboptimal for various reasons. The most reliable treatment in terms of obtaining a cure remains oral therapy with either terbinafine or itraconazole. Many patients, however, are unwilling to accept even a small risk of a severe of life-threatening side effect for the sake of their toenails. Laser therapy is likely safer than oral therapy but data on efficacy, particularly long term efficacy, remains limited. The future of onychomycosis treatment may depend on improved drug delivery of existing topical agents.

Disclosure

The author has not disclosed any relevant conflicts.

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