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Beta Blockers
An Innovation in the Treatment of Infantile Hemangiomas

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IN THIS ISSUE

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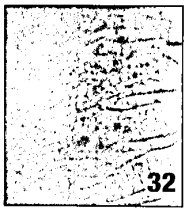

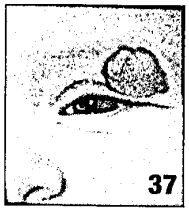

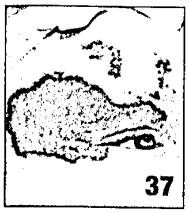

[LITERATURE REVIEW]

The Role of Topical Antifungal Therapy for Onychomycosis and the Emergence of Newer Agents

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ABSTRACT

Onychomycosis is a common infection of the nail unit that is usually caused by a dermatophyte (tinea unguium) and most frequently affects toenails in adults. In most cases, onychomycosis is associated with limited treatment options that are effective in achieving complete clearance in many cases. In addition, recurrence rates are high in the subset of treated patients who have been effectively cleared, usually with an oral antifungal agent. There has been a conspicuous absence of medical therapies approved in the United States since the introduction of topical ciclopirox (8% nail lacquer), with no new effective agents introduced for more than 10 years. Fortunately, newer agents and formulations have been under formal development. While patients might prefer a topical therapy, efficacy with ciclopirox 8% nail lacquer, the only available agent until the very recent approval of efinaconazole 10% solution, has been disappointing. The poor therapeutic outcomes achieved with ciclopirox 8% nail lacquer were not unexpected as the cure rates achieved in the clinical trials were unimpressive, despite concomitant nail debridement, which was an integral part of the pivotal trials with ciclopirox 8% nail lacquer. Efinaconazole 10% solution and tavaborole 5% solution are new topical antifungals specifically developed for the treatment of dermatophyte onychomycosis. In Phase 3 clinical trials, both newer agents were applied once daily for 48 weeks without concomitant nail debridement. Mycologic cure rates with efinaconazole 10% solution are markedly superior to what was achieved with ciclopirox 8% nail lacquer. To add, they appear to be nearly comparable to those achieved with oral itraconazole in pivotal clinical trials. However, it is important to remember that direct comparisons between different studies are not conclusive, are not generally considered to be scientifically sound, and may not be entirely accurate due to differences in study design and other factors. Well-designed and properly powered head-to-head studies are needed in order to draw definitive conclusions about efficacy comparisons between therapies, at least based on academic and regulatory standards. Although tavaborole 5% solution is in an earlier phase of development for onychomycosis, treatment success rates reported thus far for both efinaconazole 10% solution and tavaborole 5% solution are superior to ciclopirox 8% nail lacquer. As a result, a new era of onychomycosis appears to be upon us that incorporates topical therapy more effectively than in the past. Not only may these newer topical agents provide viable monotherapy alternatives to oral therapy for onychomycosis, topical therapy for onychomycosis that is effective, well tolerated, and easy to use may also find a role in combination therapy, and/or as continued therapy after initial clearance to reduce recurrence or re-infection. (*J Clin Aesthet Dermatol.* 2014;7(7):10–18.)

Onychomycosis is the most common fungal infection of the nail bed, matrix, and/or plate, representing up to 50 percent of all nail disorders seen in dermatology practice.[1] Overall prevalence, noted to be approximately 14 percent, appears to be increasing, with onychomycosis reported to affect half the population by the time they reach 70 years of age.[2-5] Left untreated, it can lead to progressive destruction and deformity of the toenails and fingernails.[1,6] Onychomycosis, especially cases caused by dermatophytes, may serve as a nidus for more widespread cutaneous involvement, spreading to other digits, body areas, and even to other predisposed family members.[7] It can be very distressing for many patients psychosocially and/or physically.[5,8-10]

Causes of onychomycosis. The vast majority of cases of onychomycosis are caused by dermatophyte fungi. In 80 to 98 percent of affected individuals, *Trichophyton rubrum* or *Trichophyton mentagrophytes* are identified as the causative pathogen.[11-14] Adults are most commonly affected with toenails being affected much more commonly than

NOTE: Tavaborole 5% topical solution was approved by the FDA for treatment of dermatophyte onychomycosis on July 7, 2014.

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fingernails.[1,3-5,11-14] Fingernail onychomycosis is frequently concomitant with toenail onychomycosis, especially when a dermatophyte is causative, and most of these patients exhibit concurrent unilateral or bilateral dry plantar (moccasin) tinea pedis and sometimes also tinea manus. Both fingernail and toenail onychomycosis can occasionally be caused by nondermatophyte fungi, such as *Scopulariopsis brevicaulis, Aspergillus spp, Fusarium spp,* and sometimes *Candida spp* (i.e., *C. albicans*), with the latter noted to be rare in toenails.[15] Increasing prevalence of nondermatophyte onychomycosis has been observed in some reports, either due to improved diagnostic techniques and/or increased awareness; however, differentiation of a laboratory contaminant from a true nail pathogen may at times be overlooked and/or problematic.[16,17] In addition, mixed infections have been reported, although their significance is less clear.[18] Identification of the fungal pathogen by culture is highly dependent on the method used to obtain the specimen, the anatomic location within the nail unit that the specimen is obtained from, and the medium used.

Patterns of nail invasion/clinical presentations of onychomycosis. Toenail onychomycosis frequently involves several nails, and as noted above, dry plantar tinea pedis is almost always present concurrently.[11,19,20] Indeed, tinea pedis is believed to be the predominant source of dermatophyte onychomycosis. This occurs in most cases as *Trichophyton spp* (usually *T. rubrum*) migrates from distal pedal skin into nail bed by violating the hyponychium. As a result, distal lateral subungual onychomycosis (DLSO) is by far the most common form of the disease.[1,3,5,11-14] Here the causative fungus, usually *T. rubrum*, invades the nail bed at the distal and lateral edges, leading to distal onycholysis, subungual hyperkeratosis, and both nail bed and nail plate thickening.[21] This subungual process of nail invasion by the fungal pathogen is the most common, with direct nail plate (endonychial) invasion much less common, especially with dermatophyte fungi.[3,5,11,15] In DLSO, the undersurface of the nail plate is often affected by fungal penetration as it is directly contiguous with the invaded nail bed. Onychomycosis involving the surface of the nail plate (superficial onychomycosis) is also usually caused by *Trichophyton spp*, is much less common, and sits on the surface of the plate as a powdery film that can be scraped away from that surface with a surgical blade or lightly with a curet. Superficial dermatophyte onychomycosis is amenable to topical therapy as the fungal pathogen is easily accessible to the applied antifungal agent.[3,5,11,15] Proximal subungual onychomycosis is also less common than DLSO and occurs when the dermatophyte organism (usually *Trichophyton spp*) migrates from pedal skin under the proximal nail fold and cuticle and extends under the nail plate and into the nail bed.[3,5,11,15]

Challenges in treating onychomycosis. Successful treatment of onychomycosis is fraught with difficulty due to several factors, especially with toenail involvement. These include slow growth; the physical presence of the nail plate interfering with nail bed access after application of a topical antifungal agent; difficulty in finding compounds with the pharmacologic/pharmacokinetic profile to allow adequate nail unit penetration; challenges in achieving therapeutic substantivity of drug levels after topical or oral administration; development of optimal vehicles for topical use that allow delivery of effective drug levels to the site(s) of nail infection (primarily nail bed); the anatomic nature of the nail unit and its vascular access, which allows for higher drug levels in nail bed/plate centrally as compared to laterally after oral antifungal administration; the high incidence of recurrence after clearance with therapy; widespread environmental exposure to dermatophytes and other fungal organisms; and the genetic predisposition of many individuals to pedal colonization and infection with *T. rubrum*, which eventually leads to invasion of the nail unit with reinfection with onychomycosis (tinea unguium).[1,3,5,7,12,16,19,21-23] Toenails may take up to 78 weeks to grow out completely, depending on the age and general health of the patient.[22,23] In addition, certain clinical presentations of onychomycosis are more difficult to clear and often represent cases that are not included in many clinical studies, including some pivotal trials. These include marked nail plate thickening, extensive onycholysis, completely affected nail plate with marked involvement of the nail matrix, dermatophytomas, band-like lateral involvement, extensive subungual debris/thickening, lack of nail growth of chronically traumatized toenails (i.e., 5th, 2nd if longest toe), and immunocompromised patients. Such cases often involve physical debridement combined with medical therapy, and may warrant repeated courses of treatment and/or more prolonged therapy than what is stated in product labeling.[1,3,5,24-28]

Poor nail unit penetration limits the use of current topical antifungal agents in the treatment of onychomycosis and directly relates to the unique physical and kinetic properties of the nail unit, its thickness, and relatively compact structure.[24-26] Due to the high potential for persistence of some organisms within the nail unit even after visible clearance and/or dermatophyte presence on pedal skin, relapse and re-infection of onychomycosis are common and can occur in at least 20 to 25 percent of patients.[1,3,5,19,20,22,23,27]

Oral treatment considerations. Current treatment of dermatophyte onychomycosis includes both oral and topical antifungal agents, adjunctive physical modalities (chemical debridement, mechanical debridement, nail avulsion), and approaches to minimize the risk of recurrence or re-infection (i.e., topical therapy to suppress pedal colonization or infection [tinea pedis]).[28] Oral antifungal therapy, such as with agents approved by the United States (US) Food and Drug Administration (FDA) for dermatophyte onychomycosis (i.e., terbinafine, itraconazole), is preferred because of their ability to penetrate the nail bed and nail plate and sustain therapeutic levels that correlate with markedly superior efficacy as compared to oral griseofulvin. This latter oral agent was the first to become FDA-approved for dermatophyte infections, including onychomycosis, despite a very low cure rate for tinea unguium even with several months of daily therapy (especially toenails).[1,3,5] Nevertheless, oral antifungal monotherapy for toenail dermatophyte onychomycosis is still

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