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Recent progress on the topical therapy of onychomycosis

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Onychomycosis is a fungal infection of the fingernails and toenails that results in thickening, discoloration, splitting of the nails and lifting of the nail from the nail bed. The disease is caused by dermatophytes and has a high incidence within the general population, especially among older individuals. Present treatment options include both oral and topical drugs, with oral therapies giving better outcomes; however, neither of these treatment options provides high cure rates that are durable. The difficulty in treating onychomycosis results from the deep-seated nature of the infection within the nail unit (nail plate, nail bed and surrounding tissue) and the inability of drugs to effectively reach all sites. Ongoing drug development activities have focused on novel delivery technologies to facilitate penetration of existing antifungal drugs through the nail plate and on the discovery of inherently penetrable antifungals. AN-2690 represents an oxaborole antifungal that is designed to penetrate the nail plate and is showing promising results in clinical trials.

Keywords: antifungal agent, dermatophyte, fungal infection, leucyl-tRNA synthetase, nail penetration, onychomycosis, oxaborole, tinea unguium

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1. Introduction

Onychomycosisis is a progressive fungal infection of the nail unit that leads to the destruction and deformity of toenails and (less frequently) fingernails. This condition is common and represents ~ 50% of all nail disorders. Onychomycosis has a high occurrence throughout the world, with recent epidemiological data indicating a prevalence of 6.5 – 13.8% in North America [1]. The infection shows an increasing incidence in older individuals and 1 study reported that 48% of people aged 70 years are infected with onychomycosis [2]. The susceptibility to onychomycosis is higher in men than in women, although women seek medical treatment more frequently.

The infection is caused by fungi that infect the nail unit (the nail bed, the nail plate and surrounding tissue) and these include yeasts, dermatophytes and other molds. By far the most common fungi that cause onychomycosis are the dermatophytes, which account for ~ 90% of all cases. Dermatophytes are also the cause of skin fungal infections [3] and many patients with a nail infection also have a co-existing skin infection. The *Trichophyton* spp., *Microsporum* spp. and *Epidermophyton* spp. are the main causative dermatophytes, with *Trichophyton rubrum* and *T. mentagraphytes* representing the two most common isolates [3-5].

2. Description of onychomycosis

Tinea unguium is the medical term that is used to describe a nail infection caused by a dermatophyte, whereas onychomycosis is used more broadly to characterize all fungal nail infections. Distal subungual onychomycosis represents the most

common presentation of tinea unguium [6]. Distal subungual onychomycosis starts by the microorganism (usually a dermatophyte) invading the stratum corneum of the hyponychium and distal nail bed. Subsequently, the infection moves proximally in the nail bed and invades the ventral nail surface of the nail plate. The infection is characterized by discoloration, separation of the nail plate from the nail bed (onycholysis), accumulation of subungual debris and nail plate dystrophy. Proximal subungual onychomycosis is the least common variant of onychomycosis. This condition starts by fungal invasion of the stratum corneum of the proximal nail fold and subsequently of the nail plate. White superficial onychomycosis occurs when the nail plate is invaded directly by the causative organism and is characterized by the presence of white, chalky patches on the nail plate. The patches may coalesce to cover the whole nail plate. The potential end point of all forms of onychomycosis is total dystrophic onychomycosis and occurs when the entire nail plate and nail bed are invaded by the fungus.

Although onychomycosis is generally not life threatening, the disease adversely affects the quality of life of its victims. In those cases in which the nail unit is seriously compromised, patients can experience pain and discomfort at the site of infection. Because of the high incidence of onychomycosis and the inadequacy of present treatment modalities, considerable research efforts have been directed to finding improved therapeutic options. This review summarizes the recent developments for new treatments of onychomycosis.

3. Challenges to the therapy of onychomycosis

Onychomycosis has proven to be a challenging infection to treat, with treatment failures and relapses being common occurrences [7-9]. In a study reported in 1998, it was found that 22.2% of patients whose toenail onychomycosis had been cured by oral therapy experienced a relapse during a 3-year follow-up period [10]. For an antifungal drug to be effective, it must disseminate throughout the nail unit and kill the pathogen. When a sample taken from the nail bed of an infected patient shows a negative culture and negative microscopy, this is termed a mycological cure; however, a clinical cure includes not only elimination of the fungi from the nail unit but also the formation of clear, new nail growth that is absent of dystrophic characteristics. Because of the slow rate of growth of toenails (~ 1 mm/month), evidence of a clinical cure can take 9 – 12 months. For this reason, drug treatment periods for onychomycosis are lengthy and require 3 – 12 months. During this treatment period, the infected nails can be monitored for growth of new clear nail and for the presence of viable dermatophytes.

The current treatment modalities for onychomycosis include mechanical procedures, systemically administered antifungals and topical drug therapy. Although infected nails can be surgically removed, recurrence of the onychomycosis can occur as the new nail grows back and there is no evidence that the surgical approach is effective in producing a sustained disease-free period. In addition, because surgical avulsion is quite traumatic, this procedure is rarely used today. An alternative procedure of chemically removing the nail using a urea ointment is also not widely used by current practitioners. In preference, podiatrists perform periodic trimming and debridement of affected nails as a means of reducing symptoms, with the added hope of minimizing progression by stabilizing the disease.

Whereas mechanical procedures to treat onychomycosis only offer marginal benefit to the patient, drug therapies have provided some advancement in the attempt to effectively treat this disease; however, the overall success in treating onychomycosis is still far from optimal (as mentioned in Section 3) and this almost certainly results from the unique anatomical features of the nail unit and its pervasive colonization by dermatophytes during infection. The varied anatomy of the nail unit provides an opportunity for the fungal pathogen to establish a deep-seated infection by invading and proliferating into the nail plate, the nail bed and the surrounding tissue. Systemically administered drugs must not only reach the nail bed but must also achieve sufficient concentration in the nail plate to eliminate dermatophytes at this location. It is more likely that systemically administered drugs reach the nail plate via the nail matrix, which is a continually proliferating epidermal tissue that serves as the origin of new nail growth. Access to the nail plate from the newly formed cells in the matrix is a slow process due to the very slow growth rate of toenails. As a consequence of this slow growth rate, oral therapy must be continued for some time and this may have the inherent disadvantage of causing systemic adverse effects.

On the other hand, topically administered drugs face even more challenges to reach all of the required sites of these deep-seated infections. This difficulty in achieving relevant fungicidal concentrations throughout the nail unit directly relates to the nail plate's unique properties, its thickness and relatively compact structure. The nail plate is a hard yet slightly elastic convex structure that consists of ~ 25 layers of dead, keratinized, flattened cells that are tightly bound together. The nail plate itself consists of three layers: the dorsal and intermediate layers derived from the matrix, and the ventral layer derived from the nail bed [11]. The upper (dorsal) layer is a few cell layers thick and consists of hard keratin. It constitutes the main barrier to drug diffusion into and through the nail plate. The intermediate layer constitutes 75% of the whole nail thickness and consists of soft keratin. Below the intermediate layer is the ventral layer of soft keratin, a layer that is a few cells thick, that connects to the underlying nail bed in which many pathological changes can occur. Thus achieving an effective drug concentration in the ventral nail plate and the nail bed is of great importance in the treatment of nail diseases.

Chemically, the nail plate mainly consists of fibrous proteins – keratins – which are highly cross-linked with disulfide bonds. Coupled with the highly compact structure

of the keratinized cells in the nail plate, these highly cross-linked proteins within the cells present a formidable barrier to the entry of topically applied agents [12]. In 1 study, the concentration of an applied drug across the nail dropped ~ 1000 times from the outer surface to the inner surface [13]. As a result, the drug concentration had presumably not reached a therapeutically effective level in the inner ventral layer.

Another factor contributing to the difficulty of topically applied antifungal drugs to penetrate the nail plate is the apparent mismatch of drug physicochemical properties with the biophysical properties of the nail plate [14]. Most existing antifungal drugs were originally designed for oral and/or skin applications and are consequently fairly lipophilic molecules, only sparingly soluble in water and have molecular weights of ≥ 300 Da. On the other hand, with its dense keratin fabric network and a high capacity for flux of water, the nail plate has been described as a hydrophilic gel [15-17]. Thus most of the known antifungal agents will not find a compatible environment in traversing the nail plate.

4. Drugs currently approved for onychomycosis in the main markets

4.1 Oral agents

Systemic drug treatment is currently the most effective method of treating onychomycosis. Even so, 20 – 25% of the patients fail to respond [18] and recurrence of disease after successful treatment is common. Terbinafine and itraconazole (**Figure 1**) are the two systemic treatments of choice, with terbinafine showing greater efficacy and lower rates of recurrence than itraconazole [19].

Terbinafine, a member of the allylamine family of antifungals, has a broad spectrum of activity and exerts fungicidal activity against most fungal pathogens. This compound also inhibits squalene epoxidase, an important enzyme in the biosynthesis of the essential membrane component ergosterol [20]. Terbinafine is active against dermatophytes, *Malassezia furfur*, *Aspergillus* spp. and some *Candida* spp. (including *Candida parapsilosis*). A single dose of terbinafine 250 mg p.o. administered to humans produces peak plasma concentrations of 1 µg/ml within 2 h. It is > 99% protein bound and has a half-life of ~ 36 h. It is administered at a dose of 250 mg q.d. with treatment duration of 6 and 12 weeks for fungal infection of the fingernail and toenail, respectively. Using this regimen, 38.2% of toenails showed a clinical cure when examined at 48 weeks [21]. Therapeutic levels of drug persist in the nail for 3 – 6 months after therapy is discontinued. Liver toxicity has been reported for terbinafine and hepatic function tests are recommended for patients who use terbinafine continuously for > 6 weeks. Terbinafine is metabolized by CYP enzymes and has been noted to have a number of drug interactions [22].

Itraconazole, which is from the azole class of antifungal agents, inhibits lanosterol 14α-demethylase and thus stops the biosynthesis of ergosterol. It has a broad spectrum of activity against species including dermatophytes, *Candida* spp., *Aspergillus* spp. and *M. furfur* [23]. Blood levels of itraconazole after a single dose of 200 mg administered to humans reached a peak level of 0.2 – 0.3 µg/ml after 4 – 5 h. It is 99.8% protein bound and has a half-life of 21 h. It is administered as either 200 mg q.d. for 12 weeks or 200 mg b.i.d. for 7 days, followed by 3 weeks with no treatment and repeated for 3 months [22]. Therapeutic levels of itraconazole persist in the nail for 3 – 6 weeks after therapy is discontinued. Itraconazole has also been associated with liver damage and liver function tests are required if continuous treatment exceeds 1 month. This agent specifically inhibits the CYP3A4 isoenzyme system and may consequently increase plasma concentrations of drugs metabolized by this pathway [22].

Griseofulvin (**Figure 1**) is a natural product that was isolated from *Penicillium griseofulvin* in 1939 [24] and has been used for treating dermatophytosis since its introduction in 1958. Griseofulvin acts by binding to microtubular proteins, which results in the inhibition of cell mitosis and the formation of multinucleated fungal cells [25]. The drug is administered orally and is effective against a wide variety of dermatophytes. Griseofulvin has been used in complicated, difficult to treat tinea capitis and onychomycosis.

Fluconazole is an orally active, synthetic, bis-triazole antifungal agent with activity against a wide range of fungi, including most *Candida* spp. and (as with other azoles) inhibits lanosterol 14α-demethylase. Although fluconazole is not approved in the US or Europe for the treatment of onychomycosis, it is used off-label for this indication. A number of clinical trials studying the kinetics and efficacy of fluconazole have been reported [22].

4.2 Topical agents

Treatment of onychomycosis by topical methods has been met with limited success for the reasons described in Section 3. The two main topical treatments that are used today are ciclopirox and amorolfine (**Figure 2**), both of which are formulated in lacquers that are painted onto the infected nails. The lacquer dries to leave a water-insoluble film on top of the infected nail, which subsequently acts like a drug depot releasing the drug into the nail plate. Ciclopirox is a synthetic compound and is a member of the hydroxypyridone family of antifungal agents. The hydroxypyridone antifungals are active against many pathogenic fungi such as dermatophytes, *M. furfur* and *Candida* spp. Ciclopirox is believed to work by inhibiting metal-dependant enzymes by chelating the polyvalent cations (Fe^{3+} or Al^{3+}) [26,27]. Ciclopirox has antifungal, antibacterial and anti-inflammatory activities. It is administered to the infected nails daily and this treatment regimen continues for ≥ 6 months. Ciclopirox persists in the nail for 14 days after therapy is completed. Clinical response rates for the treatment of onychomycosis are in the range of 7 – 10%.

Amorolfine belongs to the morpholine group of synthetic antifungal agents. Its mechanism of action involves the

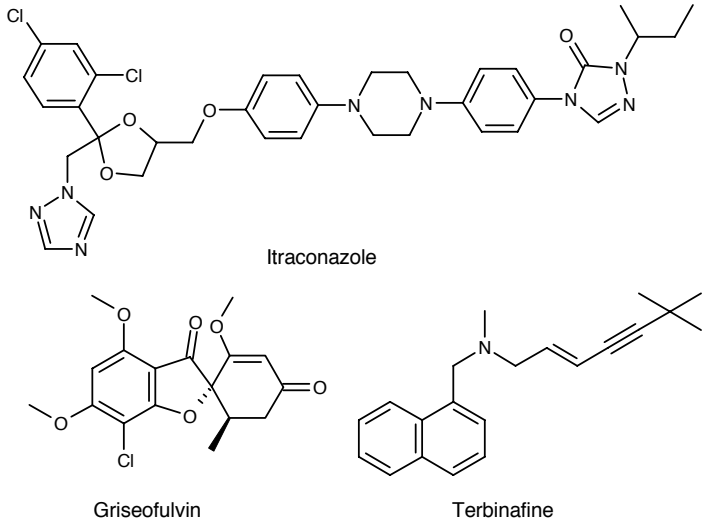

Figure 1. Chemical structures of itraconazole, griseofulvin and terbinafine.

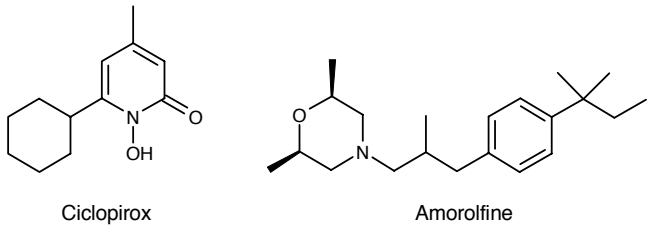

Figure 2. Chemical structures of ciclopirox and amorolfine.

inhibition of two important steps in the ergosterol pathway [28]. Amorolfine is fungicidal against *C. albicans* and *T. mentagrophytes.* It is administered once or twice weekly to the infected nails for 6 – 12 months and (as with ciclopirox) persists in the nail for 14 days after therapy is completed.

5. New antifungal compounds in development for onychomycosis

Due to the treatment limitations described in Section 3 for onychomycosis, it is not surprising that significant R&D efforts have focused on the discovery of improved therapies. In general, these efforts have emphasized eliminating the deficiencies of currently approved drugs, which include long treatment times, concurrent side effects of oral drugs and poor efficacy of topical agents. The new treatment modalities that are presently in clinical development for onychomycosis are listed in **Table 1**.

As noted from the entries in **Table 1**, most of the approaches represent re-formulations of known antifungal compounds with penetration enhancers in an effort to increase penetration of the active agent into and through the nail plate. The only systemic drug in development is itraconazole (Hyphanox™), which is being developed by Barrier Therapeutics as a once-daily oral formulation. With respect to topical treatments for onychomycosis, the use of novel delivery vehicles and permeation enhancers applied to existing classes of antifungals (e.g., azoles or allyl amines) represents the main R&D approach that has been pursued over the past 10 years. Very little work has been reported on approaches focusing on discovering antifungal compounds that have intrinsic nail-penetrating properties. S-291-ND is one such compound and involves the use of a topical NO-generating formulation that can be applied directly to the toenail. NO is a highly reactive molecule that has antimicrobial activity [29] and may also have intrinsic nail-penetrating capabilities due to is low molecular weight. The other novel approach is represented by the boron-containing antifungal compound, AN-2690. Now in clinical trials, this agent was specifically designed to overcome the nail barrier when applied topically so that it can achieve high concentrations in the nail bed [30].

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