Progress on New Therapeuties for Fungal Nail Infections

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1. INTRODUCTION

Onychomycosis is a fungal infection of the toe and finger nails, with the majority of cases involving infection of the toe nails [1]. The disease is mostly caused by a class of fungi known as the dermatophytes, which are also responsible for skin fungal infections. Dermatophytes flourish on dead keratinized tissue and normally infect the stratum corneum layer of skin, scalp hair and nails [2]. Non-dermatophyte species including yeasts and molds can also be involved. The dermatophytes account for around 90% of all cases of onychomycosis [1,3] and include *Trichophyton*, *Microsporum* and *Epidermophyton* species. However, *Trichophyton rubrum* and *Trichophyton mentagrophytes* are by far the major causative agents accounting for 60–70% of the cases [1,3,4]. The fungi can infect the nail plate, nail bed and surrounding skin folds (proximal fold at the cuticle and lateral folds on either side of the nail plate). Onychomycosis damages the nail plate causing thickening and discoloration. In more advanced cases, the nail plate lifts away from the nail bed, termed onycholysis, which causes discomfort and sometimes can be painful.

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Clinical presentations of onychomycosis have been divided into four categories: distal subungual (infection occurs at or near the tip of the nail plate and involves the underlying nail bed), proximal subungual (infection is at or near the cuticle and involves the underlying nail bed), superficial (infection is in the nail plate only with no nail bed involvement) and total dystrophic onychomycosis (whole nail involvement and considered a combination of the other types) [5]. Between 6.5 to 13.8% of the population in North America is reported to be infected with this disease and the prevalence increases with age [1,4,6,7]. One study reported 48% of 70 year olds are infected with onychomycosis [6].

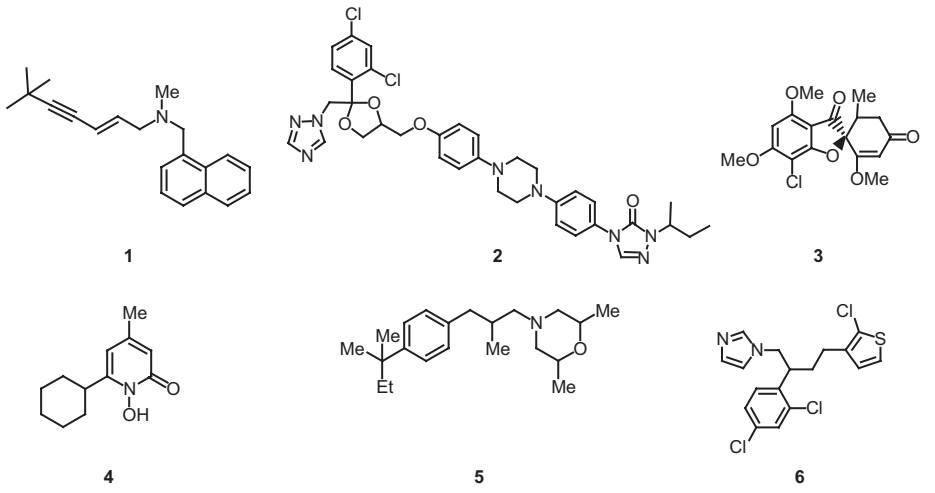
2. DRUG THERAPY

Onychomycosis is difficult to permanently cure. Treatment failures and relapses are common, which exacerbate the problem [8–10].

In order for an antifungal drug to be effective, it must presumably disseminate throughout the nail plate, nail bed and other locations occupied by the fungi, and reach concentrations that will eliminate the pathogen. This can be especially difficult when the nail plate has lifted from the bed (onycholysis). Unlike damaged skin that can repair itself, the nail plate cannot, therefore results of therapeutic treatment are not evident until new nail growth occurs and is clear of infection. Toe nails typically take about 1 year to fully grow out.

Because of the length of time required to observe new nail growth, clinical trials typically take around 9–12 months (either 3 months systemic treatment with 6–9 months follow up or 6–9 months topical treatment with 3–6 months follow up). During this time, the infected nails can be monitored for growth of new clear nail and for presence of viable dermatophytes. Efficacy is usually recorded in one of three ways: mycological cure, clinical cure or complete cure. Standard definitions of these cures are not completely uniform; each report usually provides the criteria that were used in the study. A mycological cure is defined by the extent of eradication of the fungi. It is assessed by removing a section of nail and screening for the presence of dermatophytes by microscopy and by culturing the nail for growth of dermatophytes *in vitro*. A clinical cure is defined by the extent of new nail growth at the proximal fold which is visibly clear of infection. A complete cure is defined when a patient has a mycological cure and clinical cure. Obviously, a complete cure is most desirable but hindering this is the fact that in many cases more than one digit is infected and not every digit may be cleared of infection.

Onychomycosis is treated both systemically and topically. Current systemic treatments include terbinafine **(1)**, itraconazole **(2)** and griseofulvin **(3)**. Current topical treatments include ciclopirox **(4)**, amorolfine **(5)** and tioconazole **(6)**.



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2.1. Systemic treatments

Currently, systemic treatment is the most effective method of curing onychomycosis. Even so, between 20–25% of patients fail to respond [11]. Terbinafine **(1)** and itraconazole **(2)** are the two systemic treatments of choice with terbinafine showing greater efficacy than itraconazole and lower rates of recurrence [11–15].

Terbinafine **(1)**, a representative of the allylamine class of antifungal agents, inhibits squalene epoxidase [16,17] and thereby prevents the biosynthesis of ergosterol, a key ingredient in the fungal cell wall. Terbinafine is active against dermatophytes, *M. furfur*, *Aspergillus* species and some *Candida* species including *C. parapsilosis*; however, it is fungistatic against *C. albicans* [2]. A single oral dose of 250 mg terbinafine given to humans produces peak plasma concentrations of 1 μg/mL within two hours [14]. It is >99% protein bound and has a half-life of about 36 hours. It is administered at a dose of 250 mg once daily for 6 weeks for finger nails or 12 weeks for toe nails [14]. One study showed that terbinafine localizes in the stratum corneum *via* sebum [18]. Terbinafine has a cLogP of 6.5 and a molecular weigh of 292 Da.

Itraconazole **(2)**, which is from the azole class of antifungal agents, inhibits lanosterol 14 α-demethylase and thus stops the biosynthesis of ergosterol. It has broad spectrum activity against species including dermatophytes, *Candida* species, *Aspergillus* species and *M. furfur* [2]. Blood levels of itraconazole after a single 200 mg dose given to humans reached a peak level of 0.2–0.3 μg/mL after 4–5 hours [15]. It is 99.8% protein bound and has a half-life of 21 hours. It is administered either 200 mg once daily for 12 weeks or 200 mg twice daily for 7 days followed by 3 weeks with no treatment and repeated for three months. Like terbinafine

itraconazole also localizes in the stratum corneum via sebum but at much lower levels [18,19]. Itraconazole has a cLogP of 3.3 and molecular weight of 706 Da.

Griseofulvin **(3)**, isolated from *Penicillium griseofulvin* in 1939 [20], has a limited spectrum of activity. It is fungistatic against dermatophytes only and works by binding to microtubular proteins thus inhibiting cell mitosis. It has a cLogP of 2.2 and a molecular weight of 353 Da.

The commonly used antifungal agent, fluconazole, has also been prescribed, off-label, for the treatment of onychomycosis.

2.2. Topical treatments

Treatment of onychomycosis by topical methods has been met with limited success and reasons for this will be explored in more detail in Section 3. As with treating skin fungal infections such as tinea pedis (athletes foot), topical application for onychomycosis would seem the obvious choice. However, unlike the stratum corneum, the nail plate is a more difficult barrier to penetrate, requiring the drug to have much different physicochemical properties than are required for skin penetration. The two main topical treatments used today are ciclopirox and amorolfine, 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 then acts like a drug depot releasing the drug into the nail plate [21,22]. Tioconazole has also been used but has been largely replaced by ciclopirox and amorolfine.

Ciclopirox **(4)** is a hydroxypyridone antifungal agent and is believed to work by inhibiting metal dependant enzymes that degrade intracellular toxic peroxides. It does this by chelating the polyvalent cations (Fe^{3+} or Al^{3+}) required by these enzymes [23–25]. Ciclopirox has antifungal, antibacterial and anti-inflammatory activities [25]. It is administered to the infected nails daily and due to the slow growth of nails, this treatment continues for at least 6 months. Ciclopirox has a cLogP of 2.5 and a molecular weight of 207.

Amorolfine **(5)** is a morpholine antifungal agent and works by inhibiting ergosterol biosynthesis. Amorolfine is administered once or twice weekly to the infected nails for 6 to 12 months. Amorolfine has a cLogP of 5.8 and molecular weight of 317.

The relative lack of clinical efficacy seen by topical antifungal treatments has led to a substantial research effort to understand the reasons for this failure. The most common belief is that treatment failure following topical therapy for onychomycosis results from the inability of the drug to penetrate and disseminate throughout the nail. This topic will be explored in more depth in Sections 3 and 4. Other factors that have been implicated include lack of microbiological activity in the presence of keratin [26,27], lack of microbiological activity against the dormant dermatophytes in the nail keratin [28] and poor penetration of drug into the dermatophytoma, a thick mass of fungi and nail debris, that builds up between the

2.3. Combination and booster treatments

Since there are no current antifungal treatments available that will provide a complete cure, practitioners are attempting combination therapy and/or booster therapy in an attempt to improve efficacy rates [30–32]. Combination therapy includes the use of oral plus oral therapy e.g. oral teribinafine plus oral itraconazole either in parallel or sequentially; oral plus topical therapy, e.g. oral terbinafine plus topical ciclopirox lacquer; or other dual, triple or quadruple combinations. However, these studies show only marginal improvement at best and further studies are warranted. Booster therapy involves giving a second course of systemic treatment, terbinafine or itraconazole, 6–9 months after systemic treatment began [30].

3. DRUG PENETRATION THROUGH THE NAIL

3.1. Composition of the nail plate

The human nail anatomy consists of nail plate, nail bed and nail matrix. The nail plate consists of three layers: the dorsal and intermediate layers derived from the matrix, and the ventral layer derived from the nail bed [33,34]. 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 three quarters of the whole nail thickness, and consists of soft keratin. Below the intermediate layer is the ventral layer of soft keratin, a few cells thick, that connects to the underlying nail bed, in which many pathological changes can occur. Thus, in the treatment of nail diseases, achieving an effective drug concentration in the ventral nail plate is of great importance. The nail bed consists of non-cornified soft tissue under the nail plate, and is highly vascularized. Beneath the nail bed at the proximal fold is the nail matrix, which is a heavily vascularized thick layer of highly proliferative epithelial tissue that forms the nail plate.

The human nail is approximately 100 times thicker than the stratum corneum of the skin, and both are rich in keratin. However, they exhibit some physical and chemical differences [35,36]. The nail possesses high sulphur content (cystine) in its hard keratin domain, whereas the stratum corneum does not. The total lipid content of the nail ranges from 0.1% to 1%, as opposed to approximately 10% for the stratum corneum.

Under average conditions, the nail contains 7% to 12% water, in comparison to 25% in the stratum corneum. At 100% relative humidity, the maximum water content in the nail is approximately 25%, in sharp contrast to that in the stratum corneum, which can increase to 200–300%.

The nail's unique properties, particularly its thickness and relatively compact construction, make it a formidable barrier to the entry of topically applied agents [37]. In one study, the concentration of an applied drug across the nail dropped about 1000-fold from the outer surface to the inner surface [38]. As a result, the drug concentration presumably had not reached a therapeutically effective level in

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