The Egyptian Journal of Hospital Medicine (January 2023) Vol. 90, Page 1760-1763

Treatment Options of Onychomycosis: Review Article

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ABSTRACT

Background: The most frequent nail problem observed in clinical practice is onychomycosis, a fungal infection of the toenails or fingernails caused by dermatophytes (also known as tinea unguium), non-dermatophyte moulds, or yeast. Many patients with Onychomycosis are resistant to most therapeutic modalities, making it difficult to determine the appropriate course of treatment. This may contribute to the high rate of recurrence.

Objective: Review of the literature on treatment options of onychomycosis.

Methods: In an effort to learn more about onychomycosis, we looked through resources like PubMed, Google Scholar, and Science Direct. However, only the most recent or extensive study was taken into account between January 2012 and May 2022. Relevant literature references were also evaluated by the writers. There are not enough resources to translate documents into languages other than English, hence those documents have been ignored. It was generally agreed that documents such as unpublished manuscripts, oral presentations, conference abstracts, and dissertations did not qualify as legitimate scientific study.

Conclusion: Topical antifungals are ineffective if applied to the nail plate without first debriding the nail bed, whereas oral therapy for Onychomycosis is limited by medication interactions and possible hepatotoxicity. Combinations of systemic and topical treatments seem to be the most successful overall.

Keywords: Onychomycosis, Topical antifungals are ineffective, Treatment options.

INTRODUCTION

In clinical practice, the most common nail problem is onychomycosis, a fungal infection of the fingernails or toenails caused by dermatophytes (also called tinea unguium), non-dermatophytic moulds, or yeast. Onychomycosis can affect the matrix, the bed, or the plate of the nail unit **(1).**

The thickening, discoloration, and separation of the nail plate from the nail bed are all clinical manifestations; this is a serious problem because it can cause local pain, paresthesias, difficulty with activities of daily living and social interactions, as well as serious physical and occupational limitations and a decrease in life quality **(2).**

About 5.5% of people all over the world suffer with infectious onychomycosis, a fungal infection of the nails. This fungus is responsible for up to 50% of all nail infections and 30% of all superficial fungal skin infections **(3).**

Different environmental media, like hotel carpets, public showers, and pool decks, are viable sources from which we might collect and cultivate the fungi; the moist, restricted environment of tight shoes and microtrauma of the nail might enable rupture of the hyponychium seal and infection of the nail bed, leading to onychomycosis in the toenails.

While in fingernails it might occur owing to continuous exposure to water for employees or housewives **(4).**

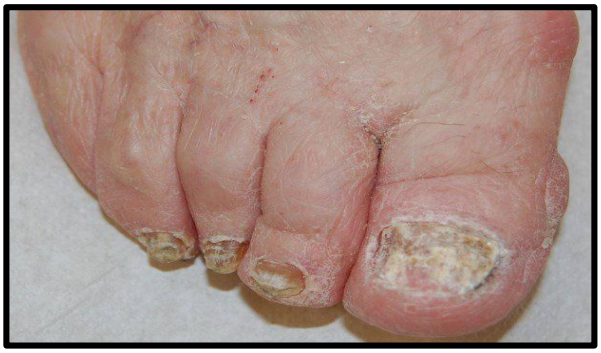

Figure (1): Nail plate is entirely infected with fungi, causing it to become brittle and prone to splitting, a condition known as total onychomycosis **(5).**

Treatment:

Many patients with Onychomycosis are resistant to most therapeutic modalities, making it difficult to determine the appropriate course of treatment. This may contribute to the high rate of recurrence. The degree to which a patient benefit from treatment depends on a number of different prognostic markers. An effective method for evaluating the severity of onychomycosis and predicting a patient's response to treatment is the Onychomycosis severity index (OSI). Patients with mild disease have a better chance of recovery with treatment than those with moderate disease, and vice versa for those with severe disease **(6).**

Received: 09/09/2022
Accepted: 12/11/2022

The patient's prognosis and the severity of the condition also rise with the number of infected nails, the duration of the infection, the chance of spontaneous remission, and the patient's age (in most cases, the infection has been present for more than five years)[5]. Topical antifungals are useless if nail plate debridement is not performed first, and oral medications can have limitations due to drug interactions and the risk of hepatotoxicity., there is room for advancement in the field of treatment. Combinations of systemic and topical treatments seem to be the most successful overall [5].

1) Antifungal Drugs:

- **Topical agents:** Because of the possibility for systemic side effects from oral medicines, there has been a rise in interest in topical treatments that have fewer side effects and no drug-to-drug interactions. As a result, the preparations have been adapted to improve medication delivery to the nail bed, where the fungal infection grows; also, the efficiency of the preparations is enhanced by the treatment of concomitant skin conditions, such as tinea pedis [6].

Topical FDA approved treatments:

1. **Ciclopirox:** It kills a wide range of microorganisms, including Gram-positive and -negative bacteria, dermatophytes, candida, and even some non-dermatophytic fungus. To treat mild to severe onychomycosis caused by Trichophyton rubrum in immunocompetent patients who do not have lunula involvement, the FDA approved a nail polish containing 8% cyclopyrex in 1999. Only local responses like burning or periungual erythema were reported [2].
2. **Efinaconazole:** Those with milder cases of onychomycosis and shorter disease durations have a better chance of experiencing a complete remission after treatment. It was only ingrown toenails and local reactions that were reported [7].
3. **Tavaborole:** The peculiar method of action of tavaborole led to its approval by the FDA in July 2014 for use as a topical therapy for onychomycosis of the toenails caused by T. rubrum or T. mentagrophytes (AARS), Because of its low molecular weight, tavaborole solution has also been shown to pass through the nail bed and several coats of nail lacquer. Exfoliation, erythema, and dermatitis are the most prevalent local adverse effects [2].

Other topical drugs:

a. Amorolfine

The affected nail is treated with amorolfine, a synthetic antifungal drug in the morpholine class, once or twice weekly for 6-12 months after as much infected tissue is surgically removed as possible. Fungicidal activity against Candida albicans and T. mentagrophytes is due to the compound's ability to block the ergosterol production pathway enzymes delta 14 reductase, delta 8 isomerase, and delta 7 isomerase. Curing a nail for 14 days ensures that it will still be present in the nail [8,9].
It has been found that amorolfine nail lacquer can be successful in about 50% of instances of distal fingernail and toenail onychomycosis, with a mycological cure rate of 30%. Prophylactic use of amorolfine against onychomycosis recurrence has also been shown to be effective [6].

Systemic therapy (Oral antifungal agents):

Onychomycosis is typically treated with systemic drugs because to their wide availability, low cost, and great efficacy. The FDA has approved terbinafine, griseofulvin, and itraconazole to treat onychomycosis, and oral fluconazole is also administered off-label [1].

a. Terbinafine:

Terbinafine is an allylamine that inhibits the activity of squalene epoxidase; this property makes it highly effective against dermatophytes but less so against non-dermatophytic moulds and Candida spp. The Food and Drug Administration (FDA) approves oral administration of 250 milligrammes (mg) once day for 6 weeks for treating onychomycosis caused by dermatophytes on fingernails and 12 weeks for treating onychomycosis caused by fungi on toenails [2].
Headache, stomach issues, and skin rashes are the most often reported adverse reactions. Occasionally, you can experience some changes in your liver enzyme levels or your sense of taste [2].

Terbinafine pulse dosing:

Despite not being approved by the FDA, pulse-dose therapy with terbinafine can be used to treat onychomycosis. The most efficacious of the pulse regimes was a 3-cycle course of 250 mg/day for 4 weeks on and 4 weeks off; mycologic and complete cure rates were comparable to those reported with continuous 250 mg/day terbinafine treatment for 12 weeks [10].

b. Itraconazole:

Triazole inhibits fungal lanosterol 14-demethylase, leading to decreased ergosterol synthesis, which in turn leads to membrane abnormalities, increased permeability, disruption of membrane integrity, and changes in the activity of membrane-bound enzymes, all of which contribute to the eventual death of the fungal cell [11].

Itraconazole is an alternate choice to terbinafine. Candida spp., other non-dermatophytic fungi, and dermatophytes are all defeated. Nail fungus caused by dermatophytes, known medically as onychomycosis, can now be treated with it, thanks to approval from the Food and Drug Administration [2].

Itraconazole pulse therapy has been shown to be more effective and acceptable than most of the other onychomycosis drugs; nevertheless, three cycles of treatment may not be enough for severe instances of onychomycosis of the toenails. As a result, there is an immediate need to devise a more efficient treatment strategy to raise the number of patients who go into complete remission [12].

Onychomycosis treatment plan: take 200 mg twice day (as capsules) for seven days, then take 21 days off. Immunocompromised patients should be given a double dose [11].

Hypertriglyceridemia and increased transaminases are two of the most prevalent unwanted effects, along with headache, upper respiratory infection, diarrhoea, abdominal pain, and other similar symptoms. Maximal bioavailability is achieved following a meal, but it is reduced in an acidic stomach environment. Extremely rare adverse effects include hepatic damage and peripheral neuropathy [2].

Patients with heart failure or a history of heart failure should not take itraconazole; the same goes for those with liver failure or disease; hepatotoxicity is a risk; and finally, itraconazole should not be taken by pregnant women because of its potential teratogenic and embryotoxic effects. Itraconazole was linked to birth abnormalities in the eyes of children whose mothers took the medicine while pregnant [13].

c. Fluconazole:

Inhibiting lanosterol 14-demethylase, like another triazole, makes it effective against dermatophytes, Candida species, and some non-disseminated fungi. Unlike itraconazole, fluconazole is absorbed well regardless of stomach acidity or whether or not food has been consumed. Treatment for onychomycosis requires 150 mg once weekly until the entire nail grows out (6-9 months for fingernails, 12-18 months for toenails). The small amount still present in the nails requires a prolonged treatment schedule. The most common side effects include headache, nausea, rash, stomach pain, and elevated transaminases. Liver damage is a rare complication, and occurs mostly in people who are immunocompromised. Fluconazole inhibits the enzymes CYP2C9 and CYP3A4 to varying degrees, necessitating care when used in conjunction with other drugs [2].

d. Second generation triazoles:

Newer azoles including posaconazole, fosravuconazole, voriconazole, and oteseconazole have been the subject of much research. The FDA has not green-lighted any of these azoles for the treatment of onychomycosis or any other superficial fungal infection [14].

- ***Posaconazole:***

Wide-ranging and effective against moulds and yeasts, posaconazole (200 mg once daily for 24 weeks) also has an effect on dermatophytes that is equivalent to that of terbinafine [1].

- ***Voriconazole:***

An initial loading dose of 400 mg bid was followed by a maintenance dose of 200 mg po bid for 12 weeks, and all dosing was based on serum drug concentration [15].

- ***Ravuconazole:***

For onychomycosis, a randomized, double-blind study looked at the pharmacokinetics, safety, and efficacy of the triazole ravuconazole, which exerts broad, potent antifungal activity. Sixty-nine percent of patients who took 200 milligrammes of ravuconazole orally once a day for 12 weeks were cured of their fungal infection, according to the study's findings [6].

- ***Fosravuconazole:***

Onychomycosis can be treated with the capsule form of fosravuconazole (NAILIN®100 mg), which has been licensed for use in Japan but is not yet available in the United States. To improve pharmacokinetics and bioavailability, a ravuconazole prodrug was developed [16].

- ***Oteseconazole:***

The antifungal tetrazole oteseconazole has a very lengthy half-life. Due to the FDA's lack of approval, there is currently no standard dosage or formulation of etaconazole [17].

- ***Albaconazole:***

Albaconazole's antifungal activities are wide-ranging, and it also has favourable pharmacokinetic and absorption profiles. It has shown significant efficacy against both Candida and Aspergillus species. Because of how long its effects last, it can be dosed once a week. The group given 400 milligrammes every week for 36 weeks fared the best. Only about 3% of patients experienced any treatment-related side effects at all, and those that did were generally mild to moderate in severity. Headache, nausea, diarrhoea, and a brief and modest elevation in liver enzymes were the most frequently reported negative effects [18].

Laser therapy:

This non-pharmaceutical treatment employs the principle of selected light thermolysis to bring about fungicidal activity in nail fungi by bringing them to an inhospitable temperature. Fungal mycelia in injured tissue are hypothesized to preferentially absorb laser energy, leading to a rapid increase in temperature and fungal cell death; however, the precise mechanism of action is still poorly characterized [19].

The laser treatment of onychomycosis has been approved by the Food and Drug Administration, but only for cosmetic purposes (the temporary growth of clear nail), not for mycological or total cure [19].

Onychomycosis treatment with lasers of several sorts has been studied. As such, neodymium-doped yttrium aluminium garnet (Nd:YAG) lasers have been the subject of the most research. Additionally, diode lasers, erbium: glass lasers, and fractional carbon dioxide lasers have been used to treat onychomycosis [19].

Photodynamic therapy (PDT):

Using light within a certain restricted spectrum, sick tissue can be selectively damaged using a photosensitizing drug applied topically and taken up by the target organism. The most often reported adverse responses included mild pain, burning, erythema, oedema, and blistering; however, these were all well tolerated and resolved within a few days [20].

One main drawback of PDT is that it may be difficult for patients to commit to the treatment due to the need for frequent and lengthy clinic visits (up to several hours each). Patients may need to attend up to 12 therapy

sessions over the course of six months, whereas oral or topical medication only requires one or two visits [20].

CONCLUSION

Topical antifungals are ineffective if applied to the nail plate without first debriding the nail bed, whereas oral therapy for Onychomycosis is limited by medication interactions and possible hepatotoxicity. Combinations of systemic and topical treatments seem to be the most successful overall.

Supporting and sponsoring financially: Nil.
Competing interests: Nil.

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