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Treating Onychomycosis

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Abstract

Background: Onychomycosis means fungal infection of nails. Causative agents are yeasts and dermatophyte or nondermatophyte molds. Toenail onychomycosis mainly caused by dermatophytes while yeasts come into prominence for fingernails. Risk factors are genetic predisposition, age, swimming, tinea pedis, psoriasis, diabetes and immunodeficiency. It is important to consider differential diagnosis including trauma, eczema, psoriasis, lichen planus, onychogryphosis before starting antimycotic treatment. Although there are different clinical forms such as distal subungual, proximal subungual, white superficial, nondermatophytic and yeast onychomycosis, treatment options are similar. Topical therapies for onychomycosis are generally not effective so systemic antifungals are required.

Introduction

Onychomycosis is fungal infection of nails caused by yeasts, dermatophyte and nondermatophyte molds. This term expresses infection of nails with any fungal agent differently from the term tinea unguium that means only dermatophytic infection of nails. Onychomycosis of toenails mainly caused by dermatophytes (so called tinea unguium) while yeasts are main pathogens for fingernails [**1, 2**].

Patients usually have concomitant tinea pedis. Genetic predisposition, age, swimming, psoriasis, diabetes and immunodeficiency are other risk factors for onychomycosis. The prevelance is 4 to 18 percent and most of them are toenail involvement. Tinea unguium has three clinical forms consisting of distal subungual, proximal subungual and white superficial with the former is most frequent. The causative agent is mainly Trichophyton rubrum. In white superficial form, T. mentagrophytes takes over. Candida albicans is major yeast causing onychomycosis [**1, 2, 3**].

Diagnosis

Nail dystrophies are caused not only by fungal infections but also trauma, eczema, psoriasis, lichen planus and onychogryphosis. It is important to mind differantial diagnoses before starting antimycotic treatment. KOH examination of scrapings is useful to observe dermatophytic hyphae and spores. Nail culture on Sabouraud's medium is helpful to determine causative agent but it takes four weeks and has one third false negative ratio. The dermatophyte test medium (DTM) is an alternative culture and results are available in seven days. Histopathological examination of the nail plate with PAS staining is more

sensitive method for diagnosis but also more expensive one. Polymerase chain reaction test is also sensitive but not widely used [**1, 4**].

Treatment

Onychomycosis may cause physical discomfort beside generating cosmetic worry. It may also increase the risk of bacterial infections. Treatment is indicated for patients having history of cellulitis or predisposition such as venous insufficiency, and also for patients having cosmetic worry. There are different clinical forms such as distal subungual, proximal subungual, white superficial, nondermatophytic and yeast onychomycosis, but treatment options are similar. Topical therapies for onychomycosis are generally not effective so systemic antifungals are required [**1**].

Antifungal therapy aims mycological clearence and clinical cure. Clinical improvement may take several months particularly in toenails so follow up period must be at least six months after therapy. In patients with white superficial form, distal subungual form affecting < 50 % of nail plate without matrix involvement and patients with intolerance to systemic therapy, topical therapy may be used. Systemic therapy is indicated in proximal subungual form, distal subungual form affecting > 50 % of the nail with matrix involvement or affecting more than two nails. Also we can switch to systemic therapy for the patients not responding to topical therapy for six months [**5, 6**]. Criteria for treatment success or failure are summarized in table modified from study of *Scher RK* et al [**Table 1**] [**4**].

Oral Therapy

Most frequently used drugs are oral terbinafine for dermatophyte onychomycosis and oral itraconazole for nondermatophyte onychomycosis and yeast onychomycosis.

Griseofulvin

Griseofulvin is the first approved antimycotic drug for onychomycosis treatment and is effective only against dermatophytes [**6, 7**]. The mechanism of action is arresting fungal cell mitosis by blocking the formation of mitotic spindle [**5, 6**]. It is ineffective against yeasts and nondermatophyte molds [**7**]. Prolonged administration, up to 18 months, is required because it takes a long time to reach therapeutic concentrations in nail plate [**6, 8**]. Griseofulvin has lower clinical cure rates and higher recurrence rates than terbinafin and itraconazole [**1, 7**]. The daily dosage for adults is 500-1000 mg [**9**]. In children, griseofulvin is the only licensed antimycotic drug and dosage is 10 mg/kg daily [**6**]. Gastrointestinal complaints and headache are the most common side effects. Hypersensitivity reactions and serious side effects such as cytopenias and hepatotoxicity are rare. Hemogram and liver function tests must be controlled during treatment. It may cause drug interactions by it's effects on cyp-450 enzyme [**5, 7**].

Terbinafine

Terbinafine is the most effective oral treatment for toenail onycomycosis [**10**]. It has fungicidal activity against dermatophytes by inhibiting the enzyme squalen epoxidase leading to accumulation of squalene in the cytoplasm and lysis of the cell. It has also fungostatic activity against C. Albicans via inhibition of ergosterol synthesis [**6, 7**].

Bioavailability is high as 70 % after oral intake and it's detectable in nail from 7 days

Table 1. Criteria for Treatment Success and Failure

Cure	Noncure
Clinically normal nails	Positive mycology
Remaining onycholysis or subungual hyperkeratosis < 10 % of nail plate, mycology negative	Residual changes compatible with fungal infection affecting more than 10 % of nail plate
Remaining nail thickening caused by other conditions, mycology negative	Lateral hyperkeratosis or onycholysis

of therapy up to 90 days after treatment. Daily dosage is 250 mg during 6 weeks for fingernails and 12 weeks for toenails [**6**]. Terbinafine was compared with other antifungal agents in a meta analysis of 36 studies by *Gupta* et al. Terbinafine is found more effective than others for treatment of dermatophyte onychomycosis [**11**]. In L.I.ON. study with 496 patients, continuous terbinafine was significantly more effective than intermittent itraconazole in the treatment of toenail dermatophyte onychomycosis [**12**]. *Gupta* et al and *Sikder* et al found intermittent terbinafine treatment as effective as continuous terbinafine and more efficacious than pulse itraconazole [**13, 14**]. Side effects are nausea, diarrhea, abdominal pain, pruritus, skin rash and taste alterations. Serious side effects are rare and include hepatitis, agranulocytosis, acute generalized exanthematous pustulosis and lupus erythematosus. Terbinafine is metabolized by cytochrome P 450 enzymes so interacted with rifampicin, cimetidine, cyclosporin, TCA antidepressants and beta blockers [**5, 6, 7**].

Itraconazole

Itraconazole is a triazole antifungal which has a broad spectrum of activity against dermatopyhtes, nondermatophytes and yeasts. The mechanism of action is interfering with the cell wall synthesis via inhibiting the enzyme called 14-alpha demethylase which transforms lanosterol to ergosterol. It is rapidly absorbed after oral intake and it has a high affinity to keratin. Itraconazole is detectable in distal nail plate 1 month after the starting of therapy and persists in nail even 9 months after the end of therapy [**15, 16**]. It is used as 200 mg daily for 3 months. Intermittent dosing regimen, with 200 mg twice daily for one week of every month, is as efficacious as continuous regimen and also more economic [**17**].

Physician must be aware of drug interactions because of binding to cyp-3A4 enzyme system. It should not be used with cisapride, midazolam, triazolam, simvastatin and lovastatin. Itraconazole is a well tolerated drug. Common side effects are nausea, vomiting, abdominal pain and headache. Serious side effects such as hepatitis are rare but hepatic function tests must be monitored during treatment. It is contraindicated in patients with congestive cardiac failure and one must pay attention when using itraconazole in patients with arrhythmia [**15, 16**].

Fluconazole

Fluconazole is a hydrophilic antifungal drug that interferes with the synthesis of ergosterol, like itraconazole does. It is effective against dermatophytes and Candida spp. but not approved for onychomycosis treatment in USA. Placebo controlled studies with fluconazole revealed cure rates of 36 to 100 %. It is administered at the dose of 150 mg daily or 300 mg weekly for up to 6 months [**6, 7**]. *Scher* et al reported that there was no significant difference in the efficacy of doses 150, 300 and 450 mg weekly for toenail onycomycosis [**18**]. Side effects are headache, nausea, skin rashes, insomnia and palpitations. Drug interactions with oral hypoglicemic agents, cyclosporine and phenytoin are important issues.

Other Azoles

Other azoles including voriconazole, posaconazole and ravuconazole also inhibit 14-alfa demethylase enzyme and interfere with the ergosterol synthesis. Voriconazole is effective against Scopulariopis brevicaulis, Fusarium spp and Scytalidium dimidiatum. It may be the drug of choice for resistant cases. Posaconazole is effective against different types of non dermatophyte, such as Aspergillus, yeasts like candida spp and zygomycete infections. Spectrum of Ravuconazole includes Candida spp, Cryptoccus neoformans, dermatophytes and dematiaceous fungi. There are also many new azoles like isavuconazole, pramiconazole and albaconzaole subjected to new clinical trails [**19, 20, 21**].

Comparison of Oral Therapies

A meta analysis performed by *Gupta* et al, mycological cure rates for dermatophyte onychomycosis in randomized controlled trials were 76±3 % for terbinafine, 63±7 % for itraconazole pulse therapy, 60±6 % for griseofulvin, 59±5 for itraconazole continuous therapy

and 48±5 % for fluconazole in a decending sort [**11**].

Sequential Therapy

Combining two oral antifungal agents may shorten the treatment and reduce the cumulative doses. In one clinical trial with 190 patients, itraconazole pulse therapy for two months followed by one or two pulses of terbinafine showed better results than usage of three or four terbinafine pulses alone [**6**].

Topical Therapy

Antifungal creams poorly penetrate the nail plate so they are formulated as lacquers to be effective topical treatment choices [**22**]. Indications for topical monotherapy are: white superficial form, distal subungual form affecting < 50 % of nail plate without matrix involvement and patients with intolerance to systemic therapy. Nail lacquers are discussed below.

Ciclopirox

Ciclopirox olamine 8 % is a topical antifungal nail lacquer which has a broad spectrum. It blocks the cellular uptake of important ingredients and become fungicidal. It is applied once a day and nail plate must be debrided once weekly after cleaned by alcohol [**1, 7**]. When used as monotherapy, complete resolution occurs in only 7 percent of the patients. Trials in which ciclopirox was used in combination with systemic terbinafine, showed no superiority of combination to terbinafine alone [**23, 24**].

Amorolfine

Amorolfine 5% lacquer has also broad spectrum and is effective against yeasts, dermatophyte and nondermatophyte molds [**19**]. It is a lypophilic molecule which blocks the synthesis of ergosterol. Amorolfine persists in the nail plate longer than ciclopirox and it may be used once a week [**1, 6, 7**].

There are no systemic side effects of nail lacquers. Local side effects are transient and include erythema, burning and discoloration [**25**].

Nail Surgery

Nails infected by fungi are mostly thickened and deformed. There may be onycholysis at distal or lateral sides of nail plate. These affected nails may be removed by chemicals or surgical procedure. These methods can be used in combination with topical or systemic therapies so it would be possible to reduce the fungal load and make drug penentration easier. Chemical removal is painless and performed with keratinolytic and keratinoplastic agents such as urea, salicylic acid and resorcin. They disrupt the bonds between keratin molecules and cause loosing of nail plate. 40 % urea is applied under occlusion for up to 2 weeks and nail can be removed more comfortably. Topical bifonazole may be used for a month following the procedure. Skin infections must be considered during surgical removal especially in patients with diabetes [**6, 7, 19, 26**].

Photodynamic Therapy

There are some case reports about patients treated with phototherapy followed by topical photosensitizer application but data are limited for this treatment modality. Fungicidal activitiy occurs via reactive oxygen species. 5-aminolevulinic acid (ALA) and methylaminolevulate (MAL) may be used as photosensitizer but one clinical trial reported only 43 % success rate [**27, 28, 29**].

Laser Therapy

Laser systems are new treatment options for onychomycosis but our knowlege about their efficacy is limited. Neodymium-doped:yttrium aluminum garnet (Nd:YAG) and diode lasers have been used for this purpose. Also ablative fractional CO2 laser combined with topical antifungal was found effective for 50 % of patients in a study with 24 patients after 12 weeks.

In a study with Q switched Nd:YAG, maximal inhibiton of dermatophytes had been reported with 4-8 J/cm2 for 1064 nm and 8 J/cm2 for 532 nm and postulated that target chromophores were melanin and xanthomegnin of fungus, respectively. The Noveon laser, a diode laser, was found effective for 85 % of the patients in one study. It had been used for four sessions on days 1, 14, 42 and

120. Ti: Sapphire laser was used in vitro study and found fungicidal on T. rubrum with appropriate energy levels [**27**].

Treatment Failure and Recurrence

Onychomycosis treatment is troublesome even with usage of systemic agents. Misdiagnosis, inadequate therapy and resistance to drugs are significant factors associated with treatment failure and recurrence. Long term recurrence rates are up to 50 % in studies. Intermittent oral therapy and topical maintenance therapy may be useful [**1**].

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