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Literature Review

COMBINATION ANTIFUNGAL THERAPY FOR ONYCHOMYCOSIS

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ABSTRACT

Onychomycosis is a fungal infection of the nail unit including the nail matrix, the nail bed and the nail plate by both dermatophyte and non-dermatophyte agents. It is disturbs not only cosmetic disfigurement, but also it may have an impact on patients' emotional, social and occupational functioning, finally affecting the overall quality of life. The incidence rate tends to increase, management of onychomycosis is still challenging. Important problems regarding antifungal monotherapy have experienced many failures and recurrences. In general, pharmacological approaches for onychomycosis can be topical or oral antifungal. Antifungal monotherapies often lead to failure treatment, also high incidence of recurrence. One strategy for this problem is a combination antifungal therapy. In vitro studies show the synergistic effect of using combination two antifungals (both oral antifungal or combination topical and oral antifungal), hence it is mycologically or clinically expected to increase the success rate of onychomycosis therapy. This review tries to evaluate the previous study exploring the effectiveness of antifungal combination therapies on onychomycosis. Two oral antifungals usually used are terbinafine as fungicidal agent and itraconazole as fungistatic agent. There is combination between topical and oral antifungal such as itraconazole or terbinafine with amorolfine or ciclopirox, also other combination like griseofulvin and amorolfone or tioconazole. All the combination therapies show better result than monotherapy alone, but it is still difficult to conclude whether antifungal combinations in onychomycosis will increase effectiveness due to variations in therapeutic duration, result definition, and statistical evaluation on existing studies. Further research is required with longer duration of observation, uniform patient criteria and definition of success, random control and blinding to minimize bias.

Keywords: *antifungal, combination, therapy, onychomycosis, effectiveness*

ABSTRAK

Onikomikosis adalah infeksi jamur pada bagian kuku baik pada matriks kuku, bantalan kuku, maupun lempeng kuku, oleh agen dermatofit maupun non-dermatofit. Onikomikosis adalah penyakit yang sangat mengganggu bukan hanya karena masalah kosmetik, namun juga dampaknya pada faktor emosional, sosial, dan pekerjaan, yang selanjutnya akan mempengaruhi kualitas hidup pasien. Angka kejadiannya cenderung meningkat, sedangkan penatalaksanaannya masih merupakan tantangan. Masalah penting oleh karena dengan antijamur monoterapi banyak mengalami kegagalan dan kekambuhan. Secara umum, pendekatan strategi farmakologi antijamur dapat berupa terapi topikal atau oral. Antijamur monoterapi sering menunjukkan kegagalan, dan kejadian rekurensi yang tinggi. Salah satu strategi untuk mengatasi masalah ini adalah dengan terapi kombinasi antijamur. Penelitian in vitro menunjukkan efek sinergisme penggunaan kombinasi dua buah antijamur (dua buah antijamur oral atau kombinasi antijamur topikal dan oral), sehingga secara klinis dan mikologi diharapkan dapat meningkatkan keberhasilan terapi onikomikosis. Telaah pustaka ini bertujuan mengkaji penelitian sebelumnya yang menunjukkan efektivitas kombinasi antijamur pada onikomikosis. Dua buah antijamur oral yang biasa digunakan adalah terbinafin sebagai agen fungisidal dan itrakonazol sebagai agen fungistatik. Untuk kombinasi oral dan topikal berupa terbinafin atau itrakonazol dengan amorolfin atau siklopiroks, dengan kombinasi lain seperti griseofulvin dengan amorolfin atau tiokonazol. Seluruh kombinasi terapi ini menunjukkan hasil yang lebih baik dibandingkan monoterapi, namun sayangnya masih sulit menarik simpulan dari penelitian yang ada apakah kombinasi antijamur pada onikomikosis akan meningkatkan efektivitas oleh

karena adanya variasi durasi terapi, variasi definisi hasil, evaluasi statistik pada penelitian-penelitian yang ada. Dibutuhkan penelitian lebih lanjut dengan durasi pengamatan yang panjang, kriteria pasien dan definisi keberhasilan yang sama, kontrol acak dan blinding untuk meminimalisir bias.

Kata kunci: *antijamur, kombinasi, terapi, onikomikosis, efektivitas*

INTRODUCTION

Onychomycosis is a progressive fungal infection of the nails and surrounding tissue, characterized by thickening and/or nail color change, as well as the separation of the nail from the nail bed. Onychomycosis can occur either on the nail bed, plate, matrix, or a combination of the parts of the nail.[1–4]

Onychomycosis accounts for about 30% of all superficial fungal infections and 50% of all nail abnormalities. The incidence of onychomycosis tends to increase due to increasing geriatric population and cases of immunocompromised patients such as diabetes, peripheral arterial disease, immunosuppressed conditions such as HIV infection and consumption of immunosuppressant agents. Onychomycosis in children is rare, usually it comes from indirect environment contamination of trauma or dystrophic nails.[5,6] In addition there are other factors influencing as climate, prolonged use of occlusive footwear, repeated trauma to the nails, and genetic predisposition.[2,3,7–9]

Onychomycosis can cause cosmetic problem, pain, discomfort, and affect the emotional or psychosocial aspects of the patient, thus requiring optimal and total therapy. The therapy remains a challenge for dermatologists, due to the duration of therapy (in accordance with the slow growth of the nail plate), poor patient compliance, and often takeing long to observe the success of therapy.[1]

The failure rate of onychomycosis therapy reaches 20%, along with a high recurrence rate of 10-53%.3,6,8,9 Some factors that also contribute to the unsuccessful therapy are patient's susceptibility, pattern of resistant fungal growth, the presence of fungal dormant spores on the nail, low bioavailability of the drug, and lack of drug penetration into the nail.[1,3]

Therefore, many methods are introduced to overcome problems in onychomycosis therapy, including a combination of two oral antifungals, or combination of both oral and topical antifungals.[4] This review will try to discuss the combination of two oral antifungal or topical and oral combination to improve therapeutic efficacy of infection in onychomycosis cases.

DEFINITION ONYCHOMYCOSIS

Onychomycosis is a fungal infection of the nails by both dermatophytes and non-dermatophytes such as yeast and mold. Ninety percent of onychomycosis cases occur in the toes and most cases of onychomycosis of the fingers are caused by dermatophytes. The most common dermatophyte species are Trichophyton rubrum, Trichophyton mentagrophytes var. digitale or Epidermophyton floccosum. Infection by other filamentous fungus or mold such as Scopulariopsis bravicaulis, Aspergillus spp., Fusarium spp., Acremonium spp., Alternaria spp., can act as primary pathogen, secondary pathogens, as well as contaminants. Yeasts such as Candida albicans, Candida parapsilosis are the third leading cause of fungal infections of the fingernails and usually arise when there are certain predisposing factors such as immunosuppression and diabetes.[2,3,10]

Clinically, onychomycosis can be differentiated into several subtypes: Distal and Lateral Subungual Onychomycosis (DLSO), White Superficial Onychomycosis (WSO), Proximal Subungual Onychomycosis (PSO), Endonyx Onychomycosis (EO), Total Dystrophic Onychomycosis (TDO), Mixed Onychomycosis, Candida Onychomycosis.[2,7,8,11]

Predilection on toe nails is more frequent (4-10 times) than fingernails, usually affecting multiple fingers and often accompanied with tinea plantar pedis. Onychomycosis of the toes is usually more difficult to treat, because the growth of toenails is slower than the hands, and limited blood flows in the area, especially in the elderly.[6,9]

Diagnosis of onychomycosis is made based on the clinical and mycological examinations by microscopic and culture examinations. Microscopic identification is considered enough to support determination of therapy, but the culture remains important as the gold standard to determine the causative species of onychomycosis.[3] There are several other investigation methods, including histopathology, onychoscopy, stripe dermatophytes, fluorescent microscopy, Raman spectroscopy, and Polymerase Chain Reaction (PCR).[2,11]

TOPICAL AND SYSTEMIC ANTIFUNGAL THERAPY

The purpose of onychomycosis therapy is eradication of fungus and restoration of the nail to be normal as before or complete clearance, which is defined as mycologically clear (including both negative direct microscopy and negative culture) and clinically clear (as disappearance of all lesions or residual disease of no more than 10% of the original total suffering surface).[12]

An ideal antifungal agent for the treatment of onychomycosis are favorable nail kinetics (ability to diffuse through the nail bed and be incorporated into the nail matrix), high mycologic and clinical cure rate, low incidence of relapse and effectiveness as short term therapy, low incidence of side effects, few drug interactions and cost effectiveness.[12] In general there are two main pharmacological strategies, oral and topical.[8]

The role of monotherapy of topical antifungal is only effective in WSO (except in transverse or striata infections), early DLSO (except for longitudinal lines) with nail plate involvement <80% and lack of associated lunula, or contraindications to systemic antifungal use.[13,14]

Some topical therapies used are azoles (ketoconazoles, clotrimazole, miconazole, sulconazole, oxiconazole and econazole); whitfield's ointment, potassium permanganate, amorolfine nail lacquer, ciclopirox olamine, allylamines (naftifine, terbinafine); organic acids (salicylic acid, phytex paint and undecenoates), halogenated phenolic esters (haloprogin); thiocarbamate derivatives (tolnaftate); and polyenes (nystatin). Amorolfine and ciclopirox are widely used than other topical agent[8,12] Lacquer is a form of drug which can maintain proper concentration of the active substance on the nail surface, and it just need to be applied once or twice weekly, which is of great convenience. And cosmetic nail varnishes would not affect the antifungal efficacy and can be applied concomitantly with amorolfine in the treatment of onychomycosis.[15]

Amorolfine is a group of morpholine which is a synthetic antifungal drug, with fungistatic and fungicide activity and broad spectrum. Amorolfine works by inhibiting the enzyme of 14 delta reductase, delta 8 and delta 7 isomerase in ergosterol biosynthesis pathways, and fungicidal against C. albicans and T. mentagrophytes. Amorolfine is available in the form of 5% nail polish and applied to affected nails 1 or 2 times a week for 6-12 months, after removing as many infected areas as possible from the nail plate. Amorolfine persists for 14 days after complete therapy.[8,11]

Ciclopirox is a hydroxypiridone derivative with extensive antifungal activity against T. rubrum, S. brevicaulis, and Candida spp. Ciclopirox will inhibit metal-dependent enzymatic processes, including nutrient uptake, cellular energy production, and toxic intracellular peroxide degradation. Ciclopirox available in the form of nail polish 8% concentration, used once a day for more than 48 weeks. Recommended duration for treatment with ciclopirox is 24 weeks for fingernails and 48 weeks for toenails. No studies has directly compared the effectiveness of amorolfine and ciclopirox but clinical improvement with ciclopirox is usually lower.[1,8,11]

Systemic antifungal therapy gives higher effectiveness than topical route. The oral antifungal therapy that has been widely used for the therapy of onychomycosis includes itraconazole, terbinafine, fluconazole, griseofulvin and ketoconazole. Itraconazole and terbinafine appear to be the best systemic drugs for the therapy of onychomycosis due to their reservoir effects in the nails.[16]

Terbinafine works by inhibiting squalene epoxidase, which is very important for ergosterol biosynthesis to be an integral component to the cell wall of the fungus, which are directly fungicidal. Recommended dosage of terbinafine is 250 mg/day for 6 weeks for fingernails and 12-16 weeks for toenails infections. For pulsed therapy some studies use a dosage of 250 mg/day for a week per month (3 months duration) or 500 mg/day for a week per month (3 months duration). Terbinafine is lipophilic and well distributed on the skin and nails. Terbinafine can be detected on the nail after one week from the start of therapy and persist for up to 6 months after complete therapy, due to the long half-life of the drug. Terbinafine has potent and extensive fungicidal activity against dermatophytes, especially T. rubrum, T. mentagrophytes, but has low fungistatic activity against Candida spp., compared with azole derivatives. Oral terbinafine is generally well tolerated. Surveillance studies show the most common side effects are on the gastrointestinal tract (49%) such as nausea, diarrhea, or taste disorders, and dermatological reactions such as rash, pruritus, urticaria, eczema, liver side effects are low. Terbinafine is not recommended for onychomycosis in children cases. Oral terbinafine has minimal drug interactions, especially with drugs that metabolized by the P450 2D6 isoenzym cytochrome.[8,11]

Itraconazole fights against fungi from dermatophytes, yeasts, and molds. The Minimum of Inhibitory Concentration (MIC) is 10 times greater than terbinafine, but not as active as terbinafine against dermatophytes. In general itraconazole is fungistatic but can become fungicidal by increasing the concentration to 10 times of MIC. The mechanism of action of itraconazole is similar to other azole derivatives, by inhibiting the P450 cytochrome oxidase mediating the ergosterol synthesis that is required for fungal cell wall synthesis. Itraconazole is absorbed optimally along with food and acidic pH. It is lipophilic and metabolized in the liver by the P450 cytochrome 3A4 system, which increases the risk of interaction with other drugs metabolized through this pathway. Itraconazole dose that can be administered is 200 mg/day for 12 weeks continuously or 400 mg/day pulse therapy for 1 week per month. Fingernails onychomycosis is recommended to be used two periods pulsation therapy and toe nails given three periods of pulse therapy. Similar to terbinafine, itraconazole has rapid penetration into the nail and can be detected one week from the start of administration, and persists in the nail up to 6-9 months after the therapy is stopped. The most common side effects of itraconazole are headache, and gastrointestinal disorders. The side effects will be lower when given with pulse therapy. Abnormalities of liver function occur in 1.9% of patients treated with itraconazole with pulsation method and 3% at a daily dosage. Hepatitis is common in continuous therapy usually after 4 weeks of therapy. Monitor liver function is recommended in patients with previous liver disorders, who receive continuous therapy for more than one month, and use other hepatotoxic drugs. Itraconazole is a contraindication to patients with congestive heart disease because of the increased risk of negative inotropes. Itraconazole may prolong the QT interval and co-administration of other drugs may increase the QT interval.[8,17]

Fluconazole is less effective than terbinafine and itraconazole in the treatment of onychomycosis, but it is a choice when patients do not tolerate other oral antifungal agents. The minimal dosage of fluconazole should be 150

mg/week for at least 6 months. Fluconazole can still be detected on toe nails 6 months after the therapy is stopped. Fluconazole can fight dermatophytes and candida. Although there is no license for the use of fluconazole for cases of onychomycosis, the study is still conducted with emphasis on the use of dosage of 450 mg once a week. This may be possible given the pharmacokinetic ability, and with weekly dosages will be able to improve adherence and decrease the cost of therapy. There have been several studies comparing the effectiveness of fluconazole with itraconazole and terbinafine, but the results show that fluconazole is less effective than both drugs. The most common side effects of fluconazole are headache, skin rash, gastrointestinal disorders, and insomnia. Fluconazole is a lower inhibitor of P450 cytochrome compared to itraconazole, resulting in little interaction with other drugs.[8,9,16]

Griseofulvin and ketoconazole were the first group of systemic antifungals but no longer used for the treatment of onychomycosis because of some reasons such as long duration of therapy, low clinical and mycologic cure rates, high probability of relapse within 2 years and potentially significant side effects. High risk of hepatotoxicity in long-term use of ketoconazole makes its use limited in the USA and Europe.[8,13]

Griseofulvin is a fungistatic agent which works by inhibiting nucleic acid synthesis, stopping cell division, and inhibiting fungal cell wall synthesis. Griseofulvin is the only licensed antifungal agent for children with onychomycosis, recommended dosage for age 1 month and above is 10 mg/kg body weight/day, along with fatty foods to increase absorption and support bioavailability. For adults, the recommended dosage is 500-1000 mg/day for 6-9 months for fingernail infection and 12-18 months for toenail infection. Contraindications for griseofulvin are pregnancy and men who plan to have children 6 months after therapy because according to an experimental study in mice, it had significant effects to the sperm. A study comparing the use of griseofulvin, terbinafine, and itraconazole showed a lower improvement for griseofulvin. Griseofulvin has several limitations including low effectiveness, long duration of therapy, greater drug interaction risk, while on the other side there are new antifungal agents with higher availability. For these reasons, the use of griseofulvin is no longer recommended for onychomycosis cases.[8,11]

ANTIFUNGAL COMBINATION THERAPY

Although monotherapy exhibited short-term effectiveness, the substantial proportion of patients does not show complete recovery forever. The use of antifungal combinations and synergistic exploitation has been performed in the field of mycology. Combination therapy is one of the ways to improve the rate of healing and overall improvement of onychomycosis cases completely.8,12,13

The combination of two antifungals can provide several advantages such as improving the effectiveness and speed of therapeutic improvements, enhancing the broader antifungal spectrum, better resistance suppression, tolerability and patient safety. This advantage is often attributed to the synergistic effects of drugs. In this context, synergism can be defined as the use of a combination of two antifungals will have a better effect than the use of both drugs individually.[4]

Combined regimens may be sequentially or paralleled. Sequential therapy means that the combination is given separately. The first drug is given for a certain duration and then followed by second drug afterwards. Parallel therapy means simultaneous combination of both drugs. There is no election guideline when sequential therapy and parallel therapy are used. Parallel therapy is recommended for the patients who are expected to experience treatment failure, for example in patients with onychomycosis with diabetes. Sequential therapy is recommended for patients with minimal response to therapy, such as patients with positive culture after 3-6 months of therapy.[4,13]

Two Oral Antifungal Combination Therapy

Onychomycosis caused by dermatophytes, molds, and yeasts shows differential susceptibility to the oral systemic treatments. This differential susceptibility to antifungals suggests that a combined therapy of oral treatments might be more effective against mixed infection or resistant fungi.[18]

There were two studies about oral antifungal combination itraconazole and terbinafine in the management of onychomycosis by dermatophytes in toenails. The first study is showed the continued combination therapy (sequential), while the other study showed a parallel combination. Sequential therapy with itraconazole and terbinafine for 12-16 weeks showed a higher cure rate than the terbinafine pulse therapy alone. Combination therapy of itraconazole and terbinafine paralel in short duration (6 weeks) showed results that were comparable with sequential therapy terbinafine or itraconazole pulse therapy for 12 weeks. These data are indicated the advantages of combination therapy depending on the length of the therapy period.[18]

On the other hand, the prospective study by Gupta in April 1996 until December 2004 compared the four treatment groups: the first group was Itraconazole 200 mg/day for weeks 1 to 4 and terbinafine 250 mg/day for weeks 3 to 6 (2-week overlap of itraconazole and terbinafine); second group was continuous terbinafine 250 mg/day for 12 weeks; third group with intermittent terbinafine (250 mg/day for 4 weeks on, 4 weeks off, 4 weeks on); forth group with pulsed itraconazole (one pulse 200 mg twice daily for 7 days on, 21 days off) for three pulses. Mycological recurrence showed 57% in the first group, 32% in the second group, 36% in the third group, and 59% in the fourth group.[19]

Combination Oral and Topical Antifungal

The combination of oral and topical antifungal therapy will provide the increas penetration effect on the infected tissue, which when given separately will not accumulate at effective concentrations. Rapid oral therapy accumulates on the nail bed, whereas effective topical therapy penetrates the nail plate and the lateral borders but not the deeper layers of the nail, therefore in combination therapy there will be two-way penetration of the nail plate by topical agents and on the nail bed by oral agents and prevent reinfection. Combination therapy with oral and topical antifungals has been shown to lead to a marked improvement of mycological and clinical outcomes, may be more cost effective, reduce duration, also minimize the side effect of systemic treatment.[3,4,18]

Systemic treatment that is widely used for combination treatment are terbinafine and itraconazole, while topical agent usually used are amorolfine and ciclopirox, eventhough some studies also reported another combintion agent. In vitro studies have shown that the use of itraconazole and amorolfine combinations in some dermatophyte and non-dermatophyte strains will show synergistic and additive effects, with no antagonistic effects. The explanation of the synergism effect of these two drugs is not known clearly.[18]

Study by Lecha in 2001 used itraconazole 200 mg/day for 12 weeks and in combination with 5% amorolfine once-weekly for 24 weeks. Combination therapy is showed a higher cure rate (93.9%) than monotherapy (69%).[20]

Another study from Rigopoulos in 2003 revealed that higher complete cure of patient with combination amorolfine 5% (weekly for 6 months) and 400 mg itraconazole (daily for 1 week on/3 weeks off for 2 months), than itraconazole alone (93% and 81%). The subjects of this study were onychomycosis patients >50% surface area involvement.[21]

The effectiveness combination of terbinafine and amorolfine are demonstrated in 2001 by Baran study with 147 patients with severe onychomycosis in the nail. Terbinafine and amorolfin for 12 weeks are showed better healing (72.3%) than monotherapy terbinafine (37.5%). Randomized controlled studies on onychomycosis dermatophytic therapy in the nail matrix are showed that 5% amorolfine in combination with oral terbinafine 250 mg per day for 3 months were more effective than the terbinafine monotherapy at the same time.[22]

Avner in 2005 used 250 mg terbinafine daily for 4 months alone and compared it with 250 mg terbinafine daily for 4 months combination with 8% ciclopirox daily for 9 months. This study is showed higher complete cure rate in combination therapy (68%) than terbinafine alone (50%). Mycological cure also higher in combination group (88%), while 65% in monotherapy group.[23]

Another evaluation is performed by Gupta in 2005 with treatment groups was similar to the previous studies, but with fewer patients over longer periods, resulting in greater mycological outcomes in combination groups than in single terbinafine. The results are obtained were 66.7% (14/21) in the first group (terbinafine 250 mg/day (4 weeks of therapy - 4 weeks stop - 4 weeks of therapy) ciclopirox combination 8% daily for 48 weeks), 70.4% (19/27) in the second group (terbinafine for 12 weeks ciclopirox combination 8% daily for 48 weeks), and 56.0% (14/25) in the third group (terbinafine 250 mg/day for 12 weeks). The results of this study are showed that p value is not significant.[24]

Jaiswal used three arm groups: first with 250 mg terbinafine twice daily for 1 week/month for 4 months; second group terbinafine with addition 5% amorolfine weekly for 4 months; and the third group terbinafine combination with 8% ciclopirox daily for 4 months. The result is showed that mycological cure for first group was 82.6%, while second group 70%, and third group 83.3%.[25]

Baran in 2007 is compared 250 mg terbinafine daily for three months with addition 5% amorolfine weekly for 15 months, and is showed higher complete cure in combination group than terbinafine alone.[26]

Even though griseofulvin no longer used in treatment onychomycosis, the combination of griseofulvin with amorolfine showed a greater effectiveness is compared to griseofulvin with placebo. Research using 233 samples are showed mycological improvement in 67% of patients with combination therapy and 45.3% for griseofulvin monotherapy group. Positive culture was found in 7.4% of patients with combination therapy, while single griseofulvin was 34.7%. The clinical cure for combination therapy groups was twice as high as the number of patients with griseofulvin monotherapy.[4]

One gram of griseofulvin in daily combination of tioconazole 28% solution was being compared to one gram griseofulvin and placebo for 1 year in the bilateral onychomycosis patients by Trichophyton rubrum. Each patient received combination therapy on one side of his leg and a placebo for the other side. Clinical and mycological improvement in combination therapy was 69%, while in griseofulvin and placebo 41%.[4]

Some literatures are said that topical treatment administration as additional therapy any systemic antifungal agent, should continue for at least 1 year and, if necessary, up to 18 months which could produce a better clinical outcome that reflects true nail pathology.[27–30]

SUMMARY

The combination of antifungal agents with different pharmacological effects is thought to improve the success of the therapy. Combination therapy will exploit the strength of each antifungal agent to achieve simultaneous treatment success. In addition, by working mechanisms of two different drugs, it improves the effectiveness and speed of therapeutic improvement, enhanced broader antifungal spectrum, better resistance suppression, tolerability and patient safety.

In vitro studies had been proven that the use of an antifungal combination has a synergistic effect, which will improve the effectiveness of therapy compared to monotherapy. However, direct clinical trials in several studies have shown mixed results, making it difficult to draw conclusions.

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