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Effectiveness of Antifungal Treatment for Onychomycosis

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ABSTRACT
Onychomycosis is a prevalent fungal infection of the nails, which causes thickening, discoloration, and detachment of the nail bed. The condition is mainly caused by various fungal species, including dermatophytes, yeasts and molds. Treatment of onychomycosis is complex, with antifungal drugs playing a key role. This research aimed to evaluate the effectiveness of various antifungal treatments, both topical and systemic, in managing onychomycosis. This research used a descriptive qualitative approach, using secondary data through documentation analysis. Data were triangulated to increase reliability and validity. The findings showed that the effectiveness of antifungal treatment varied depending on the type of drug, duration of treatment, and patient compliance. Systemic antifungals, such as terbinafine and itraconazole, showed higher cure rates compared to topical treatments such as ciclopirox and amorolfine. However, all treatments had high relapse rates, underscoring the need for continuous monitoring and customized therapy. The implications of this research demonstrate the importance of personalized treatment plans and the development of strategies to prevent relapse, which remains a significant challenge in the management of onychomycosis.

Keywords: Antifungal, Treatment, Onychomycosis.

INTRODUCTION

Onychomycosis, or fungal nail infection, is when a fungus infects one or more nails. This infection can affect both hand and toenails, but is more common in toenails (Leung et al., 2020). Onychomycosis is often caused by different types of fungi, including dermatophytes, yeasts, and other molds. Risk factors include age, excessive sweating, a history of fungal infections, and medical conditions such as diabetes or a weakened immune system (Thappa, 2007).

The incidence of onychomycosis increases with age due to several contributing factors. Decreased blood circulation in the extremities in older adults can weaken the body's ability to fight off infections. Additionally, nails grow more slowly with age, reducing the chances of naturally clearing the infection. Medical conditions such as diabetes and poor circulation, which are more common in older adults, further increase the risk of developing onychomycosis. Preventive measures include keeping feet clean, wearing appropriate footwear, avoiding damp

environments, and properly trimming nails. It is also advisable to consult a healthcare professional promptly if an infection occurs(Anugrah, 2016)

Several treatment options are available, including oral, topical, and device antifungals. Oral antifungals have higher cure rates and shorter treatment periods than topical treatments but have adverse side effects such as hepatotoxicity and drug interactions. Terbinafine, itraconazole, and fluconazole are most commonly used, and new oral antifungals such as fosravuconazole have been evaluated. Topical treatments, such as efinaconazole, tavaborole, ciclopirox, and Amorolfine, have less serious side effects but also have a lower cure rate and more extended treatment regimens (Gupta & Paquet, 2015).. Oral and topical drug delivery systems are the most desirable in treating onychomycosis. However, the efficacy of the results is low, resulting in a 25-30% relapse rate (Aggarwal et al., 2020). The treatment options for onychomycosis that have been approved by the Food and Drug Administration (FDA) include the use of antifungal drugs both systemically and topically (Axler & Lipner, 2024).

Previous research conducted (by Westerberg and Voyack, 2013) stated that the treatment of onychomycosis aims to eliminate the organisms causing the infection and restore the nail to a normal appearance. Systemic antifungal drugs are considered the most effective, with a meta-analysis showing mycotic cure rates of 76% for terbinafine, 63% for itraconazole with pulse dosing, 59% for itraconazole with continuous dosing, and 48% for fluconazole. The addition of nail debridement can improve the healing rate. While topical therapy using ciclopirox is less effective, with a failure rate of more than 60%. Several non-prescription treatments have also been tested. Laser and photodynamic therapies show potential based on in-vitro evaluation but require more clinical research. Even with treatment, the recurrence rate of onychomycosis remains between 10% to 50%, caused by re-infection or incomplete mycotic healing.

The increasing incidence of onychomycosis, particularly among older adults and individuals with predisposing conditions such as diabetes, underscores the urgent need for more effective treatment options. Despite advances in antifungal therapy, high relapse rates and cases of treatment resistance are still significant challenges. This highlights a critical gap in understanding the mechanisms of resistance to antifungal treatments and the strategies necessary to prevent recurrence. In Indonesia, no studies have yet focused specifically on these issues, particularly in examining the mechanisms of drug resistance in onychomycosis treatment and developing localized strategies to mitigate recurrence rates. This research is urgently needed to address these gaps and provide more comprehensive insights into managing this condition in Indonesia.

The novelty of this research lies in understanding the mechanism of resistance to antifungal drugs as well as developing strategies to overcome onychomycosis recurrence. The novelty of this research lies in the in-depth understanding of the mechanisms of resistance to antifungal drugs as well as the development of strategies to overcome the recurrence of onychomycosis.

Based on the above background, this research aims to evaluate the effectiveness of various antifungal treatments in managing onychomycosis, including analysis of how drug resistance

develops and what strategies can be taken to prevent recurrence of infection. There has been no similar research conducted in Indonesia that explicitly examines the mechanism of antifungal drug resistance and strategies for managing onychomycosis recurrence locally. This research has the benefit of making a significant contribution to the development of science in the health sector, especially related to the management of fungal infections of the nails. By evaluating the effectiveness of antifungal treatment and understanding the mechanisms of resistance, this research is expected to provide more precise recommendations in the selection of effective antifungal therapy. In addition, the results of this research are also expected to help medical practitioners in formulating strategies to prevent recurrence of onychomycosis, which has been a major challenge in the treatment of this infection.

RESEARCH METHOD

This research uses a qualitative descriptive method. Descriptive qualitative research is a research that focuses on answering research questions about what, who, where, and how a phenomenon occurs until it is analyzed in depth to form patterns present in the phenomenon (Yuliani, 2018). The data source used in this research is secondary data with documentation data collection techniques. Documentation is a data collection technique that collects data from various documents or other written materials related to the research. Documentation that can be used can be in the form of reports, books, notes, or other official sources (Ardiansyah et al., 2023). This research's analysis was carried out using triangulation. Triangulation in qualitative data analysis increases the validity and reliability of research findings by combining various data sources, methods, or perspectives. The aim is to gain a deeper and more comprehensive understanding of the phenomenon being studied.

RESULT AND DISCUSSION

The leading cause of onychomycosis has long been reported to be various types of fungi, such as dermatophytes, nondermatophyte molds, or yeasts. Some of the non dermatophyte molds often found to cause infection are *Aspergillus spp., Scopulariopsis spp., Alternaria spp., Acremonium spp., and Fusarium spp.,* which are responsible for 2-25% of all onychomycosis cases (Mahariski et al., 2023). This condition is common and can cause the nails to become thick, brittle, discolored, or flake off.

Moreover, onychomycosis is not only an aesthetic issue. It can also cause physical discomfort in the form of pain in the infected nail. This condition can impact one's psychosocial well-being, lowering self-confidence and affecting quality of life. If not appropriately treated, onychomycosis can also pave the way for secondary infections, worsening the health condition. Therefore, people with onychomycosis need appropriate treatment to address this problem effectively (Axler & Lipner, 2024).

Treatments with antifungal properties are the first line in addressing onychomycosis (Latupeirissa, 2016). These treatments aim to eradicate the fungus causing the infection and aid healthy nail growth. This treatment can be done using antifungal medications, either taken orally or applied directly to the nail (topical) (Leelavathi & Noorlaily, 2014). The first oral antifungal treatment is taken in capsule or tablet form. These drugs are more potent and usually used to treat more severe infections or if topical treatments do not produce the desired results. The following are some of the types of oral treatments used for onychomycosis:

Griseofulvin Medicine

Griseofulvin was the first oral antifungal drug approved by the FDA in 1959 to treat onychomycosis (Axler & Lipner, 2024). Although it used to be the first choice, its popularity has declined due to its longer treatment duration, lower effectiveness, and higher relapse rates compared to other oral antifungal drugs. Griseofulvin is absorbed through the gastrointestinal tract and targets the keratinized structures of the skin, which explains its success in treating dermatophytosis and onychomycosis infections (Carmo et al., 2023).

The drug griseofulvin works by being absorbed by the newly growing nail, thus requiring continuous treatment during nail growth (Axler & Lipner, 2024). Because of this, Griseofulvin is usually prescribed for long periods, with a recommended daily dose of between 500-1000 mg for 6-9 months for hand nails and 12-18 months for toenails, depending on the rate of nail growth (Olson & Troxell, 2021). This long duration of treatment often creates problems in terms of patient compliance, which tends to be low.

Itraconazole Drug

The FDA approved Itraconazole in 1995 for treating onychomycosis caused by dermatophytes. The drug exhibits broad-spectrum activity against dermatophytes, non-dermatophyte fungi, and candida species (Axler & Lipner, 2024). Reported complete cure rates were 47% for hand nails and 14% for toenails, while mycological cure rates reached 61% for hand nails and 54% for toenails (Falotico & Lipner, 2022).

Itraconazole is an antifungal of the triazole group that is lipophilic and keratinophilic, with a mechanism of action that inhibits ergosterol synthesis through inhibition of the cytochrome P450 enzyme 14-alpha-demethylase, thereby affecting the integrity of the fungal cell membrane. Pulse therapy with itraconazole is effective for treating onychomycosis, with the required duration of treatment for toenail infections being 3-4 months (Mamuaja et al., 2017). The dose of itraconazole used is a pulse dose of 2 x 200 mg per day for seven days, followed by a 3-week break, performed as two pulses for the fingernails and 3-4 pulses for the toenails (Gupta & Paquet, 2015).

Terbinafine Drug

Terbinafine is currently considered the most effective oral antifungal drug for treating onychomycosis, with reported overall cure rates of 59% for fingernails and 38% for toenails, and mycological cure rates of 79% for fingernails and 70% for toenails (Falotico & Lipner, 2022).

Terbinafine is a synthetic allylamine that acts by competitively inhibiting the enzyme squalene epoxidase, which interferes with ergosterol synthesis and causes intracellular accumulation of squalene, exerting a fungicidal effect (Bhatia et al., 2019).

In vitro, terbinafine exhibits broad-spectrum antifungal activity against dermatophytes. Also, it has some activity against yeasts and non-dermatophytic fungi (Axler & Lipner, 2024). The recommended dose of terbinafine is 250 mg daily for 6 weeks for the treatment of hand nail onychomycosis and 12 weeks for toenails. The use of pulsed dosing may also be considered, given the pharmacologic properties of terbinafine that remain in the nail for several weeks after cessation of treatment (Leelavathi & Noorlaily, 2014).

Fluconazole Medicine

Fluconazole is an alternative that can be used to treat onychomycosis. However, it requires a longer treatment time than itraconazole and only gives moderate results (Leelavathi & Noorlaily, 2014). Fluconazole is a drug from the triazole group that works by inhibiting the enzyme lanosterol 14α-demethylase. It is approved for treating onychomycosis in Europe and China and is used off-label in the US. Fluconazole is effective against dermatophytes, *Candida spp*., as well as some non-dermatophytic fungi (Falotico & Lipner, 2022).

Fluconazole has several advantages over itraconazole, such as absorption, which is not affected by stomach pH or food. This treatment only requires weekly dosing and can be used in patients with additional medical conditions, including cardiac disorders. In a research (Falotico & Lipner 2022), a randomized, double-masked trial was conducted in 362 patients who received fluconazole 150, 300, or 450 mg once weekly. The complete cure rates for toenails after 12 months were 37%, 46%, and 48%, respectively, with a low % relapse rate of 4% six months after treatment.

Meanwhile, in addition to oral treatment, onychomycosis can be treated with topical antifungals, usually creams or ointments applied directly to the infected nail. This topical treatment is effective for mild to moderate cases of infection. The first topical antifungal medication used was Amorolfine 5% nail polish. Amorolfine 5% nail polish is a morpholine derivative that inhibits the synthesis of ergosterol, an essential component of the fungal cell membrane. The drug gained approval in Europe in 1991 and has been approved for treating onychomycosis in several countries, such as Australia, Brazil, Russia, Germany, and the UK. However, Amorolfine is not approved for use in onychomycosis in the United States or Canada (Axler & Lipner, 2024). Amorolfine is effective against various types of fungi, including dermatophytes (such as *Trichophyton spp., Microsporum spp., and Epidermophyton spp*.), yeasts (such as *Candida spp., Cryptococcus spp., and Malassezia spp*.), as well as some types of molds and other pathogenic fungi. However, it is ineffective against bacteria, except for Actinomyces (Tabara et al., 2015).

In a retrospective research involving 53 cases of Neoscytalidium dimidiatum-associated onychomycosis treated with twice-weekly Amorolfine 5% nail polish, 89.3% of the patients

achieved mycological cure, and 50% achieved complete cure within an average time of 112 to 176 days (Bunyaratavej et al., 2016). The use of Amorolfine once weekly is also thought to improve patient compliance compared to cyclopyrox, which must be applied daily.

Secondly, another antifungal drug is Cyclopyrox 8%. Cyclopyrox is a hydroxy-pyridone derivative that has been researched since 1973. However, its use in varnish form only started in the 1990s. It is available in various formulations, such as creams, suspensions, shampoos, gels, solutions, powders, and globules. It is used to treat skin, scalp, and onychomycosis infections (Tabara et al., 2015).

Cyclopyrox exerts antifungal effects by binding trivalent cations such as Fe^{3+} and Al^{3+}, which inhibit enzymes that require these metals. The drug has broad antifungal activity, being effective against dermatophytes (such as *Trichophyton spp., Microsporum spp*., and *Epidermophyton floccosum*), yeasts (including *Candida spp., Malassezia furfur, Cryptococcus neoformans,* and *Saccharomyces cerevisiae*), as well as molds such as Aspergillus spp., Scopulariopsis brevicaulis, and Fusarium solani. In addition, cyclopyrox has also been shown to be effective against a wide range of bacteria, including Gram-positive (such as *Trichophyton spp., Microsporum spp.,* and *Epidermophyton floccosum*) and Gram-negative (such as *Escherichia spp., Proteus spp., Klebsiella spp., Salmonella spp., Shigella spp., Bacillus spp.,* and *Pseudomonas spp.*) bacteria, as well as Mycoplasma and Trichomonas vaginalis (Tabara et al., 2015).

The drug shows activity against dermatophytes, non-dermatophyte fungi, and Candida both in vitro and in vivo. Ciclopirox has a seven times higher fraction of unbound keratin and a better rate of keratin release than Amorolfine, which contributes to better nail penetration and higher fungicidal activity (Axler & Lipner, 2024).

Third, another antifungal drug is tavaborole, a boron-based molecule that works very specifically as an inhibitor of fungal protein synthesis. The drug targets the LeuRS enzyme in fungi, which disrupts tRNA function and inhibits fungal protein synthesis. Tavaborole 5% topical solution was approved by the FDA in 2014 for treating mild to moderate onychomycosis and is applied once daily for 48 weeks (Jinna & Finch, 2015). In two studies involving 1,198 participants, tavaborole 5% solution was shown to be more effective than placebo in achieving mycological cure (RR = 3.40; 95% CI, 2.34 to 4.93; high-quality evidence) and complete cure (RR = 7.40; 95% CI, 2.71 to 20.24; moderate-quality evidence) (Rey et al., 2021). In vitro studies show that tavaborole is effective against various types of fungi such as *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Epidermophyton floccosum*, *Microsporum audouinii*, *Malassezia furfur*, *Candida albicans*, *Fusarium solani*, and *Aspergillus fumigatus* (Elewski & Tosti, 2014).

These onychomycosis treatments, either oral or topical, can be an alternative option for treating this infection. However, the effectiveness of antifungal treatment for onychomycosis often varies and is affected by each individual's specific condition. There are reasons why antifungal therapy is sometimes unsuccessful, including the fact that current treatment options

for onychomycosis are limited, and treatment failure and disease recurrence are frequent (Mahariski et al., 2023).

Onychomycosis patients (10-53%) may experience recurrence or recurrent infections after treating the initial infection. Some of the factors that contribute to the high rate of recurrence or recurrent infection include genetic predisposition to onychomycosis, improper diagnosis at the start of therapy, presence of non-dermatophyte fungal infections, mixed infections (dermatophytes and non-dermatophytes), pharmacokinetic and pharmacodynamic properties of antifungals, comorbidities such as diabetes or HIV, presence of biofilms, as well as the presence of dormant fungal reservoirs (*arthroconidia*) under the nail that are resistant to antifungals (Mahariski et al., 2023).

The effectiveness of treatment may vary depending on the type of fungus causing the infection, the duration of treatment required, and how the individual responds to therapy, which may vary from one person to another. Suppose oral and topical treatments are impossible, especially in severe cases. In that case, doctors may recommend alternative therapies that involve the use of specialized devices, such as laser therapy, surgical removal of the nail (avulsion), scraping of the infected part of the nail (debridement), or a combination of different treatment methods (Falotico & Lipner, 2022). (Falotico & Lipner, 2022). This suggests that the treatment of onychomycosis requires a flexible approach tailored to each patient's specific condition.

CONCLUSION

Based on the research's results, the effectiveness of antifungal treatments for onychomycosis can be determined by evaluating the various types of treatments available, topical and systemic. These treatments aim to eradicate the fungal infection that causes onychomycosis, which is often characterized by discoloration, thickening, and nail breakage. The effectiveness of treatment may vary depending on the type of fungus causing it, the duration of treatment, as well as the individual's response to therapy. It is important to periodically monitor the patient's progress and adjust the therapy regimen if needed to optimize results and prevent the recurrence of the infection. This research is expected to make a sustainable contribution to the development of onychomycosis treatment, especially in understanding more about the mechanism of fungal resistance to antifungal therapy. In the future, the results of this research can be the basis for further research that focuses on developing new antifungal drugs that are more effective and have fewer side effects. In addition, this research also opens up opportunities to conduct long-term clinical research on the prevention of onychomycosis recurrence through more adaptive and personalized treatment strategies based on patient conditions.

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