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Original Research

A Retrospective Study on Toenail Onychomycosis: Efficacy of Combination Therapy and Correlating Factors to Washout Time

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A B S T R A C T

Onychomycosis in the toenail is a common fungal infection. Moderate to severe onychomycosis, especially, may persist chronically with a considerable recurrence rate that can be a challenge for management. Oral antifungal therapy is the current gold standard to treat for moderate to severe toenail onychomycosis. However, there are alternative combination modalities including topical agents and/or procedural modalities that are emerging because of potential adverse effects of oral antifungals and to prevent recurrence. In this study, oral terbinafine with debridement combination therapy had the shortest washout time. Factors that were related to longer washout times were female sex, extreme body mass index, and diabetes.

Onychomycosis, a fungal infection of the fingernails or toenails, is a common, global disorder that is estimated to account for 50% to 60% of abnormal nails[1] and can result in significant morbidity.[2] Toenails are 7 times more likely to be affected than fingernails[3] because of their slower growth, reduced blood supply, and exposure to moist environments.[4] It is estimated that the worldwide prevalence of onychomycosis will rise as predisposing factors become more prevalent.[5] The identified predisposing factors include diabetes, advancing age, trauma, a history of tinea pedis, and immunosuppression, among others.[6] Diabetes is considered an independent risk factor for onychomycosis as a condition contributing to poor peripheral circulation with one third of patients with diabetes affected.[7]

Onychomycosis is a chronic infection caused by dermatophytes, nondermatophyte molds, and yeasts that can be difficult to treat.[8] Clinical signs of this condition include nail discoloration, hyperkeratosis, and onycholysis.[8] Clinical cure refers to the improvement of the appearance of the nail, often defined as a normal appearance of 80% to 100% of the nail.[4] Various treatment modalities are available for the management of onychomycosis. The most common therapies for onychomycosis include oral and topical antifungals, often used concomitantly with physical treatments such as clipping, debridement, and so on.[9] Onychomycosis treatment should take into account the severity of the toenail condition and the characteristics and preferences of the individual patient for best outcomes while avoiding undesirable side effects.

Background and Significance

Oral antifungal therapy is currently considered the gold standard treatment option for moderate to severe onychomycosis because it is delivered through systemic distribution into the nail bed.[9] Twelve weeks of treatment with oral terbinafine and itraconazole is the United States Food and Drug Administration—approved oral antifungal therapy.[10] Among the 2, terbinafine daily dosing is considered the primary choice for oral treatment and is preferred over itraconazole.[10] Although oral medications are generally efficacious, there are safety concerns such as drug-drug interactions, smell/taste disturbances, allergic reactions, and possible liver toxicity.[10]

Topical antifungal therapy can effectively treat mild to moderate onychomycosis, particularly when patients adhere to treatment instructions. They are relatively safe with no potential for drug-drug interactions.[11] However, topical monotherapy requires longer treatment courses (often 48 weeks or longer) than oral therapy.[10] Tavaborole 5% solution, ciclopirox 8% nail lacquer, and efinaconazole 10% solution are the Food and Drug Administration—approved topical antifungal medications that require 48 weeks of once-daily application for the treatment of onychomycosis in the US.[11]

Combination treatments with oral medications, topical medications, and/or a procedural modality (e.g., laser or debridement) have been considered in cases in which poor responses to monotherapy are expected, there is greater than 50% to 60% nail involvement, or there are more than 3 affected nails.[12] Nail debridement (partial removal) as a treatment modality was found to be useful, especially in severe onychomycosis, by reducing fungal mass and increasing the penetration of antifungal treatment.[3] In a randomized controlled trial, a combination of debridement and a topical antifungal agent resulted in better (77%) mycological cure than debridement alone (0%).[13] It is theorized that combination therapy with systemic oral antifungal therapy, topical agents, and periodic debridement may produce better results than systemic

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medication alone.[14] However, research on combination antifungal therapy and procedural modalities for onychomycosis is sparse, and the most recent reviews date from 1999 to 2006.[12] Although periodic thorough debridement is unlikely to clear onychomycosis, it was found to improve immediate patient satisfaction and aid the efficacy of other medications that were concurrently used.[14]

In a systematic review of onychomycosis clinical trials, Falotino et al[12] reviewed 30 different clinical trials that involved combination therapies with medication only as well as medication and procedural therapy combined. The authors concluded that there were conflicting results, a lack of robust design and sufficient follow-up, costs, and safety concerns associated with combination therapy; therefore, they recommended combination therapy as a second-line treatment option in patients with poor prognostic factors or for those who failed monotherapy for onychomycosis.[12] In addition, the understanding of the current literature lacks evaluation of the combination therapy of oral antifungal agents and topical antifungal agents along with nail debridement. This study fills this current gap in knowledge.

Onychomycosis can have a significant impact on quality of life and will progress if left untreated.[15] With millions of dollars being spent annually to treat onychomycosis with different types of treatment modalities, it is obvious that people are bothered by the clinical manifestations and are determined to get rid of them. Although toenail fungal infection is not life-threatening, it has enormous morbidity, and management requires an interprofessional approach to emphasize patient education on the drug therapy and behavior commitment.[14]

Different approaches to treat toenail onychomycosis have been attempted, and combination therapy is clinically being practiced. Although combination therapy being more efficacious in treating toenail onychomycosis compared with monotherapy is theoretically proven, there is a lack of evidence regarding the recommended combination modalities, efficacy depending on the severity of the disease, treatment duration for clinical cure (or complete washout), and factors that affect the washout time. This retrospective study aims to evaluate the efficacy of combination therapies and factors that affect the washout time of severe onychomycosis.

Methods

Study Design

This study was a retrospective chart review study design that was performed at a podiatric medical practice located in the State of New Jersey. The patient charts that were reviewed were office visits between January 1, 2020, to December 31, 2021, a duration of 2 years. Approval to conduct the study was obtained through the institutional review board at the second author's institution. In addition, the site approval was acquired from the practice administrator. The university's institutional review board and the podiatric medical practice granted approval before the data collection began.

Study Population

The inclusion criteria for chart review were consistent with the *International Classification of Diseases, Tenth Revision, Clinical Modification* diagnosis code B35.1 (tinea unguium) with a severe clinical presentation and patients between 18 and 79 years of age. Clinical presentation of the involvement of more than 6 toenails with greater than 76% of each toenail area involved was defined as severe disease. The exclusion criteria were patients under 18 years old and over 80 years old and presenting with mild to moderate clinical toenail onychomycosis. Three hundred patient charts were initially reviewed using the diagnosis code B35.1, and 57 charts met the inclusion criteria.

Study Procedures

The purpose of this study was to evaluate factors such as age, sex, and comorbidities, and to examine the efficacy of the different combination therapies that affected the treatment outcome, which was evaluated with washout time, on adult patients receiving combination therapy who were clinically diagnosed with severe toenail onychomycosis. Although recent articles suggested that combination therapy for toenail fungal infection is necessary to attack the fungus from above and below the nail plate, it was noted that adding debridement can better target nonpenetrable areas from the surface areas.[16] This study used toenail debridement in all therapies. Debridement of a mycotic toenail was performed with an electric grinder and manually using a straight nail nipper, which involves the removal of the diseased toenail plate in thickness and length to reduce the bioburden of the fungal presentation. The 4 combination therapies, either double or triple methods, included the following: 1) debridement plus oral terbinafine, 2) debridement and oral terbinafine plus tolnaftate, 3) debridement and oral terbinafine plus efinaconazole, and 4) debridement and oral terbinafine plus tea tree oil. In addition, there were "other" therapies explored that used debridement with or without other topical agents.

The factors evaluated in this study that affected the treatment outcome for patients receiving combination therapy to treat severe toenail onychomycosis were demographic data and preexisting conditions such as diabetes mellitus (DM) and body mass index (BMI).

Data Analysis

Data were collected using a data collection checklist created for the study, transferred to an Excel (Microsoft) spreadsheet, and then transferred to SPSS Version 28 (IBM Corp) for data analysis. As seen in Table 1, the demographic data included sex, the age of the patient, and clinical factors of a history of DM type 1 or 2 and BMI. As described in Table 2, the mean washout time in months as a treatment outcome was examined in categories including sex, age, a history of DM, BMI, and different modes of combination therapies.

Table 1
Baseline Demographic and Clinical Characteristics (N = 57)

Characteristics	Number of Patients (%)
Sex	
Male	22 (38.6)
Female	35 (61.4)
Age (y)	
18-29	6 (10.5)
30-39	4 (7)
40-49	7 (12.3)
50-59	8 (14)
60-69	18 (31.6)
70-79	14 (24.6)
Clinical factors	
History of diabetes	16 (28.1)
Nondiabetic	41 (71.9)
BMI 19-24	6 (10.5)
BMI 25-30	21 (36.8)
BMI 31-35	18 (31.6)
BMI 36-43	12 (21.1)

BMI = body mass index.

Table 2
The Mean Washout Time in Months by Characteristics

Characteristics	Washout Time (mo)	P Value
Sex		.39
Female	7.27	
Male	5.15	
Age (y)		.14
18-29	3.16 (F: 3.0, M: 3.3)	
30-39	10.37 (F: 12.8, M: 3.0)	
40-49	4.42 (F: 5.7, M: 2.6)	
50-59	6.25 (F: 7.0, M: 4.0)	
60-69	8.11 (F: 10.0, M: 5.9)	
70-79	5.74 (F: 4.9, M: 7.7)	
Clinical factors		
Diabetes		.78
History of diabetes	6.7	
Nondiabetic	6.35	
BMI		.43
BMI 19-24	9.24 (F: 9.25, M: NA)	
BMI 25-30	6.21 (F: 6.7, M: 5.5)	
BMI 31-35	5.6 (F: 3.0, M: 3.2)	
BMI 36-43	6.75 (F: 6.1, M: 7.6)	
Therapy type		.001
DT (n = 21)	4.88 (F: 6.3, M: 3.3)	
DTC (n = 12)	6.5 (F: 8.2, M: 4.1)	
DTE (n = 3)	7.6 (F: 6.5, M: 10.0)	
DTT (n = 6)	11.25 (F:15.8, M: 6.6)	
Others (n = 15)	6.46 (F: 5.5., M: 10.0)	

P value indicates the statistical significance between the variables and washout time of each characteristic.
BMI = body mass index; DT = debridement plus oral terbinafine; DTC = debridement and oral terbinafine plus tolnaftate; DTE = debridement and oral terbinafine plus efinaconazole; DTT = debridement and oral terbinafine plus tea tree oil; F = female; M = male; NA = not applicable.

The specific focus examined was the mean washout time in months of the 4 combination therapies (either double or triple methods).

Results

All patients treated were clinically diagnosed with severe onychomycosis by the physician based on the patient's presentation and observation of the toenail; therefore, washout times were determined by clinical observation of the clearance of toenail fungal infection and diminished associated symptoms.

Demographic Data

The sample size was 57 subjects ranging from 18 to 79 years old. Approximately 61% (n = 35) were men, with 70.2% (n = 40) being 50 years or older. DM was reported in 16 of the subjects, with 41 reporting being nondiabetic. Twenty-one subjects used 1 of the 3 triple combination therapies, and 21 subjects used the double combination therapy. Fifteen patients used alternate therapies, which were determined by the ease of use and convenience with a lack of consistency in the treatment modality; therefore, they were not included in the data analysis for treatment outcome measures.

Influence of Sex and Age on Washout Time

This study found that men achieved shorter washout times than women. Only 66% of women compared with 88% of men achieved a washout time of 6 months or less, leaving women with a longer washout time. With three quarters of the study sample over 49 years old, trends in age were difficult to determine. Age did not show any statistically significant findings regarding washout time ($P = .14$). Fifty-seven percent of patients over the age of 60 years compared with 43% of those below the age of 60 years achieved a washout time less than 6 months, although older subjects with high BMIs did obtain some of the highest washout times. All patients from 18 to 29 years old (n = 6) had washout times below 4 months.

Influence of BMI and a History of Diabetes on Washout Time

BMI was grouped into the following 4 categories: low (19-24), low-medium (25-30), medium (31-35), and high (36-43). With no clinical or statistical significance, women with a lower BMI reported the longest washout times among the 4 BMI categories, whereas men with a high BMI reported the longest washout times. For subjects over 50 years old with a BMI of 30 or above, 30% had washout times over 7 months. With one quarter of the patients reporting a history of DM (n = 16), washout times were only slightly longer for diabetics (6.7) compared with nondiabetics (6.35) without statistical significance ($P = .78$).

Influence of Therapy Type on Washout Time

The Kruskal-Wallis test revealed a statistically significant difference in washout times across the 4 therapy types (χ^2_4 [n = 57] = 18, $P = .001$): debridement plus oral terbinafine (n = 21, mean = 4.8), debridement and oral terbinafine plus tolnaftate (n = 12, mean = 6.5), debridement and oral terbinafine plus efinaconazole (n = 3, mean = 7.6), and debridement and oral terbinafine plus tea tree oil (n = 6, mean = 11.2). As described in Table 2 and the Figure, using a double-therapy mode (ie, debridement plus oral terbinafine) showed a significantly shorter washout time (4.88) compared with other combination therapies. A washout time within 5 months occurred in 86% of patients receiving double therapy, which appeared to be favored in patients $\geq$ 50 years old as well as in younger patients.

Discussion

Why Do Women Have Longer Washout Times Than Men?

Historically, in patients with mild to moderate severity of onychomycosis, female patients have shown better outcomes for the treatment of toenail onychomycosis compared with male patients.[17] According to Rosen,[18] females tended to be more compliant with treatment than males. The study reported a treatment compliance rate of females at 93.4% compared with males at 88.6%.[18] Overall, this resulted in a shorter time to be cured of onychomycosis for female patients.[2,18,19] As they age, men tend to have a higher prevalence of onychomycosis with less adherence to treatment.[18] In this study, women with severe onychomycosis showed a longer washout time compared with male patients. Consistent with these findings was reporting from the physician that women were more compliant in completing the topical treatment as recommended after the initial triple therapy and the desire to achieve a complete cosmetic cure. In addition, it was noted that the use of soaps, creams, or lotions has the ability to elevate pH, causing a disruption in the barrier, although this is transient.[20,21] The use of creams and lotions on feet beyond the therapy to treat the toenail onychomycosis by women may be a potential factor that contributed to longer washout times. However, further investigation is needed.

Why Do Nondiabetics Have Similar Washout Times as Diabetics?

DM has been reported as a critical comorbidity to onychomycosis. About one third of diabetic patients have reported onychomycosis as their limb condition after DM has been diagnosed.[2,12] Overall, onychomycosis can be a limb-threatening infection if it is left untreated.[2] This study reported that there is no statistically

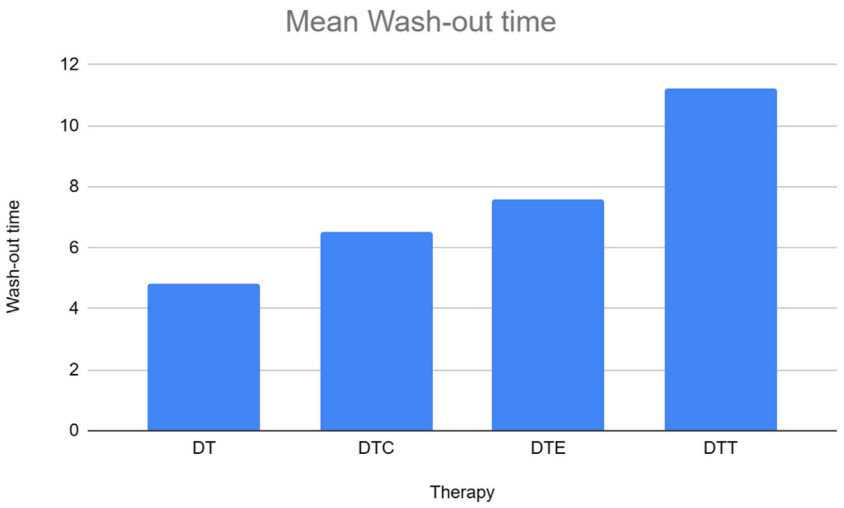

Figure. The mean washout time in months by therapy type. DT, debridement plus oral terbinafine; DTC, debridement and oral terbinafine plus tolnaftate; DTE, debridement and oral terbinafine plus efinaconazole; DTT, debridement and oral terbinafine plus tea tree oil.

significant difference in washout time between diabetic and nondiabetic patients with onychomycosis caused by differing invading organisms.[2] Likewise, the current study showed no statistically significant difference in washout time between diabetic and nondiabetic patients with onychomycosis, but the difference in invading organisms was not measured. Future larger-scale studies are recommended to determine if there is a difference in invading organisms between nondiabetic and diabetic individuals and the impact of the microbe difference.

On the contrary, Akkus et al[19] identified that fungal infections such as onychomycosis significantly increased in patients with diabetes compared with patients without diabetes. It is known that fungal infections are frequently observed with poor glucose control and peripheral vascular disease in diabetic patients, and the presence of fungal infections is believed to be the result of the development of foot ulcers in the diabetic patient.[19] This study only included severe onychomycosis, whereas the evidence reported study samples with mild to moderate severity. These findings warrant repeating this study in a larger and randomized sample on the influence of the diabetic condition as a comorbidity of different severity levels of onychomycosis.

Why Is There an Inconsistency in Washout Time for BMI Categories?

Although BMI has been recognized as one of the public health problems, little is known about its impact on the prevalence of onychomycosis or its outcomes. Commonly, there is a positive relationship between the onset of onychomycosis and obesity.[2,12,22] Consistent with the current study findings, although not citing a rationale, in this study, toenail onychomycosis washout times were longer in patients with an extreme BMI, high and low, possibly consistent with existing comorbidities[23] or the loss of protective immune responses.[24] In addition, Chan and Chong[25] reported that obesity with vascular disease and diabetes was one of the most prevalent predisposing factors among patients with fungal nail infections.

Study Limitations and Future Study Directions

Although the current evidence showed that females tended to have shorter washout times than their counterparts,[1] this study showed contradictory results. Careful interpretation is required because the sample was collected retrospectively, and it was a nonrandomized sample. The limited sample may not have been generalizable. In addition, the existence of potential causes, such as higher compliance and effort in preventing the recurrence of disease, the desire to achieve complete cure for cosmetic reasons, and high pH changes related to foot lotion use in women should be further considered for the longer washout times.

Our study suggests that double combination therapy (debridement and oral terbinafine) provided a shorter washout time compared with the triple combination therapies that included a topical agent. A repeat of the study in a prospective study design with randomized sampling using a larger sample size is warranted.

Conclusion

Debridement of the toenails was a consistent treatment for all 4 measured modalities to treat severe onychomycosis. The gold standard oral terbinafine therapy combined with debridement showed the shortest washout time for severe onychomycosis in our studied population. A triple therapy consistent with debridement and oral terbinafine plus tolnaftate provided a clinically significant washout time compared with other multitherapies.

Sex as a predictor of washout times proved to be inconsistent with some other studies but was considered to be associated with some unique factors related to women. In addition, for women, longer washout times may be associated with comorbidities; hormonal fluctuations; work-associated injuries; the use of soaps, creams, or lotions elevating the nail pH; and overuse. The higher toenail pH may favor the production of fungal spores including *Trichophyton rubrum*, one of the most common causes of onychomycosis.[26]

Age was not a consistent predictor of washout times, although it was identified that increasing age increased washout times, especially for men. Although persons with diabetes had a longer washout time, there was no statistically significant difference in washout time between diabetic and nondiabetic individuals. It could be theorized that differences in the invading organisms affecting the diabetics and nondiabetics may have influenced the effectiveness of treatment. Washout times were longer in extremes of BMI, low and high.

Currently, there are many treatment options for onychomycosis, including debridement in combination with oral and topical

antifungal agents, procedural modalities, complementary therapies, and natural home remedies. A study by Cheung et al[27] indicated that among natural home remedies, a foot soak into warm to hot diluted vinegar solution for 15 to 30 minutes daily has been one of the methods used to treat superficial toenail onychomycosis. Clinically, individuals either take a white vinegar foot soak or an apple cider vinegar foot soak and mix it with warm water for daily soaking. Although not clear, it has been suggested that the acidity of the vinegar (pH = 2-3) may have fungicidal activity.[27] The authors concluded that vinegar is theoretically efficacious in eradicating toenail fungal infection but may jeopardize the epidermal barrier because of its acidity, especially in individuals with sensitive skin.[27] The limitation is that it is unlikely that a vinegar foot soak on its own will eradicate severe toenail onychomycosis.[27]

The severity of the onychomycosis determines the management plan; however, when it comes to the combination therapy in treating severe clinical presentation, there seems to be a lesser consensus to the exact protocol. Further studies need to be conducted to understand the effectiveness of topical agents in treating toenail onychomycosis in combination with oral terbinafine and understand the relationship between the characteristics of an individual in their prognosis with related therapy.

Declaration of competing interest

In compliance with standard ethical guidelines, the authors report no relationships with business or industry that would pose a conflict of interest.

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