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HEPATIC SAFETY OF ORAL TERBINAFINE IN ONYCHOMYCOSIS: IS ROUTINE MONITORING OF LIVER FUNCTION TESTS NECESSARY?

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Abstract

Objectives: Onychomycosis is the most common disease of the nail treated commonly with oral antifungals mainly with terbinafine, itraconazole, and fluconazole. Given concerns regarding the potential hepatotoxic effects of systemic antifungal therapy, our study aims to investigate the hepatic safety profile of terbinafine in patients with onychomycosis.

Materials and Methods: A retrospective study was carried out at our dermatology clinic between October 2024 and February 2025. 150 patients (aged 18–65 years) with onychomycosis, who underwent liver function tests before and after two months of terbinafine (250 mg daily) treatment were included. Patients with known renal, liver, biliary, or pancreatic diseases, abnormal baseline liver function tests, or potential drug interactions were excluded. Aspartate transaminase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transferase (GGT) were analyzed. P-values < 0.05 are considered as a level of significance.

Results: 52 (34.7%) of the patients were female 98 (65.3%) were male, and the mean age was 48.53 ± 7.85 years. The mean age for females was 49.38 ± 7.73 years and 48.07 ± 7.91 years for males (p = 0.329). The mean ALT values were 30.74 ± 11.94 IU/L pre-treatment and 32.41 ± 12.15 IU/L post-treatment (p = 0.169). AST values were 26.45 ± 10.46 IU/L pre-treatment and 28.17 ± 8.60 IU/L post-treatment (p = 0.055), while GGT levels were 35.21 ± 13.65 IU/L pre-treatment and 35.87 ± 13.35 IU/L post-treatment (p = 0.084).

Conclusion: After two months of treatment, oral terbinafine did not cause significant alterations in laboratory values among patients with onychomycosis. Based on our limited patient sample and short follow-up duration, baseline liver function testing may not be necessary in otherwise healthy patients; however, further prospective studies are needed to confirm this finding.

Keywords: Onychomycosis, liver, terbinafine.

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Introduction

Onychomycosis (OM) is a chronic infection of the nail plate and nail bed, caused mainly by dermatophytes, less frequently molds other than dermatophytes, and rarely yeasts.[1] As the most prevalent nail disease, OM is considered for over half of nail pathologies, and its global prevalence is approximately 5.5 %, varying depending on geographic and population-based factors.[2, 3] Clinically, OM manifests as nail discoloration, hyperkeratosis, and detachment of the nail bed. It is observed more frequently in males than in females, and the likelihood of occurrence increases significantly with advancing age. [4] Multiple risk factors contribute to the development of OM, including diabetes, peripheral arterial pathologies, psoriasis, immunosuppressive condition, concomitant tinea pedis, tobacco smoking, repetitive nail trauma or traumatic nail conditions, use of occlusive footwear, sports participation, peripheral neuropathies, and other traumatic nail conditions.[3] The infection can be transmitted via direct contact or through fomites contaminated with the keratin or skin scales of infected individuals.[1] OM can considerably impair the quality of life, both due to cosmetic deformities and their psychological implications.[5]

OM treatment is often delayed or avoided because of the prolonged treatment duration, costs, and the potential adverse effects associated with systemic antifungals.[6] Oral treatments, mainly terbinafine, less commonly itraconazole, and fluconazole, are the first choices for OM treatment due to their high efficacy and accessibility. However, these medications may have some adverse effects: terbinafine may rarely lead to gastrointestinal upset, hepatotoxicity, gustatory and visual alterations, and rashes—all usually self-limiting. Itraconazole shares a similar side effect profile, including upper respiratory tract infections and gastrointestinal discomfort. Fluconazole use is frequently associated with gastrointestinal discomfort and other adverse events are myalgia, dizziness, paresthesia, QT prolongation, agranulocytosis, gustatory disturbances, and drug eruptions. Additionally, elevated liver enzymes and hepatotoxicity were reported previously with fluconazole, terbinafine, and itraconazole use.[7,8,9] Nonetheless, adverse effects of systemic antifungal medications are mild, transient, and reversible with the cessation of the drug in general.

Standard dosing of OM includes 250 mg daily terbinafine, and 200 mg daily itraconazole with a duration of 6 weeks for fingers or 12 weeks for toes, with itraconazole also available with a pulse dosing option. Fluconazole is also used for OM treatment 150 mg/week for 6 to 9 months for fingers, and 12 to 18 months for toes.[10]

A meta-analysis has shown that asymptomatic elevation in transaminases occurs in approximately less than 2% of patients receiving oral antifungals, and half of those required treatment discontinuation. As such, liver function monitoring is recommended at baseline and again one month after initiating treatment.[11]

Despite terbinafine's widespread use and general safety profile, there is a gap in knowledge regarding the necessity of routine liver function test monitoring during treatment. Current guidelines suggest baseline and follow-up testing, yet the clinical value of these recommendations in asymptomatic patients without liver disease remains unclear. This uncertainty highlights the need for updated real-world data on the hepatic safety of terbinafine.

In this study, changes in liver function tests before treatment and at the second month of treatment will be examined in patients receiving terbinafine due to onychomycosis, and the effect of terbinafine treatment on these changes will be investigated. In this way, the study will contribute to the literature regarding the necessity of routine liver function test monitoring in patients receiving terbinafine treatment.

Materials and Methods

This retrospective study is performed in the dermatology clinic between October 2024 and February 2025 with the approval of the ethics committee (number: 1-24-601 date: 25/09/2024). Onychomycosis-diagnosed patients prescribed with terbinafine 250 mg daily were screened from the database. Patients aged between 18 and 65 years who underwent blood tests both before and during the second month of terbinafine treatment were included in the study. Patients with a diagnosis of onychomycosis through clinical evaluation and/or potassium hydroxide (KOH) examination were enrolled. Patients with known renal, hepatic, biliary, or pancreatic diseases, those with abnormally elevated liver function tests before treatment, and those taking medications known to interact with terbinafine and pregnant individuals were excluded from the archive screening. Additionally, patients who did not have venous blood drawn after at least 8 hours of fasting were excluded from our study.

Age, gender, known diseases, and chronic medications were obtained from the hospital's database. Laboratory values of aspartate transaminase (AST), alanine aminotransferase (ALT) levels, and GGT (gamma-glutamyl transferase) were retrospectively evaluated before and after the second month of therapy. The normal range was 5-30 IU/L for AST, 4-36 IU/L for ALT, and 6-50 IU/L for GGT.[12] Patients with elevated levels of ALT, AST, or GGT before or during therapy are referred to internal medicine.

A power analysis was conducted to determine the required sample size for evaluating pre- and post-treatment changes in liver function tests using paired t-tests. Assuming a medium effect size (Cohen's d= 0,5), a significance level adjusted for multiple comparisons (Bonferroni correction; $\alpha = 0{,}0167$), and a desired statistical power of 95 % ($1-\beta = 0{,}95$), the minimum required sample size was calculated as 54 patients. The

analysis of the data was performed with SPSS 26.0 (IBM, Armonk, NY). The data distribution was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests as appropriate. Categorical data were presented as counts and percentages. Laboratory parameters and continuous variables were expressed as mean and standard deviation. To compare laboratory values before and after treatment, the paired t-test was applied for normally distributed data, while the Wilcoxon signed-rank test was employed for those not meeting normality assumptions. Pearson correlation analysis was used for the evaluation of correlations between age and laboratory values. A p-value of lower than 0.05 is considered a threshold for statistical significance.

Results

In total, 150 patients prescribed oral terbinafine were eligible for the study, with 52 females (34.7%) and 98 males (65.3%). The mean age of the population was 48.53 ±7.85 years (range: 22–67). The mean age for females was 49.38 ±7.73 years, while for males it was slightly lower at 48.07 ±7.91 years; however, this was not considered a statistically significant difference (p = 0.329). Among the 150 patients, 28 had diabetes mellitus (18.7%), 31 had hypertension (20.7%), and 18 had venous insufficiency (12.0%). The mean ALT value was 30.74 ±11.94 before treatment and 32.41 ±12.15 after treatment, with no significant difference between them (p = 0.169). The mean AST value was 26.45 ±10.46 before treatment and 28.17 ±8.60 after treatment, and the difference was also not statistically significant (p = 0.055). The mean GGT value was 35.21 ±13.65 before treatment and 35.87 ±13.35 after treatment, with no statistically significant difference observed (p = 0.084). The changes in the laboratory values are presented in Table 1. No significant difference was observed between genders in liver function tests before and after treatment (Table 2). No correlations were found between patient age and ALT, AST, and ALT values (p= 0.074, 0.684, and 0.625, respectively). Adverse effects included gastrointestinal upset in 14 patients, altered taste sensation in 10 patients, headache in 6 patients, and tinnitus in 1 patient.

Table 1. Laboratory changes in liver enzymes after the second month of terbinafine therapy

	Before treatment	The second month of treatment	p-value
ALT	30.74±11.94	32.41±12.15	0.169
AST	26.45±10.46	28.17±8.6	0.055
GGT	35.21±13.65	35.87±13.35	0.084

AST: Aspartate transaminase; ALT: alanine aminotransferase, GGT: gamma-glutamyl transferase.

Table 2. Comparison of liver enzymes between genders before and after therapy

	Before treatment			After treatment		
	Women (n=52)	Men (n=98)	p-value	Women (n=52)	Men (n=98)	p-value
ALT	32.4±12.5	29.8±11.6	0.210	32.7±11.4	32.3±12.5	0.839
AST	26.2±10.7	26.6±10.3	0.812	28.4±8.4	28.0±8.7	0.797
GGT	32.3±12.0	36.8±14.2	0.056	33.1±11.8	37.3±13.9	0.068

AST: Aspartate transaminase; ALT: alanine aminotransferase, GGT: gamma-glutamyl transferase.

Discussion

This study demonstrated that oral terbinafine therapy did not lead to any clinically significant hepatotoxicity in patients with onychomycosis. Although mild increases in AST and ALT levels were observed in some patients, none of these elevations exceeded three times the upper limit of normal, and no cases required treatment discontinuation due to liver-related adverse effects. These findings support the growing evidence suggesting that serious liver injury from terbinafine is rare and often idiosyncratic.

While severe drug-induced liver injury (DILI) is uncommon, a retrospective analysis of the United Network for Organ Sharing (UNOS) liver transplant registry, covering approximately 51,000 transplants between 1990 and 2002, identified only 492 cases of medication-related acute liver failure requiring transplantation in adult and pediatric patients. Notably, none of these cases were attributed to terbinafine.[13]

DILI remains the main cause of post-marketing drug withdrawal, with individuals suffering from conditions such as nonalcoholic fatty liver, hepatitis C, iron overload, cholestasis, or alcohol use being at greater risk.[14] While terbinafine has been associated with hepatotoxicity, its underlying mechanism remains poorly understood.[15] A study performed by Chalasani et al. documented 300 DILI cases, among which terbinafine was implicated in 4 cases, while no cases were associated with griseofulvin.[16] Similarly, another study by Kao et al., among patients using oral antifungals observed that 8 among 18,677 patients treated with griseofulvin, and 2 among 12,376 patients treated with terbinafine had DILI.[17]

According to a study by Fontana et al., terbinafine hepatotoxicity is uncommon but can present with significant liver injury in susceptible individuals, particularly those with the HLA-A*33:01 allele which is more prevalent

among Caucasian and African American patients.[18] However, the overall incidence of severe liver injury remains low.

Stolmeier et al. performed a retrospective study assessing the utility of laboratory monitoring in patients taking terbinafine. They found that the frequency of elevated ALT and AST were low and comparable to baseline values, suggesting that routine liver enzyme monitoring may not be necessary without a history of pre-existing liver conditions.[19]

Kramer and Albrecht reviewed cases of severe liver injury associated with terbinafine and observed that most patients were symptomatic, presenting with abdominal distress, malaise, and jaundice. They found no evidence supporting the utility of routine liver function test monitoring in asymptomatic patients.[20] In addition to this study, Etgü has observed that patients with onychomycosis who were prescribed either terbinafine or itraconazole showed no signs of hepatotoxicity.[21]

In a meta-analysis encompassing 19,298 immunocompetent patients, treatment discontinuation due to adverse events was reported in 3.4% of patients receiving terbinafine, 2.6% with the pulsed regimen of itraconazole, and 4.2% with daily itraconazole therapy. Furthermore, no association was found between extended duration of terbinafine use and elevated risk of liver injury.[11] This finding may reinforce the notion that adverse reactions to oral antifungal agents are largely idiosyncratic, typically emerging within the initial weeks of therapy and showing no linear relationship with treatment duration.

Certain populations are more prone to terbinafine-induced liver toxicity. In a previous review, of 24 cases of terbinafine-related acute liver injury, more than 90% of affected individuals were over 40 years old, and most of these patients were taking the drug for three to four weeks. The majority of cases are resolved following drug discontinuation and/or appropriate medical management.[22] Preexisting hepatic disorders are considered an important risk factor for terbinafine-induced liver toxicity.[19]

A retrospective study by Wang et al which involves 944 patients undergoing terbinafine therapy for onychomycosis found that isolated elevations in AST and ALT accounted for approximately 90% of liver test alterations, respectively. These findings suggest that monitoring ALT alone, along with baseline testing, could detect most hepatic changes and reduce monitoring costs.[23]

This study has some limitations. First, its retrospective design limits the ability to establish causality. Second, the lack of long-term follow-up prevents the evaluation of delayed hepatotoxicity. Third, the relatively small sample size may limit the generalizability of the findings. Lastly, the absence of genetic data, such as HLA typing, restricts the assessment of individual susceptibility to terbinafine-induced liver injury.

Laboratory testing is a convenient and rapid method for family physicians and dermatologists to obtain objective data. In today's clinical setting, where time limitations and medicolegal concerns are increasingly prominent, lab tests offer a practical approach to exclude serious complications. However, abnormal lab findings are frequently clinically insignificant. Controlled studies have shown that even widely used over-the-counter drugs like acetaminophen can cause frequent, asymptomatic lab abnormalities—often at rates exceeding those seen with terbinafine and griseofulvin in this study—which typically resolve upon cessation of the drug.[24] There is a growing tendency among physicians to prioritize lab results over thorough history-taking and physical examination. Additionally, hepatotoxicity associated with terbinafine is considered idiosyncratic. Due to the rare and unpredictable nature of severe DILI, routine liver enzyme monitoring lacks reliability as a screening method. Tests with normal range do not rule out the risk of future idiosyncratic reactions, and minor abnormalities rarely require clinical action.

In conclusion, this study evaluated liver enzymes before and after terbinafine therapy and revealed no significant differences in liver enzyme levels. This finding aligns with existing literature that suggests terbinafine-associated hepatotoxicity is relatively rare and often idiosyncratic.

Ethical Considerations: The study was approved by the local Ethics Committee on 25/09/2024 (number: 1-24-601). This study was prepared following the principles of the Declaration of Helsinki.

Conflict of Interest: The authors declare no conflict of interest.

**** This manuscript was mentioned as a poster presentation at the Indercos Dermatology Congress.***

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