A pharmacovigilance study of terbinafine indication and liver enzyme elevation

To the Editor: Terbinafine is a commonly administered oral and topical antifungal medication. Terbinafine oral treatment regimens are based on the site of infection; nail infections often require a 6 to 12-week treatment schedule, but non-nail (ie, skin or hair) infections can usually be treated for 2 to 6 weeks. While it is commonly regarded that terbinafine-induced liver injury occurs within 30 days,[1] we hypothesize that indications necessitating longer treatment durations are more likely associated with liver injury/liver enzyme elevation (LEE) events. To analyze this question, we computed a reporting odds ratios (ROR) using drug-event reports extracted from both the FDA Adverse Drug Event Reporting System (FAERS) and Canada Vigilance Adverse Reaction Online (CVARO) databases. It is important to highlight that one of the limitations of these commonly used databases is that the data entered by physicians or pharmaceutical companies is not corroborated or confirmed independently.

Raw database files were downloaded from: https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html (USA) and https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-database/canada-vigilance-online-database-data-extract.html. The FAERS database included reports logged between January 1, 2014, and December 31, 2020. The CVARO database included all publicly available reports from 1965 to September 2021 inclusively. To capture all terbinafine-associated drug reports, we searched both databases using "%terbinafine%" and "%lamisil%" (% represents a wildcard modifier) terms. Additionally, we made sure to exclude topical terbinafine preparations from the search results. Adverse events are encoded in both databases using MedDRA's list of accepted terminologies. There was a total of 21,034 and 3913 oral terbinafine-associated adverse drug reaction reports in both the FAERS and CVARO databases, respectively. Notably, 247 (FAERS) and 125 (CVARO) of these reports were related to LEE events. Unfortunately, the degree of LEE (eg, 2-fold vs. 100-fold) or its clinical significance is not detailed in the databases. Furthermore, details on other possible interacting medications that patients might be taking are not available from these sources. Following data extraction, the ROR, a classically accepted method of signal generation for common adverse drug reactions in pharmacovigilance studies, was computed.[2,3] Table I demonstrates the RORs for terbinafine and LEE events and is further stratified by indication. Isoniazid, a well-known hepatotoxic agent, was used as a comparator to better contextualize the magnitude of terbinafine-LEE associated RORs.

Table I. ROR for terbinafine-LEE reports according to indication

Variables assessed	FAERS ROR (CI)	CVARO ROR (CI)
Terbinafine-LEE Reports Non-Onychomycosis	1.71 (1.07-2.72)	1.51 (0.37-6.09)
Terbinafine-LEE Reports Nail Infections	4.58 (3.84-5.46)	4.51 (2.64-7.68)
Isoniazid-LEE Reports	5.35 (5.06-5.67)	5.51 (5.00-6.07)

RORs are listed for terbinafine and onychomycosis and non-onychomycosis indications. In brackets are each ROR's confidence intervals. FDA adverse event reporting system and Canada Vigilance Adverse Reaction Online RORs are listed in their respective columns.
CVARO, Canada Vigilance Adverse Reaction Online; *FAERS*, FDA Adverse Drug Event Reporting System; *LEE*, liver enzyme elevation; *ROR*, reporting odds ratio.

Terbinafine-LEE RORs were more than 2-fold higher for onychomycosis versus non-onychomycosis (ie, skin and nail) infections in both FAERS and CVARO databases (Table I, Supplementary Table I, available via Mendeley at https://doi.org/10.17632/n8pkb4tzyz.1). Additionally, onychomycosis-indicated LEE RORs more closely approximated isoniazid-LEE RORs compared with non-onychomycosis-LEE RORs in both databases, possibly suggesting a greater likelihood of LEE and liver injury with longer terbinafine use.

Our analysis suggests a possible relationship between liver injury and longer usage of terbinafine, which is comparable to that of isoniazid, where older patients undergo monthly blood tests to evaluate for this idiosyncratic event.[4] As a result, we emphasize the importance of further investigating this potentially duration-sensitive adverse drug reaction, assessing its clinical significance and impact on patients to better direct clinicians in the safe prescribing of terbinafine in populations at higher risk of liver-related injuries and complications.

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Key words: adverse drug reaction; Canada Vigilance Adverse Reaction Online; dermatology; drug event reporting system; hepatotoxic; liver enzymes; pharmacovigilance; terbinafine.

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Conflicts of interest

None disclosed.

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