Antifungal Drugs caused Liver Damage & Death

A rare unpredictable idiosyncratic event

Jaundice, flulike symptoms, abdominal discomfort, and Itching

Eliot N Mostow MD, MPH

Severe, usually idiosyncratic, drug-induced liver injury (DILI) due to terbinafine is universally symptomatic and can lead to liver transplantation and death.[1] A large-scale cohort of 69,830 patients treated with oral antifungal agents estimates incidence rates of DILI to be 134.1, 10.4, and 2.5 per 100,000 person-months for ketoconazole, itraconazole, and terbinafine, respectively.[2]

This article was chosen to be our Story of the Week because it emphasizes the importance of listening to the patient, counseling the patient, and ordering lab tests based on the best available data. A cursory review of this article could lead the reader to surmise that more lab monitoring is needed since terbinafine can cause significant injuries and even death. Of course, we agree with the authors that the data tell a different story. The good news is that ordering liver function tests is not hopelessly expensive; but, as the authors state in their own comments, laboratory monitoring is not completely safe. They note that it conveys the belief to the patient that the testing has clinical utility and is somehow protective of symptomatic drug-induced liver injury.

A key take-home point is that all cases of terbinafine-induced hepatotoxicity were clinically symptomatic. Most of these patients had jaundice, flulike symptoms, abdominal discomfort, and pruritus. The authors could not find any specific point in time when laboratory monitoring would be ideal, especially for patients who were asymptomatic. In fact, they didn't find a single report of terbinafine-induced liver injury in an asymptomatic patient identified through laboratory screening.

I believe most dermatologists order labs for patients treated with terbinafine because they lump this medication with other onychomycosis medications that are associated with more significant hepatotoxicity (ketoconazole and itraconazole) Ketoconazole has even earned a black box warning from the FDA. Terbinafine-induced hepatotoxicity is a very rare idiosyncratic event, and there are other potential idiosyncratic events that can happen as well (eg, idiopathic thrombocytopenia). As the word idiopathic, or idiosyncratic, implies, we have no idea why this occurs.

In my practice, I like to minimize exposure to medication when possible. Although the FDA-approved method of treating onychomycosis is with continuous therapy for 3 months, there have been a number of articles that demonstrate the effectiveness of a variety of pulsed regimens. Ever since terbinafine became generic, I've prescribed 250 mg once daily for

1 week. Patients wait 3 weeks and repeat this treatment each month for a total of 4 weeks of treatment over 4 months. In the United States, this generally cost the patients $10 for their 28 tablets. As for blood monitoring, I ask them about hepatic symptoms to start, although I probably don't counsel them as much about idiosyncratic reactions as I should (but I'm going to start doing a better job on this, having been thinking about this article). Then I get a CBC and a comprehensive metabolic panel at baseline. The truth is that I am looking for an idiosyncratic reaction that might affect their white cell count or platelets, kidney, or liver. This is repeated at the end of the first week. Patients are instructed that there is no guarantee that they will not have a problem with the subsequent pulses, but it is comforting to know that they did not have a hypersensitivity (idiosyncratic) reaction on the first pulse. The cost of a CBC and a comprehensive metabolic panel is affordable for most patients even if they do have high deductibles or no insurance.

I recognize that the cure rate of pulsed dosing does not match that of continuous therapy, but recurrences are quite common even with continuous dosing; so, I favor a "minimalist" approach to onychomycosis. I do use continuous therapy for tinea capitis and more severe tinea corporis, monitoring bloodwork at baseline and then at 1 to 3 weeks. This may detect idiopathic reactions in these patients as well. Most importantly, all patients are instructed to call the office if they develop jaundice, abdominal pain, flulike symptoms, or pruritus. I have become convinced that monthly lab studies in all patients treated with antifungal drugs wastes healthcare dollars, gives patients a false sense of security, and is not warranted on scientific grounds. I am unsure if rank and file dermatologists will feel they can defend themselves in a court of law if a lawsuit occurs as a result of an idiosyncratic reaction.

References

1. US Food and Drug Administration. Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htmPublished July 2009. Accessed August 15,

2017.
2. Garcia Rodriguez LA, Duque A, Castellsague J, et al. A cohort study on the risk of acute liver injury among users of ketoconazole and other antifungal drugs. Br J Clin Pharmacol 1999; 48(6): 847-852. http://onlinelibrary.wiley.com/doi/10.1046/j.1365-2125.1999.00095.x/abstract