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Utility of Laboratory Test Result Monitoring in Patients Taking Oral Terbinafine or Griseofulvin for Dermatophyte Infections

Deirdre A. Stolmeier, MD; Hannah B. Stratman; Thomas J. McIntee, MD; Erik J. Stratman, MD

IMPORTANCE Terbinafine hydrochloride and griseofulvin are effective oral treatments for dermatophyte infections but have been associated with hepatic and hematologic abnormalities. The prevalence of alanine aminotransferase elevations, aspartate aminotransferase elevations, anemia, lymphopenia, and neutropenia among adults and children taking terbinafine and griseofulvin is unclear.

OBJECTIVE To measure the rate of laboratory test result abnormalities in healthy adults and children taking terbinafine or griseofulvin for dermatophyte infections.

DESIGN, SETTING, AND PARTICIPANTS This retrospective study assessed adults and children taking terbinafine or griseofulvin for dermatophyte infections from January 1, 2006, to December 31, 2016. Data were collected from one Midwest health care system. Exclusion criteria were preceding diagnosis of hepatic or hematologic condition and preceding or concurrent use of oral ketoconazole, amphotericin, or itraconazole.

MAIN OUTCOMES AND MEASURES The rates of elevated alanine aminotransferase measurements, elevated aspartate aminotransferase measurements, anemia, lymphopenia, and neutropenia in adults and children taking terbinafine, griseofulvin microsize, or griseofulvin ultramicrosize were calculated. Secondary measures included rates of baseline abnormalities, frequency of laboratory test results that required additional testing or discontinued use of medication, and laboratory test result monitoring practices.

RESULTS This study included laboratory data from 4985 patients (mean [SD] age, 42.8 [20.3] years; 2288 [45.9%] female) receiving 4309 courses of terbinafine, 634 courses of griseofulvin microsize, and 159 courses of griseofulvin ultramicrosize. We identified a low rate of laboratory test result abnormalities in patients taking terbinafine or griseofulvin. When laboratory test result abnormalities occurred, most were low grade (212 [93.4%] grade 1) and did not require subsequent laboratory test result evaluation or discontinued use of medication (15 051 [99.9%]). Elevations in alanine aminotransferase measurements were detected infrequently and were comparable to baseline detection rates (61 [3.5%] vs 95 [3.6%] for terbinafine, 2 [2.1%] vs 3 [3.7%] for griseofulvin microsize, and 0 vs 2 [5.0%] for griseofulvin ultramicrosize). Rates of elevated aspartate aminotransferase measurements, anemia, lymphopenia, and neutropenia were also infrequent and comparable to baseline rates.

CONCLUSIONS AND RELEVANCE In this study. the rates of alanine aminotransferase elevations, aspartate aminotransferase elevations, anemia, lymphopenia, and neutropenia in adults and children taking terbinafine or griseofulvin were low and equivalent to the baseline rates of abnormalities in this population. Routine interval laboratory test result monitoring appears to be unnecessary in adults and children without underlying hepatic or hematologic conditions taking terbinafine or griseofulvin for dermatophyte infections. Abandoning frequent laboratory monitoring can decrease unnecessary health care spending, decrease patient psychological angst associated with blood draws, and allow for expanded use of these effective oral medications.

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Supplemental content

Author Affiliations: Department of Dermatology, Marshfield Clinic, Marshfield, Wisconsin (Stolmeier, McIntee, E. J. Stratman); University of Wisconsin, La Crosse (H. B. Stratman).

Corresponding Author: Erik J. Stratman, MD, Department of Dermatology, Marshfield Clinic, 1000 N Oak Ave, Marshfield, WI 54449 (stratman.erik@marshfieldclinic.org).

Terbinafine hydrochloride and griseofulvin are effective oral treatment options for onychomycosis and widespread, resistant, and follicular-based dermatophyte infections.[1-3] Although generally well tolerated, terbinafine and griseofulvin have been reported to cause hepatic and hematologic laboratory test result abnormalities, including abnormal liver function test (LFT) results, anemia, lymphopenia, and neutropenia.[1-3] The prevalence of hematologic and hepatic abnormalities among patients taking terbinafine and griseofulvin for suspected dermatophyte infections is unclear, but previous studies[4-9] have found a low rate of LFT result abnormalities, suggesting routine laboratory test result monitoring may be unnecessary.

Many physicians check baseline laboratory test results on patients before prescribing griseofulvin and terbinafine therapy and order the monitoring of laboratory test results at various intervals during therapy. Package inserts are unclear regarding frequency of laboratory testing, offering recommendations such as testing before initiating treatment and periodically during therapy.[1-3] Physician desire to detect laboratory test result abnormalities early and to minimize potential patient harm drives continued testing, which increases health care costs and deters many from using these effective medications. The objective of this retrospective study was to measure the rate of monitoring laboratory test result abnormalities in a large population of children and adults taking oral terbinafine and griseofulvin for suspected dermatophyte infections to determine the value of laboratory test result monitoring in this population.

Key Points

Question What is the rate of laboratory test result abnormalities in healthy adults and children taking terbinafine or griseofulvin for dermatophyte infections?

Findings In this study of 4985 patients, alanine aminotransferase elevations, aspartate aminotransferase elevations, anemia, neutropenia, and lymphopenia were infrequently detected by monitoring laboratory test results, and rates were similar to baseline rates in our cohort. When laboratory abnormalities occurred, most were low grade and did not require additional laboratory tests or discontinued use of the medication.

Meaning Routine interval laboratory test result monitoring appears to be unnecessary in healthy adults and children taking oral terbinafine or griseofulvin for dermatophyte infections.

Methods

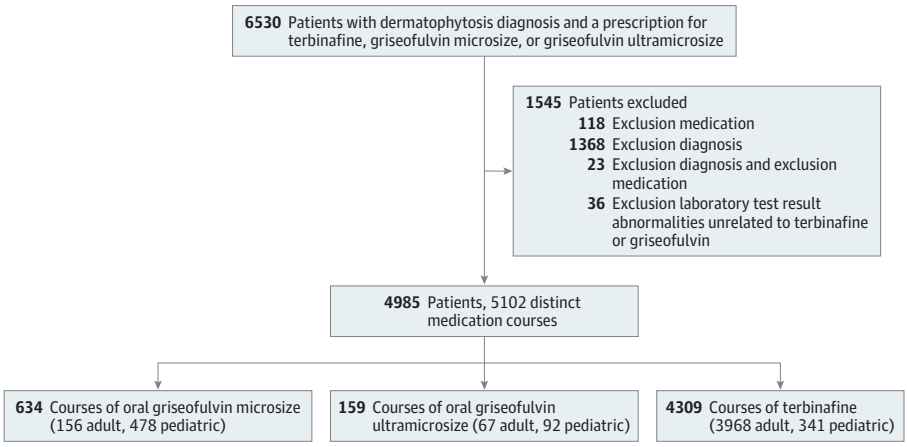
Patient cohort data were extracted from Marshfield Clinic Cattails electronic health records (EHRs). Patients seen at Marshfield Clinic from January 1, 2006, to December 31, 2016, with a diagnosed dermatophyte infection and prescription for oral terbinafine, griseofulvin microsize, or griseofulvin ultramicrosize were included. Inclusion criteria used *International Classification of Diseases, Ninth Revision* (*ICD-9*) and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* diagnosis codes for dermatophyte infections (*ICD-9* codes 110.0-110.9 and *ICD-10* codes B35.0-35.9). Medication courses were estimated by setting the date of first prescription as the start date and calculating an end date from the dosage, quantity, refill, and renewal information. In cases in which a record identified premature discontinuation of treatment, the discontinue date was used as the end of the course. The study was approved by the Marshfield Clinic Health System Institutional Review Board. No informed consent was required. Data were left identifiable as 10% of data, and all grade 2 or higher abnormalities were verified.

Medication courses were excluded if the patient had an *ICD-9* or *ICD-10* code corresponding to an exclusion criterion, including a preceding diagnosis of hepatitis, cirrhosis, primary biliary cirrhosis, primary sclerosing cholangitis, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, anemia, myelodysplastic syndrome, leukemia, or alcohol abuse. Medication courses were only excluded if the patient was diagnosed with an exclusion diagnosis before the medication course start date. Courses were also excluded if patients received prescriptions for oral ketoconazole, amphotericin, or itraconazole (3 antifungal medications well known to cause laboratory abnormalities) 3 months before starting or concurrently with oral griseofulvin or terbinafine therapy.

Laboratory records for alanine aminotransferase (ALT) measurement, aspartate aminotransferase (AST) measurement, hemoglobin measurement, neutrophil count, and lymphocyte count were recorded for each patient. These laboratory tests were selected for review based on monitoring recommendations in packaging inserts, reports of adverse effects, and recommendations on common resources, including UptoDate and Micromedex.[10-14] Laboratory test results were considered abnormal if they were outside the reference range of the laboratory at which the samples were drawn on the date the laboratory tests were performed, as indicated in the EHR by high or critical high for AST and ALT measurements and low or critical low for hemoglobin measurement, neutrophil count, and lymphocyte count. The Common Terminology Criteria for Adverse Events reference ranges were used to grade laboratory test result abnormalities (eTable in the Supplement).[15] Laboratory test results were considered baseline if they were drawn between 90 days before starting use of the medication to within the first week of the medication course. This time frame was selected because many physicians in our system will not redraw samples if patients have had laboratory tests just before starting use of the medication. In the case of multiple baseline laboratory test results, the result closest to the course start date was considered the baseline. Laboratory test results obtained 7 days after the course start date to the completion or discontinuation of medical therapy date were considered monitoring results. The results of all laboratory tests performed during the medication course, regardless of the ordering practitioner, were included to maximize the rate of abnormality detection.

Ten percent of the data were kept and all information manually verified (D.A.S. and H.B.S.) for quality assurance. For

Figure. Flowchart of Cohort Selection



In total, 6530 patients were initially identified through the electronic health record data query. Of these, 4985 patients with 5102 distinct medication courses were included in the analysis.

Table 1. Patient Characteristics[a]

Characteristic	Patients With Dermatophytosis Diagnosis (n = 6530)		
	Prescription of Interest (n = 4985 Patients, 5102 Courses)	Prescription of Interest and Baseline Laboratory Values (n = 2847 Patients, 3044 Courses)	Prescription of Interest and Monitoring Laboratory Values (n = 2023 Patients, 2125 Courses)
Age, mean (range), y	42.8 (0-95)	47.4 (1-95)	48.0 (0-89)
Pediatric patient courses	911 (18.2)	206 (6.8)	174 (8.2)
Female patients	2288 (45.9)	1369 (48.1)	823 (40.7)
Onychomycosis or tinea unguium[b]	4133 (81.0)	2909 (95.6)	2175 (102.3)
Tinea pedis	1302 (25.5)	818 (26.9)	595 (28.0)
Tinea manuum	178 (3.5)	113 (3.7)	92 (4.3)
Tinea cruris	383 (7.5)	196 (6.4)	132 (6.2)
Tinea corporis	1163 (22.8)	454 (15.0)	325 (15.3)
Tinea barbae or tinea capitis	574 (11.2)	139 (4.6)	130 (6.1)
Tinea, site unspecified	182 (3.6)	86 (2.8)	64 (3.0)
Deep dermatophytosis	27 (0.5)	17 (0.6)	11 (0.5)

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

[b] If patients were diagnosed with both onychomycosis and tinea unguium during 1 medication course, this outcome resulted in 2 diagnoses.

laboratory abnormalities graded at least grade 2, corresponding medical records were individually reviewed (D.A.S.) to evaluate for other clearly documented causes of laboratory abnormalities. Laboratory test result abnormalities were considered clinically actionable if additional laboratory tests were ordered or use of the medication was discontinued within 2 weeks of an abnormal laboratory test result. For all actionable laboratory test results, the corresponding medical records were individually reviewed (D.A.S.) to confirm that the action was caused by the laboratory test result abnormality and attributed to the medication.

The rates of interval ALT measurement elevation, AST measurement elevation, anemia, lymphopenia, and neutropenia were determined. Secondary measures included rates of baseline abnormalities, frequency of laboratory test results that required additional testing or discontinued use of medication, and laboratory test result monitoring practices. Descriptive statistics, including the mean, median, and range for continuous variables and the number and percentage for discrete data, were calculated.

Results

Cohort Selection

This study included laboratory data from 4985 patients (mean [SD] age, 42.8 [20.3] years; 2288 [45.9%] female). The initial query identified 6530 patients with a dermatophytosis diagnosis and prescription of interest. Of these patients, 1545 were excluded; 118 were excluded because of concurrent or recent use of exclusion medications, 1368 because of exclusion diagnoses, 23 because of exclusion diagnoses and exclusion medications, and 36 because of clearly documented causes of laboratory abnormalities unrelated to oral terbinafine or griseofulvin. Of the remaining 4985 patients, 4884 experienced a single medication course and 101 experienced multiple medication courses. This resulted in 4309 courses of terbinafine, 634 courses of griseofulvin microsize, and 159 courses of griseofulvin ultramicrosize (**Figure**). Patients included children and adults with a variety of dermatophyte infections (**Table 1**). Some patients had more than one diagnosis because of multiple sites

Table 2. Frequency of Laboratory Testing[a]

Test	Terbinafine (n = 4309)	Griseofulvin Microsize (n = 634)	Griseofulvin Ultramicrosize (n = 159)
Overall			
Patients with any baseline laboratory test result	2682 (61.2)	118 (18.6)	47 (29.6)
Patients with at least one monitoring laboratory test result	1862 (42.2)	118 (18.6)	43 (27.0)
Patients with baseline and monitoring laboratory test results	1376 (31.9)	48 (7.57)	26 (16.4)
ALT			
Patients with baseline ALT measurement	2642 (61.3)	81 (12.8)	40 (25.2)
Patients with monitoring ALT measurement	1720 (39.9)	96 (15.1)	31 (19.5)
Total No. of monitoring ALT measurements	4176	175	61
Mean No. of monitoring ALT measurements per patient with monitoring laboratory test results	2.43	1.82	1.97
AST			
Patients with baseline AST measurement	2388 (55.4)	77 (12.1)	36 (22.6)
Patients with monitoring AST measurement	1508 (35.0)	96 (15.1)	28 (17.6)
Total No. of monitoring AST measurements	3662	169	55
Mean No. of monitoring AST measurements per patient	2.43	1.76	1.96
Hemoglobin			
Patients with baseline hemoglobin measurement	1485 (34.5)	82 (12.9)	25 (15.7)
Patients with monitoring hemoglobin measurement	813 (18.9)	76 (12.0)	27 (17.0)
Total No. of monitoring hemoglobin measurements	2297	132	51
Mean No. of monitoring hemoglobin measurements per patient	2.82	1.74	1.89
Neutrophil count			
Patients with baseline neutrophil count	1275 (29.7)	68 (10.7)	24 (15.1)
Patients with monitoring neutrophil count	725 (16.8)	67 (10.6)	24 (15.1)
Total No. of monitoring neutrophil counts	1993	119	45
Mean No. of monitoring neutrophil counts per patient	2.75	1.78	1.88
Lymphocyte count			
Patients with baseline lymphocyte count	1275 (29.7)	68 (10.7)	24 (15.1)
Patients with monitoring lymphocyte count	716 (16.6)	70 (11.0)	24 (15.1)
Total No. of monitoring lymphocyte counts	1971	122	45
Mean No. of monitoring lymphocyte counts per patient	2.75	1.74	1.88

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

of involvement, resulting in a higher total number of diagnoses than number of patients. Prescriptions for terbinafine were most commonly prescribed by primary care or family medicine physicians (2157 [43.2%]), podiatrists (1016 [20.4%]), dermatologists (782 [15.7%]), and internal medicine physicians (738 [14.8%]). Prescriptions for griseofulvin were most commonly prescribed by primary care or family medicine physicians (318 [37.0%]), pediatricians (266 [30.9%]), and dermatologists (177 [20.6%]). Only 16 patients were receiving pulsed dosing of terbinafine instead of the standard 250-mg/d dosing or equivalent weight-based dosing for children.

Practice of Laboratory Test Result Monitoring

Overall, 2847 patients of 5102 courses (55.8%) had baseline laboratory test results and 2023 patients (39.7%) had at least one monitoring or interval laboratory test result. In patients with monitoring LTF results, ALT was measured a mean of 2.43 times in patients taking terbinafine, 1.82 times in patients taking griseofulvin microsize, and 1.97 times in patients taking griseofulvin ultramicrosize (**Table 2**). In patients with monitoring complete blood cell counts, hemoglobin was measured a mean of 2.82 times in patients taking terbinafine, 1.74 times in patients taking griseofulvin microsize, and 1.89 times in patients taking griseofulvin ultramicrosize (Table 2). Laboratory test results were more commonly checked for patients taking terbinafine than griseofulvin microsize or griseofulvin ultramicrosize. This occurrence was likely secondary to a far larger percentage of children taking griseofulvin than terbinafine, with a decreased frequency of laboratory test results in children. Overall, 478 patients (75.4%) taking griseofulvin microsize were children and 92 patients (57.9%) taking griseofulvin ultramicrosize were children compared with only 341 patients (7.9%) taking terbinafine. For patients with at least one monitoring laboratory test result, the treatment course ranged from 7 to 513 days for terbinafine, 7 to 196 days for griseofulvin microsize, and 7 to 120 days for griseofulvin ultramicrosize. The patients with unusually long courses were primarily patients with onychomycosis treated by nondermatologists. Patients with at least one monitoring laboratory test result were more likely to have longer treatment courses than those who did not have any monitoring laboratory test results (66 vs 44

Table 3. Rates of Baseline and Monitoring Laboratory Test Result Abnormalities[a]

	No. (%) of Patients					
	Terbinafine		Griseofulvin Microsize		Griseofulvin Ultramicrosize	
Test	Baseline	Monitoring	Baseline	Monitoring	Baseline	Monitoring
ALT						
Patients with elevated ALT measurements	95 (3.6)	61 (3.5)	3 (4)	2 (2)	2 (5)	0
Grade 1 ALT measurement elevation	92 (3.5)	57 (3.3)	3 (4)	2 (2)	2 (5)	0
Grade ≥2 ALT measurement elevation	3 (0.1)	4 (0.2)	0	0	0	0
Patients with actionable ALT measurements (retest or discontinued)	10 (0.4)	10 (0.6)	1 (1)	0	1 (3)	0
No. of ALT measurements with no clinical action	NA	4166 (99.8)	NA	175 (100)	NA	61 (100)
AST						
Patients with elevated AST measurements	84 (3.5)	46 (3.1)	2 (3)	9 (9)	1 (3)	1 (4)
Grade 1 AST measurement elevation	77 (3.2)	45 (3.0)	2 (3	9 (9)	1 (3)	1 (4)
Grade ≥2 AST measurement elevation	7 (0.3)	1 (0.07)	0	0	0	0
Patients with actionable AST (retest or discontinued)	7 (0.3)	8 (0.5)	0	0	0	0
No. of AST measurements with no clinical action	NA	3654 (99.9)	NA	169 (100)	NA	55 (100)
Hemoglobin						
Patients with anemia	76 (5.1)	57 (7.0)	2 (2)	4 (5)	1 (4)	0
Grade 1 anemia	68 (4.6)	56 (6.9)	2 (2)	4 (5)	1 (4)	0
Grade ≥2 anemia	8 (0.5)	1 (0.1)	0	0	0	0
Patients with actionable hemoglobin measurements (retest or discontinued)	7 (0.5)	1 (0.1)	0	0	0	0
No. of hemoglobin measurements with no clinical action	NA	2296 (99.9)	NA	132 (100)	NA	51 (100)
Neutrophil count						
Patients with neutropenia	23 (1.8)	15 (2.1)	2 (3)	3 (4)	0	0
Grade 1 neutropenia	17 (1.3)	15 (2.1)	1 (1)	0	0	0
Grade ≥2 neutropenia	6 (0.5)	0	1 (1)	3 (4)	0	0
Patients with actionable neutrophil counts (retest or discontinued)	0	2 (0.3)	0	0	0	0
No. of neutrophil counts with no clinical action	NA	1991 (99.9)	NA	119 (100)	NA	45 (100)
Lymphocyte count						
Patients with lymphopenia	67 (5.3)	23 (3.2)	9 (13)	6 (9)	2 (8)	0
Grade 1 lymphopenia	34 (2.7)	18 (2.5)	9 (13)	5 (7)	2 (8)	0
Grade ≥2 lymphopenia	33 (2.6)	5 (0.7)	0	1 (1)	0	0
Patients with actionable lymphocyte count (retest or discontinued)	2 (0.2)	1 (0.1)	0	0	0	0
No. of lymphocyte counts with no clinical action	NA	1970 (100)	NA	122 (100)	NA	45 (100)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; NA, not applicable.

[a] Sample sizes vary for each group because of a varying distribution and number of laboratory tests per patient. For griseofulvin microsize and ultramicrosize, the sample size is small and allows for reporting percentages to only 1 significant digit.

days for terbinafine, 54 vs 36 days for griseofulvin microsize, and 38 vs 32 days for griseofulvin ultramicrosize).

Laboratory Test Result Abnormalities With Terbinafine

The rate of baseline and monitoring laboratory test result abnormalities for patients taking terbinafine was low, with few having clinically actionable abnormalities identified (**Table 3**). Overall, monitoring laboratory test results identified 4 cases of grade 2 or higher ALT measurement elevations (0.2%), 1 case of grade 2 or higher AST measurement elevation (0.1%), 1 case of grade 2 or higher anemia (0.1%), and 5 cases of grade 2 or higher lymphopenia (0.7%). One asymptomatic patient with grade 3 ALT and AST measurement elevation was diagnosed with terbinafine-induced hepatotoxicity 45 days into treatment. The ALT and AST measurement elevations resolved after discontinued use of terbinafine. Overall, 6 patients discontinued use of terbinafine because of grade 1 to 3 terbinafine-attributed LFT result abnormalities. Eight patients with abnormal LFT results, 2 patients with neutropenia, and 1 patient with lymphopenia had subsequent laboratory tests performed because of the abnormalities. One patient with a grade 1 anemia had hemoglobin measurement rechecked with im-

provement, but terbinafine use was still discontinued. There were no significant differences in the comparison between the adult and pediatric populations. Abnormalities were low in both populations. Of note, only 1 child had an actionable laboratory test result abnormality (elevation in ALT and AST), resulting in discontinued use of medication.

Laboratory Test Result Abnormalities With Griseofulvin Microsize

The rate of baseline and monitoring laboratory test result abnormalities for patients taking griseofulvin microsize was low, with no clinically actionable laboratory test results (Table 3). Monitoring laboratory test results identified 3 patients with grade 2 neutropenia (4%) and 1 patient with grade 2 lymphopenia (1%). In all 4 cases, the patients' physicians had no concerns, and use of the medication was continued uneventfully. The rates of grade 2 or higher monitoring ALT measurement elevation, AST measurement elevation, and anemia were all 0%. No patients had griseofulvin microsize use discontinued or subsequent laboratory tests performed because of monitoring laboratory test result abnormalities.

Laboratory Abnormalities With Griseofulvin Ultramicrosize

The rate of monitoring laboratory test result abnormalities in patients taking griseofulvin ultramicrosize was low, with no clinically actionable abnormalities identified (Table 3). Monitoring laboratory test results detected 1 patient with a grade 1 AST measurement elevation. No cases of ALT measurement elevation, anemia, neutropenia, or lymphopenia were identified via monitoring laboratory test results. No patients discontinued use of griseofulvin ultramicrosize or underwent subsequent short-term laboratory tests because of monitoring laboratory abnormalities.

Discussion

Our study found low rates of monitoring or interval laboratory test result abnormalities in patients taking oral terbinafine, griseofulvin microsize, or griseofulvin ultramicrosize. Less than 0.23% of patients had grade 2 or higher LFT abnormalities, and only 1 patient experienced hepatotoxicity. The rates of grade 1 and grade 2 ALT and AST measurement elevation, anemia, lymphopenia, and neutropenia for all medications were similar to the baseline rates in our population.

Previous studies[4-9] have also found low rates of abnormalities. A study by Elewski et al[4] on the safety and efficacy of terbinafine vs griseofulvin in children with tinea capitis found that hematologic and biochemical abnormalities were "infrequent without evidence of drug effect." However, the study did not provide the rates of abnormalities and did not explain how many of the test results required subsequent laboratory tests or cessation of medication use. A recent article by Patel et al[5] of children taking oral terbinafine for onychomycosis recommended against routine monitoring laboratory tests in this population given a low rate of grade 1 abnormalities (4.2%) with no grade 2 or higher abnormalities. A meta-analysis by Chang et al[6] studied the safety of oral antifungals for superficial dermatophytosis and onychomycosis, which included 122 studies with approximately 20 000 enrolled patients. The risk of transaminase elevation that required termination of terbinafine treatment was 0.35%, and the risk of asymptomatic elevation of transaminase measurements that did not require treatment discontinuation was 0.70%.[6] However, this study did not specifically evaluate other laboratory test result abnormalities attributable to terbinafine, such as anemia, lymphopenia, and neutropenia, and did not evaluate laboratory test result abnormalities with griseofulvin.

Although case reports of serious liver injury are rare, a retrospective study[7] of the United Network for Organ Sharing liver transplant database on 51 741 transplants from 1990 to 2002 found that only 492 adult and pediatric patients received liver transplants for acute liver failure secondary to medications. Terbinafine and griseofulvin were not implicated in any of these cases. A prospective study[8] using the Drug-Induced Liver Injury Network (a cooperative between the National Institutes of Health and 5 academic clinical centers) between 2004 and 2008 found 300 cases of drug-induced liver disease, of which 4 were attributed to terbinafine and 0 to griseofulvin. Similarly, a population-based study[9] from the Taiwan National Health Insurance Database of patients using oral antifungal agents from 2002 to 2008 found that 8 of 18 677 patients taking griseofulvin and 2 of 12 376 patients taking terbinafine experienced drug-induced liver injury.

In our study, most patients had more than 1 round of monitoring or interval laboratory tests, resulting in at least 4412 LFTs and 2480 complete blood cell counts. Overall, 99.9% of monitoring laboratories resulted in no clinical action. When considering the total number of monitoring laboratory tests performed for each medication, one would need to check 417 ALT measurements in patients taking terbinafine to identify one actionable ALT measurement. Similarly, one would need to check 455 AST measurements, 2297 hemoglobin measurements, 997 neutrophil counts, and 1971 lymphocyte counts to find one actionable abnormality. Because no laboratories for griseofulvin microsize or ultramicrosize resulted in subsequent laboratory tests or medication use discontinuation, the number of laboratories needed to test to find one actionable laboratory test result could not be calculated.

According to the clinical laboratory fee schedule by the Centers for Medicare & Medicaid Services, the cost of a single serum ALT or AST test from 2006 to 2016 ranged from $7.22 to $7.40.[16] However, within our system, a serum LFT panel costing $54.91 is often ordered with an additional venipuncture cost of $18.82. Within our study population, the latter panel equals up to $325 296.76 in LFT monitoring that failed to yield clinically actionable results for most patients. This number does not include the additional cost of baseline LFT evaluation. A complete blood cell count with differential costs $50.18 within our system. Excluding venipuncture costs, the cost of hematologic monitoring in our study population equals up to $124 446.40, with no clinically actionable results for most patients.

There was substantial variability in the ordering, timing, and frequency of interval monitoring laboratory tests. Given the lack of regular interval laboratory test result monitoring

and overall low rate of abnormalities, there was no clear time frame in which abnormalities were most likely to occur.

Laboratory tests are easy for a physician to order and provide quick, objective data to analyze. In an environment with increasing time constraints and concerns of liability, laboratory tests provide an efficient way to rule out potential complications. However, laboratory test result abnormalities are often without clinical significance. When studied in controlled environments, even commonly used over-the-counter medications, such as acetaminophen, have frequent asymptomatic laboratory test result abnormalities (occurring at higher rates than reported with terbinafine and griseofulvin in this study) that resolve with discontinued use.[17] Physicians may be relying on laboratory test results instead of focusing on history and the physical examination. Furthermore, hepatotoxicity with terbinafine and griseofulvin is idiosyncratic. Because of the rarity and unpredictability of severe drug-induced liver injury, routine monitoring laboratory tests are ineffective as a screening tool. Normal monitoring laboratory test results do not indicate whether a patient will later develop an idiosyncratic reaction, and minor abnormalities rarely result in clinical action.

We identified a low rate of laboratory test result abnormalities in patients taking oral terbinafine or griseofulvin for suspected dermatophyte infections. When laboratory test result abnormalities occurred, most were low grade (212 [93.4%] grade 1) and did not require subsequent laboratory tests or discontinued medication use (15 051 [99.9%]). On the basis of these findings, we suggest that routine laboratory test result monitoring should no longer be performed in children and adults without known underlying hepatic and hematologic conditions. Instead, physicians should screen for potential underlying hepatic or hematologic disease, counsel patients on symptoms of liver toxic effects (pruritus, jaundice, abdominal pain, and flulike symptoms), and perform an appropriate history and review of systems for patients with longer treatment courses.

The aim of our study was to evaluate the rate of laboratory test result abnormalities and utility of interval laboratory test result monitoring while patients were taking terbinafine and griseofulvin. This study does not include patients who never received terbinafine or griseofulvin because of abnormal baseline laboratory test results. Thus, we are unable to evaluate or make conclusions on the utility of baseline laboratory test results before starting use of terbinafine and griseofulvin. However, our study found that 50% of patients taking terbinafine who had elevated monitoring ALT measurements had an elevated ALT measurement at baseline. Future studies looking at the utility of baseline laboratory test results are needed.

In our practice, patients are often hesitant to use oral medications to treat dermatophyte infections because of concerns about toxic effects of medication. Patients and physicians may have restricted their use of oral terbinafine and griseofulvin because of concerns of laboratory test result abnormalities and the need for laboratory monitoring. Abandoning frequent laboratory monitoring can decrease unnecessary health care spending, decrease patient psychological angst associated with blood draws, and allow for expanded use of these effective oral treatment options for onychomycosis and widespread, resistant, and follicular-based dermatophyte infections.

Limitations

This study was performed within one Midwest health care system with a predominantly white patient population, which may reflect only a subset of the national population and laboratory test result monitoring practices. Samples for laboratory tests ordered during the medication course may have been drawn for purposes unrelated to medication monitoring. We believe that inclusion of all laboratory values obtained during the medication course allowed us to best determine the rate of laboratory test result abnormalities. However, this approach may overestimate the rate and cost of monitoring in our population. A significant subset of patients did not have laboratory test result monitoring during their treatment course, and potential hepatic and hematologic abnormalities may have been missed. Although our health system has a high rate of capturing all health care obtained by our patient population, as shown by a prior study[18] looking at the Marshfield Epidemiologic Study Area, it is possible that patients may have obtained laboratory results outside our system. Thus, additional abnormal laboratory test results may have occurred that were not captured by our study.

Medication courses were based on filed prescriptions within the EHRs. Given the nature of this study, we cannot confirm that the medication was actually taken by the patient, taken correctly, or taken during the specific dates reflected in the EHRs. However, therapeutic dates matched in all EHRs that were manually reviewed. Although most patients taking terbinafine were taking 250 mg/d, alternate terbinafine dosing schedules, such as pulsed therapies, were not considered an exclusion criterion and all doses were included. Data were pulled from multiple years with laboratory values from multiple laboratories. The range of laboratory values considered normal varies by laboratory and over time. Laboratory values from different clinics using different machines were included, with potential variability in laboratory values. This variability was accounted for in the study by only considering laboratory test results abnormal if they were outside the reference range of the laboratory at which the samples were drawn on the date it occurred. However, for grading of abnormal laboratory test results per Common Terminology Criteria for Adverse Events, current, stricter criteria for the upper and lower limits of normal were used.[15]

Conclusions

Our results suggest that routine interval laboratory test result monitoring is unnecessary for adults and children without known hepatic or hematologic conditions taking oral terbinafine, griseofulvin microsize, and griseofulvin ultramicrosize for dermatophyte infections. The low rate of monitoring laboratory test result abnormalities may encourage more physicians and patients to consider the use of these medications

for onychomycosis and widespread, resistant, and follicular-based dermatophyte infections. Abandoning frequent laboratory monitoring can decrease unnecessary health care spending, decrease patient psychological angst associated with blood draws, and allow for expanded use of these effective oral medications.

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Drafting of the manuscript: Stolmeier, H.B. Stratman, E.J. Stratman.
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