Standardized laboratory monitoring with use of isotretinoin in acne

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Background: Laboratory monitoring for adverse effects to isotretinoin occurs with variability. Standardization of laboratory monitoring practices represents an opportunity to improve quality of care.

Objective: We sought to develop an evidence-based approach to laboratory monitoring of patients receiving isotretinoin therapy for acne.

Methods: We reviewed laboratory data from 515 patients with acne undergoing 574 courses of isotretinoin from March 2003 to July 2011. Frequency, timing, and severity of abnormalities were determined.

Results: Clinically insignificant leukopenia or thrombocytopenia occurred in 1.4% and 0.9% of patients, respectively. Elevated liver transaminases were detected infrequently and not significantly increased compared with baseline detection rates (1.9% vs 1.6% at baseline). Significant elevations occurred with triglyceride (19.3%) and cholesterol (22.8%) levels. The most severe abnormalities were grade 2 (moderate). Mean duration of treatment before abnormalities were detected was 56.3 days for hypertriglyceridemia, 61.9 days for alanine transaminitis, and 50.1 days for hypercholesterolemia.

Limitations: This was a single-center experience examining variable isotretinoin laboratory monitoring practices.

Conclusions: In healthy patients with normal baseline lipid panel and liver function test results, repeated studies should be performed after 2 months of isotretinoin therapy. If findings are normal, no further testing may be required. Routine complete blood cell count monitoring is not recommended. (J Am Acad Dermatol 2016;75:323-8.)

Key words: acne; hypercholesterolemia; hypertriglyceridemia; isotretinoin; laboratory monitoring; leukopenia; thrombocytopenia; transaminitis.

The US Food and Drug Administration (FDA) approved isotretinoin for the treatment of severe cystic acne in 1982.[1] Most recent labeling recommends monitoring lipid levels and liver function at weekly or biweekly intervals until the response to isotretinoin has been established, which is defined as "usually [occurring] within 4 weeks."[2] Prescribers of isotretinoin use varied protocols for laboratory monitoring and dose escalation for their patients, with many studies reporting a monthly interval of monitoring rather than weekly or biweekly, throughout the course of

Abbreviations used:

ALT: alanine aminotransferase
CBC: complete blood cell count
FDA: Food and Drug Administration

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treatment.[3-5] Case reports indicating possible thrombocytopenia and leukopenia have prompted providers to also monitor complete blood cell counts (CBC).[6,7] There is little consensus and no standardized comprehensive clinical practice guidelines regarding appropriate frequency and interval of laboratory testing. Development of a standardized approach to laboratory monitoring of isotretinoin would benefit patients, providers, and the health system by eliminating unnecessary testing and reducing overall cost, while ensuring safe administration of the medication. The aim of this study was to develop an evidence-based approach for laboratory monitoring of isotretinoin therapy for acne.

CAPSULE SUMMARY

- The optimal timing of laboratory tests for patients on isotretinoin treatment for acne is uncertain.
- In this series, although abnormalities in serum lipids in patients receiving isotretinoin were not infrequent, they were mild to moderate, and were generally noted around the second month of treatment.
- For healthy patients on isotretinoin, we recommend that a lipid panel and liver function test be performed at baseline and at month 2, when peak dosing is achieved. Further testing should be considered if a significant abnormal value is noted.

METHODS

The study cohort consisted of patients treated from May 2003 through July 2011 at the Department of Dermatology, Pennsylvania State/Hershey Medical Center. This study was approved by our institutional review board. Patients were eligible if they received at least 1 course of isotretinoin. Patients were excluded if isotretinoin was used for a condition other than acne vulgaris. Patients were identified using the iPLEDGE database followed by chart review. Patient demographic data, cumulative isotretinoin dose, number of courses, and characteristics of laboratory testing during treatment were recorded. Laboratory results for the following tests were recorded: serum triglyceride level, total cholesterol, alanine aminotransferase (ALT), white blood cell count, and platelet count. Abnormalities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 grading system[8] (Table I). Because white blood cell count and platelet abnormalities do not fall into this grading system, values above or below the reference ranges were considered abnormal. Aspartate aminotransferase levels were not included, as the standard liver profile at our institution includes ALT only, as this transaminase shows better organ specificity.

The rate of laboratory abnormalities was calculated as the proportion of patient courses with abnormalities at baseline and at any time during therapy. The interval to detection of laboratory abnormalities was calculated in months for patients with normal baseline values who developed abnormalities during therapy. Descriptive statistics were tabulated. The data were summarized by proportions and percentages or mean, 95% confidence intervals, and SD. Both P values less than .05 and 95% confidence intervals that did not overlap with 1 were considered statistically significant. Laboratory values were further evaluated using paired comparisons (McNemar test) for statistical significance. No power or sample size calculations were performed because the sample is a convenience sample of a defined population. Analyses were performed with software (SAS, Version 9.3, SAS Institute, Cary, NC).

RESULTS

The iPLEDGE database revealed 1008 patients registered to our institution; 515 patients receiving 574 courses of isotretinoin were identified to have recorded dosage and laboratory data (Table II).

Fig 1 illustrates the percentage of patients with detected abnormalities for each laboratory test at any time during treatment. Common Terminology Criteria for Adverse Events v3.0 grades are noted in Table III. No values above grade 2 were detected. Leukopenia was detected during 14 (2.4%) patient courses. The lowest white blood cell count value was 2200/μL, found at baseline and resolved to normal range despite continued therapy. Thrombocytopenia was detected during 9 (1.6%) patient courses and proved clinically insignificant.

ALT elevations were found during 19 (3.3%) courses of isotretinoin. The most severe transaminitis occurred 2 months into treatment in a male patient who had just began a new vitamin supplement, with ALT values peaking at 264 U/dL. The vitamin supplement was discontinued, dose of isotretinoin was halved, and ALT values normalized within a month. A possible spurious grade-2 transaminitis was detected in a male patient after 1 month of therapy, with 4-fold elevation of ALT. Repeated measurement showed normal values with no dosage alteration.

Lipid abnormalities occurred most frequently; hypercholesterolemia occurred in 148 (25.8%) courses and hypertriglyceridemia occurred in 129