Laboratory Monitoring During Isotretinoin Therapy for Acne
A Systematic Review and Meta-analysis

Young H. Lee, MD; Thomas P. Scharnitz, BS; Joshua Muscat, PhD; Allshine Chen, MS; Gaytri Gupta-Elera, BS; Joslyn S. Kirby, MD, MEd, MS

IMPORTANCE Oral isotretinoin has been associated with several adverse effects, but evidence-based estimates of laboratory changes during isotretinoin therapy in large patient samples are limited.

OBJECTIVE To develop estimates of the laboratory changes that occur during isotretinoin therapy for acne using extant data and meta-analytic methods.

DATA SOURCES A comprehensive search strategy using Ovid/MEDLINE, EMBASE, and gray literature was conducted (1960-August 1, 2013) to identify all relevant studies of isotretinoin use in acne vulgaris. Terms related to acne treatment, isotretinoin, and diagnostic procedures were searched with all available synonyms.

STUDY SELECTION Inclusion criteria consisted of clinical trials using oral isotretinoin, doses of 40 mg/d or more, duration of at least 4 weeks, patients aged 9 to 35 years with acne vulgaris, and 10 or more participants. Studies from all countries published in any language were included. Exclusion criteria were use of modified isotretinoin products, isotretinoin therapy for conditions other than acne vulgaris, and concomitant acne therapy. The initial search yielded 342 records; 116 of these were screened for full-text examination.

DATA EXTRACTION AND SYNTHESIS Two authors independently reviewed the publications to determine eligibility, and disagreements were resolved by a third author. Generated weighted means and 99% CIs were calculated using the reported means (SDs or SEs). A random effects model was created, and statistical heterogeneity was quantified. Data were analyzed from August 25, 2014, to December 4, 2015.

MAIN OUTCOMES AND MEASURES Laboratory values for lipid levels, hepatic function, and complete blood cell count were evaluated.

RESULTS Data from 61 of the 116 studies were evaluated; 26 studies (1574 patients) were included in the meta-analysis. The mean (99% CI) values during treatment (nonbaseline) for triglycerides was 119.98 mg/dL (98.58-141.39 mg/dL); for total cholesterol, 184.74 mg/dL (178.17-191.31 mg/dL); for low-density lipoprotein cholesterol, 109.23 mg/dL (103.68-114.79 mg/dL); for high-density lipoprotein cholesterol, 42.80 mg/dL (39.84-45.76 mg/dL); for aspartate aminotransferase, 22.67 U/L (19.94-25.41 U/L); for alanine aminotransferase, 21.77 U/L (18.96-24.59 U/L); for alkaline phosphatase, 88.35 U/L (58.94-117.76 U/L); and for white blood cell count, 6890/μL (5700/μL-8030/μL). This meta-analysis showed that (1) isotretinoin is associated with a statistically significant change in the mean value of several laboratory tests (white blood cell count and hepatic and lipid panels), yet (2) the mean changes across a patient group did not meet a priori criteria for high-risk and (3) the proportion of patients with laboratory abnormalities was low.

CONCLUSIONS AND RELEVANCE The evidence from this study does not support monthly laboratory testing for use of standard doses of oral isotretinoin for the standard patient with acne.

Severe nodulocystic acne can be treated with isotretinoin, which can result in dramatic improvement within months. Although very effective, isotretinoin has been associated with several adverse effects, including teratogenicity, hyperlipidemia and associated pancreatitis, leukopenia, thrombocytopenia, and transaminitis. Monitoring of pregnancy during therapy is mandated via the iPledge program (https://www.ipledgeprogram.com). The package insert recommends baseline fasting lipid and hepatic panels with repeated testing at weekly or biweekly intervals until “the response has been established.” There are no specific suggestions in the document for laboratory monitoring.

Prior studies have investigated the usefulness of laboratory monitoring during isotretinoin therapy and made recommendations ranging from performance of only baseline testing to baseline testing with 1 follow-up set of tests. The latter recommendations were based on samples of approximately 140 to 200 patients and at single centers.6,7 In addition, Hansen et al reviewed 574 isotretinoin courses for 515 patients and across multiple published studies to develop estimates of laboratory frequency, and small sample sizes in some studies. The aim of this systematic review and meta-analysis was to combine data from all 20 studies to baseline testing with 1 follow-up set of tests.6,7 The latter recommendations were based on samples of approximately 140 to 200 patients and at single centers.6,7 In addition, Hansen et al reviewed 574 isotretinoin courses for 515 patients and found that grade 2 abnormalities were uncommon (0.2%-1.6% of patients) and 67.7% of the abnormalities occurred within the first 60 days of treatment. Nevertheless, overall, the evidence to guide laboratory monitoring during isotretinoin therapy is limited by differences in tests ordered, testing frequency, and sample size. The aim of this systematic review and meta-analysis was to combine data across multiple published studies to develop estimates of laboratory changes during isotretinoin therapy for acne.

Methods

A systematic review and meta-analysis were performed. The study was registered with the PROSPERO International prospective register of systematic reviews.9 The PRISMA and AMSTAR checklists were used to guide the project (eAppendix 1 in the Supplement).

Search Strategy

We conducted a comprehensive search strategy designed by a Master of Library and Information Science-trained librarian to identify all relevant studies of oral isotretinoin use in adolescents and adults (age 9-35 years) with acne vulgaris. Articles in any language were included; all searches covered 1960 to August 1, 2013. A comprehensive search was performed in MEDLINE using the Ovid platform. The search terms related to acne treatment, isotretinoin, and diagnostic procedures were searched with all available synonyms. A second search of EMBASE was performed through Proquest. Duplicate citations were removed. A final search for relevant gray literature was performed on Google Scholar with citations and patents removed. A complete description of the search methods is described in eAppendix 2 of the Supplement.

Selection Criteria

Inclusion criteria were developed a priori and included studies of acne vulgaris, use of oral isotretinoin (altered sustained-release or lipid-enhanced products were excluded), dose regimens of 40 mg or more daily (or ≥0.5 mg/kg), duration of treatment for at least 4 weeks, and treatment of children and adults (aged 9-35 years). Studies with a cohort or comparison design as well as case series of 10 or more participants were eligible. The study must have reported values for the laboratory tests of interest: complete blood count, hepatic panel (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and alkaline phosphatase [AP]), and/or lipid panel (triglycerides [TG], total cholesterol, low-density lipoprotein cholesterol [LDL-C], and high-density lipoprotein cholesterol [HDL-C]). Studies were separated into 2 groups; those that reported mean values for laboratory tests were included in the meta-analysis, and studies that reported the proportion of patients with an abnormal test were described separately in a narrative review.

Study Selection

Titles and abstracts from the search results were screened, and full articles of all citations that met the predefined selection criteria were obtained for review. Subsequently, full articles were examined for inclusion or exclusion and data extraction. Two reviewers (T.P.S. and G.G.-E.) independently assessed each potentially relevant study for eligibility. Disagreements were resolved by a third reviewer (Y.H.L.).

Data Extraction

The selected studies were reviewed and the data were abstracted by one of us (T.P.S.); the accuracy was confirmed by another one of us (Y.H.L.). Information was entered into a Google document (Google Inc) and included study characteristics (country, design, sample size, and duration of therapy), patient characteristics (age and sex), and therapeutic interventions (isotretinoin dose and treatment duration). Laboratory tests of interest included the complete blood cell count, hepatic panel (AST, ALT, and AP), and lipid panel (TG, total cholesterol, HDL-C, and LDL-C). The timing of laboratory monitoring during isotretinoin therapy (eg, at week 6, month 1, and month 3) was recorded. The mean (SD) of the laboratory result and the proportion of patients with abnormal results were recorded. Studies that did not report specific values at identified time points were not included in the meta-analysis, but their findings are described in a separate narrative. The National Institutes of Health Clinical Center reference ranges10 were used to define significant or high-risk laboratory changes for white blood cell count, which corresponded to 3000 cells/μL (to convert to × 10^9/L, multiply by 0.001), TG corresponding to 200 mg/dL (to convert to millimoles per liter, multiply by 0.0113), and total cholesterol, LDL-C, and HDL-C corresponding to 240, 160, and 40 mg/dL, respectively (to convert to millimoles per liter, multiply by 0.0259). The Common Terminology Criteria for Adverse Events reference ranges11 were used to define grade 2 or significant laboratory changes for the hepatic panel including AP, AST, and ALT corresponding to 367.5 U/L, 108 U/L, and 111 U/L, respectively (to convert to microkatal per liter, multiply by 0.0167).

Statistical Analysis

Trials reported findings from different laboratory studies and at varying intervals of repeated measurements in time. The 99% CI for each laboratory test in each study was calculated...
based on the reported mean (SD). The meta-analytic method used weighted means (SEs) to estimate the mean and 99% CI for the pool of participants. Midtreatment and late effects of isotretinoin therapy on laboratory results were analyzed whenever possible depending on the data available in published studies. Midtreatment was defined as 6 to 8 weeks of therapy. Late effects of prolonged isotretinoin therapy were examined for 16 to 20 weeks. A random effects model was used and statistical heterogeneity was quantified using the $I^2$ and $\tau^2$ statistics. An assessment of the quality of the evidence was not performed. Data were analyzed from August 25, 2014, to December 4, 2015, using Stata, version 13 (StataCorp) and Comprehensive Meta-analyses software (Biostat Inc).

**Results**

The initial search identified 342 references (Figure 1); 116 of these (33.9%) were selected for full-text examination. The meta-analysis of changes in laboratory values included 22 randomized clinical trials and 4 retrospective studies, with a total of 1574 participants. The individual studies are described in eTable 1 in the Supplement. Seven of these studies reported discontinuation rates for subjects owing to laboratory abnormalities, which ranged from 0.71% (1 of 140) to 22.5% (9 of 40), with a mean (SD) of 4.4 (6.9) (eTable 2 in the Supplement). There were 25 randomized clinical trials and 10 retrospective studies with a total of 17 915 participants that lacked data on laboratory values, which are summarized below in a narrative review. The excluded references are listed in eTable 3 in the Supplement.

**Lipid Panel**

**Triglycerides**

The mean value of nonbaseline measurements (Figure 2A) or those made during isotretinoin therapy was 119.98 mg/dL (99% CI, 98.58-141.39 mg/dL). The difference in mean values between baseline and the mean follow-up period (11.3 weeks) (Figure 2B) was 36.96 mg/dL (99% CI, 22.12-51.79 mg/dL).

To examine midtreatment and later effects of isotretinoin therapy, the difference in means between baseline and 8 weeks and 20 weeks (eFigure 1A and B in the Supplement) was examined. For 8 weeks, the difference from baseline was 45.32 mg/dL (99% CI, 22.73-67.92 mg/dL), and for 20 weeks, the difference from baseline was 45.63 mg/dL (99% CI, 5.15-80.11 mg/dL). The 2 analyses consisted of different studies because not all studies reported values for all time points. However, the change in TG levels from baseline to 8 weeks and 20 weeks does not demonstrate a substantial late effect of isotretinoin therapy.

**Total Cholesterol**

The mean value of nonbaseline measurements (Figure 3A) or those made during isotretinoin therapy was 184.74 mg/dL (99% CI, 178.17-191.31 mg/dL). All but one study reported all observations as within the reference range. In one study, the 99% CI extended above 240 mg/dL, with a mean of 235.90 mg/dL (99% CI, 206.02-265.78 mg/dL). The difference in mean values between baseline and the mean follow-up period (11.1 weeks) (Figure 3B) was 19.73 mg/dL (99% CI, 16.00-23.47 mg/dL). In 3 studies, there were patients who had a change in total cholesterol of up to 60 mg/dL. At 16 weeks (eFigure 2A in the Supplement), the difference from baseline was 23.51 mg/dL (99% CI, 16.84-30.18 mg/dL), and for 20 weeks (eFigure 2B in the Supplement),
the difference was 17.72 mg/dL (99% CI, 6.83-28.61 mg/dL).
The 2 analyses consisted of different studies because not all studies reported values for all time points. However, the change in total cholesterol from baseline to 16 weeks and 20 weeks did not demonstrate a substantial late effect of isotretinoin therapy.
Figure 3. Measures for Total Cholesterol (TC)

A  Mean nonbaseline total cholesterol values

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean (SE)</th>
<th>99% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buckley et al, 1990</td>
<td>201.34 (4.40)</td>
<td>189.99 to 212.68</td>
</tr>
<tr>
<td>Ragos et al, 1998</td>
<td>200.51 (3.12)</td>
<td>192.46 to 208.56</td>
</tr>
<tr>
<td>Michaëlsson et al, 1986</td>
<td>192.20 (4.60)</td>
<td>180.35 to 204.05</td>
</tr>
<tr>
<td>Hanstad and Thune, 1985</td>
<td>195.70 (5.26)</td>
<td>182.13 to 209.26</td>
</tr>
<tr>
<td>Pigatto et al, 1986</td>
<td>163.56 (11.69)</td>
<td>133.45 to 193.68</td>
</tr>
<tr>
<td>Laker et al, 1987</td>
<td>197.10 (12.10)</td>
<td>165.93 to 226.27</td>
</tr>
<tr>
<td>Melnik et al, 1987</td>
<td>181.30 (5.88)</td>
<td>166.15 to 196.45</td>
</tr>
<tr>
<td>Lyons et al, 1982</td>
<td>235.90 (11.60)</td>
<td>206.02 to 265.78</td>
</tr>
<tr>
<td>Ostlere et al, 1996</td>
<td>192.60 (7.48)</td>
<td>173.34 to 211.86</td>
</tr>
<tr>
<td>Strauss et al, 2001</td>
<td>185.60 (2.31)</td>
<td>179.64 to 191.56</td>
</tr>
<tr>
<td>Koistinen et al, 2001</td>
<td>167.80 (8.50)</td>
<td>145.91 to 189.70</td>
</tr>
<tr>
<td>Altman et al, 2002</td>
<td>184.57 (3.12)</td>
<td>176.52 to 192.61</td>
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<td>Ferahbas et al, 2004</td>
<td>162.07 (6.76)</td>
<td>144.65 to 179.49</td>
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<td>Koistinen et al, 2006</td>
<td>166.30 (7.70)</td>
<td>146.47 to 186.13</td>
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<td>Polat et al, 2008</td>
<td>175.90 (3.39)</td>
<td>165.60 to 186.20</td>
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<td>Roodarsi et al, 2010</td>
<td>181.90 (4.97)</td>
<td>169.09 to 194.71</td>
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<td>Ertugrul et al, 2011</td>
<td>168.20 (4.39)</td>
<td>156.87 to 179.53</td>
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<td>Dursun et al, 2011</td>
<td>173.75 (4.77)</td>
<td>161.46 to 186.04</td>
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<td>Karadag et al, 2011</td>
<td>179.50 (4.02)</td>
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<td>Erturan et al, 2012</td>
<td>184.40 (5.96)</td>
<td>169.04 to 199.76</td>
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<td>Bershad et al, 1985 (females)</td>
<td>169.97 (5.02)</td>
<td>157.03 to 182.91</td>
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<tr>
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<td>185.13 (5.02)</td>
<td>175.03 to 195.23</td>
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<tr>
<td>Strauss et al, 1984 (0.5-mg/kg dose)</td>
<td>194.24 (4.47)</td>
<td>173.34 to 211.86</td>
</tr>
<tr>
<td>Strauss et al, 1984 (1.0-mg/kg dose)</td>
<td>203.42 (6.02)</td>
<td>182.74 to 224.10</td>
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<tr>
<td>Random model</td>
<td>184.74 (2.55)</td>
<td>178.17 to 191.31</td>
</tr>
</tbody>
</table>

B  Mean difference from baseline to mean follow-up

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean (SE)</th>
<th>99% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buckley et al, 1990</td>
<td>26.14 (2.95)</td>
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<td>Ragos et al, 1998</td>
<td>28.01 (2.27)</td>
<td>22.16 to 33.85</td>
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<td>Michaëlsson et al, 1986</td>
<td>15.90 (3.08)</td>
<td>7.98 to 23.82</td>
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<tr>
<td>Hanstad and Thune, 1985</td>
<td>27.10 (4.55)</td>
<td>15.39 to 38.81</td>
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<tr>
<td>Pigatto et al, 1986</td>
<td>7.56 (9.26)</td>
<td>−16.28 to 31.41</td>
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<tr>
<td>Laker et al, 1987</td>
<td>36.60 (8.06)</td>
<td>15.84 to 57.37</td>
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<tr>
<td>Melnik et al, 1987</td>
<td>7.40 (4.46)</td>
<td>−4.10 to 18.89</td>
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<td>Lyons et al, 1982</td>
<td>38.70 (7.74)</td>
<td>18.77 to 58.63</td>
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<tr>
<td>Ostlere et al, 1996</td>
<td>34.80 (8.52)</td>
<td>10.28 to 59.32</td>
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<td>Strauss et al, 2001</td>
<td>23.20 (1.56)</td>
<td>19.18 to 27.22</td>
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<tr>
<td>Koistinen et al, 2001</td>
<td>17.40 (5.66)</td>
<td>2.83 to 31.97</td>
</tr>
<tr>
<td>Altman et al, 2002</td>
<td>13.27 (2.20)</td>
<td>7.61 to 18.92</td>
</tr>
<tr>
<td>Ferahbas et al, 2004</td>
<td>12.47 (4.48)</td>
<td>0.92 to 24.02</td>
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<td>Koistinen et al, 2006</td>
<td>19.40 (5.43)</td>
<td>5.42 to 33.38</td>
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<td>Polat et al, 2008</td>
<td>21.90 (2.72)</td>
<td>14.90 to 28.90</td>
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<td>Roodarsi et al, 2010</td>
<td>20.30 (3.43)</td>
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<td>Ertugrul et al, 2011</td>
<td>11.30 (2.95)</td>
<td>3.70 to 18.90</td>
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<td>Dursun et al, 2011</td>
<td>14.75 (3.24)</td>
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<td>Erturan et al, 2012</td>
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<td>Bershad et al, 1985 (females)</td>
<td>13.94 (4.10)</td>
<td>3.42 to 24.53</td>
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<td>Bershad et al, 1985 (males)</td>
<td>24.13 (5.78)</td>
<td>9.25 to 39.01</td>
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<tr>
<td>Strauss et al, 1984 (0.5-mg/kg dose)</td>
<td>13.04 (3.36)</td>
<td>6.40 to 20.71</td>
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<td>Strauss et al, 1984 (1.0-mg/kg dose)</td>
<td>30.72 (4.00)</td>
<td>20.42 to 41.02</td>
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<tr>
<td>Random model</td>
<td>19.73 (1.45)</td>
<td>16.00 to 23.47</td>
</tr>
</tbody>
</table>

Separate analyses were performed for TC values at various points in time, including mean (99% CI) nonbaseline values (A) and mean differences from baseline to mean follow-up (B). The National Institutes of Health Clinical Center reference value for high risk for TC level is 240 mg/dL. For the graph showing the mean difference from baseline to mean follow-up (B), a negative value indicates a decreased value at follow-up; a positive value, an increased value. SI conversion factor: To convert to millimoles per liter, multiply by 0.0259.

Low-Density Lipoprotein Cholesterol

The mean value of nonbaseline measurements or those made during isotretinoin therapy was 109.23 mg/dL (99% CI, 103.68-114.79 mg/dL). The difference in mean values between baseline and the mean follow-up period (9.7 weeks) was 16.08 mg/dL (99% CI, 13.37-18.78 mg/dL) (eFigure 3A and B in the Supplement). Analyses for late effects could not be made because of lack of available data.
Aspartate Aminotransferase

High-Density Lipoprotein Cholesterol

The mean value of nonbaseline measurements or those made during isotretinoin therapy was 42.80 mg/dL (99% CI, 39.84 to 45.76 mg/dL). The difference in mean values between baseline and the mean follow-up period (9.1 weeks) was −4.82 mg/dL (99% CI, −6.72 to −2.92 mg/dL) (eFigure 3C and D in the Supplement). Analyses for late effects could not be made because of a lack of available data. The mean value of nonbaseline measurements or those made during isotretinoin therapy was 21.77 mg/dL (99% CI, 19.41 to 23.19). Analyses for late effects could not be made because of a lack of available data.

Hepatic Panel

The mean value of nonbaseline measurements or those made during isotretinoin therapy was 22.67 U/L (99% CI, 20.30 to 24.04 U/L). The difference in mean values between baseline and the mean follow-up period (6.6 weeks) (Figure 4B) was −4.23 U/L (99% CI, 19.41 to 23.19). Analyses for late effects could not be made because of a lack of available data.

Alkaline Phosphatase

The mean value of nonbaseline measurements or those made during isotretinoin therapy was 3.72 U/L (99% CI, 2.00 to 5.45 U/L). The difference in mean values between baseline and the mean follow-up period (6.5 weeks) (Figure 5B) was −0.24 to 4.92 U/L (99% CI, 0.99 to 5.45 U/L). Analyses for late effects could not be made because of a lack of available data.

Complete Blood Cell Count

Analyses of hemoglobin, hematocrit, and platelet counts were not performed because of a lack of data. The mean value of nonbaseline measurements of the white blood cell count or those made during isotretinoin therapy was 6890/μL (99% CI, 6.13 U/L); for 8 weeks, the difference from baseline was 3.72 U/L (99% CI, 2.34-5.09 U/L). The 2 analyses consisted of different studies because not all studies reported values for all time points. However, the change in AST from baseline to 6 weeks and 8 weeks does not demonstrate a substantial midtreatment effect of isotretinoin therapy.
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5700/μL to 8030/μL. The difference in mean values between baseline and the mean follow-up period (11.5 weeks) was −1130/μL (99% CI, −2140/μL to −110/μL) (eFigure 6 in the Supplement). Analyses for late effects could not be made because of a lack of available data.

**Narrative Summary of Remaining Studies**

**Lipid Panel**

Thirty-five studies were included in the qualitative analysis (Figure 1). A subset of studies reported no significant elevations in total cholesterol, triglycerides, HDL-C, and LDL-C levels but did not report specific laboratory values. Several studies reported measurable increases in serum lipids but did not include details on the lipid type.

Triglyceride level elevations were reported, including increases above 200 mg/dL in 5.0% (20 of 400), 46 8.7% (41 of 473, with 3 [0.6%] discontinuing treatment), 47 35.9% (75 of 209), 48 and 8.3% (5 of 60) 49 of the patients; above 300 mg/dL in 10.0% (1 of 10) 50 and 4.3% (4 of 94) 50 of the patients; and above 400 mg/dL in 1.5% (14 of 907), 51 3.3% (7 of 209), 52 and 10.0% (1 of 10) 50 of the patients. Other studies reported significant increases in 12.1% (7 of 58) 53 and 35.8% (19 of 53) 54 of the patients but did not specify the threshold value.

Kaymak and Ilter 55 reported elevated TG levels between the fourth and eighth week in 22.0% (22 of 100) of the patients. Sixteen percent (16 of 100) had a TG level of 210 to 350 mg/dL, but 1.0% (1 of 100) had a TG level greater than 730 mg/dL at the fourth month, which decreased with a lowered dosage. Cyrulnik et al 56 reported that 18.8% (15 of 80) of the patients had elevated TG levels, with 12.5% (10 of 80) between 150 and 375 mg/dL and 6.3% (5 of 80) between 376 and 750 mg/dL. Zane et al 57 reported that 44.0% (4231 of 9620) of the patients with normal baseline TG levels had an elevation during treatment: 40.4% (3882) had mild elevations (150-375 mg/dL) and 3.6% (349) had transient and reversible moderate to severe elevations (>375 mg/dL).

Elevated total cholesterol levels above the high-risk threshold (240 mg/dL) were reported in 3.2% (3 of 94), 58 13.8% (55 of 400), 46 18.2% (4 of 22), 59 5.0% (5 of 100), 53 and 3.2% (2 of 63), 59 and 10.5% (22 of 209) 55 of the patients; elevations above 300 mg/dL were reported in 0.6% (5 of 907) 50 and 1.4% (135 of 9641) (with 0.1% [19] abnormal at baseline) 50 of the patients. For patients with normal values at baseline testing, Zane et al 55 reported mild elevations (201-300 mg/dL) in 31.2% (2283 of 7325) and severe elevations (≥301 mg/dL) in 0.1% (9 of 7325) of the patients. Kaymak and Ilter 55 reported elevated total cholesterol levels (278-372 mg/dL) in 5.0% (5 of 100) of the patients. Two studies reported elevated total cholesterol levels in 8.9% (4 of 45) 55 and 7.5% (4 of 53) 54 of the patients but did not define the threshold value.

Studies reported abnormal HDL-C levels in 42.0% (58 of 138) 57 and 20.0% (2 of 10) of the patients. 46 A few studies commented on a significant 40,42,56,59 or slight 50 increase in total cholesterol levels, significant 42,58,59 or slight 54 increase in TG
levels, significant increase in LDL-C levels, and significant decrease in HDL-C levels but did not provide more specific data.

Liver Function Tests
Many studies reported no significant elevations in any of the liver function tests during treatment. Several other studies reported no elevations in individual components including ALT, AST, or AP levels. Two studies mentioned a “liver panel” was performed, and 4 reported that AP levels were determined, but specific information was missing.

Moderate or higher elevations in liver function tests were reported in 2 studies, but the thresholds were not consistently defined, so they may not agree with the Common Terminology Criteria for Adverse Events reference ranges. Zane et al described moderate elevations (>101 U/L) in either AST or ALT levels in 1.5% (79 of 11 676) of the patients; in comparison, 0.4% (49 of 12 503) had a moderate abnormality at baseline. McElwee et al reported moderate elevations in 1.8% (6 of 341) of the patients without baseline abnormalities (0.9% [17] discontinued the medication). One patient (0.3%) with an elevated baseline AST level had a transient rise to 7 times the upper limit of normal, but treatment was not discontinued. Two studies reported a small percentage of patients who withdrew owing to elevations in ALT or AST levels. Strauss et al reported 3.1% (9 of 295) of the patients withdrew owing to elevated TG, ALT, or AST levels, and Ertam et al indicated that 1.1% (1 of 91) of the patients discontinued therapy owing to increased ALT or AST levels; the exact value was not reported.

Several studies reported elevations in liver function tests without specific values. Four studies did not specify the component (ALT, AST, or AP) but reported an increase in 3.8% (3 of 78), 45% (8 of 45), 56% (3 of 127), 53% (6 of 100), and 3.7% (1 of 27) of the patients. Other studies reported elevations in ALT in 7.9% (18 of 228) and AST in 7.0% (16 of 228) of the patients; AST elevation in 7.0% (16 of 228) and AP elevation in 3.4% (7 of 206) of the patients. No patients in any of the above studies required a reduction in isotretinoin dose or discontinuation of therapy.

Discussion
This study was performed with the intent to shed more light on laboratory monitoring for isotretinoin therapy since there are major differences between the suggestions in the package insert and multiple studies that suggest less frequent testing. This meta-analysis showed that (1) isotretinoin is associated with a statistically significant change in the mean value of several laboratory tests (white blood cell count and hepatic and lipid panels), yet (2) the mean changes across a patient group did not meet a priori criteria for high-risk and (3) the proportion of patients with laboratory abnormalities was low.

All of the 99% CIs calculated in the meta-analyses showed a change from baseline; however, none of the intervals crossed the predefined thresholds for high-risk or grade 2 abnormalities. This finding indicated that 0.5% of patients, similar in characteristics and treatment to study participants, are expected to have a test result above or below the boundaries of the 99% CI. The results of the narrative review also indicated that laboratory changes are frequent, especially in TG and total cholesterol levels, yet high-risk or severe abnormalities are infrequent. The meta-analysis determined that changes in total cholesterol and TG levels were similar alterations from baseline to 8 weeks to 20 weeks. These findings support the suggestions by Barth et al and Altman et al to perform laboratory monitoring at baseline and during the first 1 to 2 months of isotretinoin therapy rather than continue monitoring throughout the course of treatment.

The results of this study should be considered in the context of its limitations. The meta-analysis is limited by the availability of extant data and the completeness of the reports. We did not have access to information about the patients or the treatment, so associations between isotretinoin doses or dose changes could not be correlated with specific laboratory abnormalities. Similarly, we were not able to investigate the fasting or nonfasting status of patients at the time of testing and correlation with laboratory results since these data were limited.

The findings of this study suggest that less frequent laboratory monitoring may be safe, with few missed high-risk laboratory changes, for many patients with acne who are receiving typical doses of isotretinoin. Clinical judgment should be used to determine monitoring frequency for each patient based on baseline laboratory findings and concomitant conditions, such as preexisting liver disease, concomitant use of hepatotoxic medications, or metabolic syndrome, which may increase the risk of laboratory abnormalities.

Conclusions
The results of this study do not support the use of monthly laboratory tests for all patients with acne who receive standard doses of isotretinoin. A decrease in the frequency of laboratory monitoring for some patients could help to decrease health care spending and potential anxiety-provoking blood sampling. At our institution, we perform a lipid and hepatic panel at baseline and after 2 months of isotretinoin treatment, with more frequent monitoring dictated by baseline abnormalities and medical history. Further studies may be needed to investigate the influence of patient characteristics, which may allow risk stratification and, subsequently, clinically indicated and cost-efficient monitoring.
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