Isotretinoin Update

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Isotretinoin
Dosing
Isotretinoin

- What is the appropriate end point?
  - Time?
  - Clinical improvement?
  - Cumulative dose?

- What is the relapse rate?

- What is the definition of relapse?
  - 20 studies (1-recurrence of acne nodules and cysts; 1- acne requiring additional therapy as judged by physician or patient; 5- acne requiring oral medication; 7-increase in acne grading scores; 1- predefined change in lesion counts; 5- unclear or unstated definition of relapse)

Isotretinoin: Current Dogma

- Severe acne and acne recalcitrant to traditional treatments
- Start at 0.5mg/kg/day
- At 4 weeks, increase dose to 1mg/kg/day
- Stop at cumulative dose of 120-150mg/kg
- Instruct patients to take isotretinoin with food (fat, in particular)
Isotretinoin

**Dose-Response Study**

- N=141
- Treatment duration-20 weeks; f/up 12-18 months

<table>
<thead>
<tr>
<th>Daily dose</th>
<th>Cumulative dose</th>
<th>Relapse Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1mg/kg/day</td>
<td>14 mg/kg</td>
<td>42%</td>
</tr>
<tr>
<td>0.5 mg/kg/day</td>
<td>70 mg/kg</td>
<td>20%</td>
</tr>
<tr>
<td>1.0mg/kg/day</td>
<td>140 mg/kg</td>
<td>10%</td>
</tr>
</tbody>
</table>

- Relapse defined loosely as those who required retreatment with oral isotretinoin

Isotretinoin

- N=88

- Treatment duration-16+ weeks; f/up mean of 9 years

- Relapse defined as deterioration in acne sufficient to merit systemic therapy

<table>
<thead>
<tr>
<th>Daily Dose</th>
<th>Relapse Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5mg/kg/day</td>
<td>39%</td>
</tr>
<tr>
<td>1.0mg/kg/day</td>
<td>22%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cumulative Dose</th>
<th>Relapse Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;120mg/kg cumulative</td>
<td>82%</td>
</tr>
<tr>
<td>&gt;120mg/kg cumulative</td>
<td>30%</td>
</tr>
</tbody>
</table>

Isotretinoin

- Overall 61% required no treatment or topical treatment for acne after one course of isotretinoin (mean f/up 9 years)
- 39% relapsed (23% repeat isotretinoin; 16% systemic antibiotic)
- 96% of relapses within 3 years; 78% of relapses within 18 months

Isotretinoin
High Dose

- N=180

- Endpoint- no new acne for 1 month during therapy; f/up 12 months

<table>
<thead>
<tr>
<th>Cumulative dose group</th>
<th>Mean cumulative dose</th>
<th>Mean length of treatment</th>
<th>Relapse (requiring RX acne treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;220mg/kg</td>
<td>170.8mg/kg</td>
<td>5.8 months</td>
<td>47%</td>
</tr>
<tr>
<td>&gt;220mg/kg</td>
<td>309.8mg/kg</td>
<td>6.5 months</td>
<td>27%</td>
</tr>
</tbody>
</table>

P=.03

- 2 subjects required retreatment with isotretinoin; both in the high dose group

Isotretinoin

High Dose

<table>
<thead>
<tr>
<th>Laboratory Test (Abnormal Value)</th>
<th>Total (N = 116)</th>
<th>&lt;220-mg/kg Group (n = 38)</th>
<th>≥220-mg/kg Group (n = 78)</th>
<th>P Value²</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST level (&gt;90 U/L)</td>
<td>4.3</td>
<td>0</td>
<td>6.4</td>
<td>.11</td>
</tr>
<tr>
<td>ALT level (&gt;105 U/L)</td>
<td>0.9</td>
<td>0</td>
<td>1.3</td>
<td>.48</td>
</tr>
<tr>
<td>Cholesterol level (&gt;300 mg/dL)</td>
<td>0.9</td>
<td>0</td>
<td>1.3</td>
<td>.48</td>
</tr>
<tr>
<td>Triglycerides level (&gt;300 mg/dL)</td>
<td>9.6</td>
<td>5.3</td>
<td>11.5</td>
<td>.28</td>
</tr>
</tbody>
</table>

Table 4. Adverse Effects of High-Dose vs Lower-Dose Therapy During Treatment

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Total (N = 116)</th>
<th>&lt;220-mg/kg Group (n = 38)</th>
<th>≥220-mg/kg Group (n = 78)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry lips</td>
<td>97.4</td>
<td>100.0</td>
<td>96.2</td>
<td>.22</td>
</tr>
<tr>
<td>Dry skin</td>
<td>98.3</td>
<td>100.0</td>
<td>97.4</td>
<td>.32</td>
</tr>
<tr>
<td>Dry eyes</td>
<td>39.7</td>
<td>31.6</td>
<td>43.6</td>
<td>.22</td>
</tr>
<tr>
<td>Itching</td>
<td>36.2</td>
<td>31.6</td>
<td>38.5</td>
<td>.47</td>
</tr>
<tr>
<td>Retinoid dermatitis</td>
<td>46.5</td>
<td>31.6</td>
<td>53.8</td>
<td>.02</td>
</tr>
<tr>
<td>Headaches</td>
<td>16.4</td>
<td>13.2</td>
<td>17.9</td>
<td>.51</td>
</tr>
<tr>
<td>Vision changes</td>
<td>6.0</td>
<td>5.3</td>
<td>6.4</td>
<td>.81</td>
</tr>
<tr>
<td>Mood changes</td>
<td>7.8</td>
<td>7.9</td>
<td>7.7</td>
<td>.97</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>0.9</td>
<td>0</td>
<td>1.3</td>
<td>.48</td>
</tr>
<tr>
<td>Muscle aches</td>
<td>22.4</td>
<td>26.3</td>
<td>20.5</td>
<td>.48</td>
</tr>
<tr>
<td>Joint aches</td>
<td>34.5</td>
<td>28.9</td>
<td>37.2</td>
<td>.38</td>
</tr>
<tr>
<td>Nose bleeds</td>
<td>37.9</td>
<td>34.2</td>
<td>39.7</td>
<td>.56</td>
</tr>
<tr>
<td>Hair changes</td>
<td>6.9</td>
<td>10.5</td>
<td>5.1</td>
<td>.28</td>
</tr>
<tr>
<td>Hearing changes</td>
<td>1.7</td>
<td>0</td>
<td>2.6</td>
<td>.32</td>
</tr>
<tr>
<td>Nail changes</td>
<td>13.8 (7.8 with paronychia)</td>
<td>10.5</td>
<td>15.3</td>
<td>.32</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5.2</td>
<td>0</td>
<td>7.7</td>
<td>.08</td>
</tr>
</tbody>
</table>

Isotretinoin

High Dose

- 2 patients in high dose group discontinued treatment early due to adverse effects

- 1st discontinued at 6 months (cumulative dose 300mg/kg) due to worsening xerosis, dry eyes, arthralgias, myalgias, occasional blurry vision, and headaches. At 12 month f/up, pt reported xerosis, cheilitis, arthralgias, and abdominal pain

- 2nd discontinued at 8.5 months (cumulative dose 422 mg/kg) due to worsening mood changes, arthralgias, and sweating. At 12 months reported xerosis, rash and hair changes.

Sebum excretion rate 
*dose-response*

- 16 weeks of isotretinoin at 3 different doses (0.1/0.5/1mg/kg/day)

- At 16 weeks, sebum excretion rates (SER) reduced by 75%, 89% and 91% respectively.

- At 32 weeks (16 weeks after discontinuation of isotretinoin), SER returned to 95% of pretreatment level in low-dose group. In the other two groups, the SER returned to 60-66% of pretreatment level.

Who relapses?

- Young age
- Male gender
- Severe acne
- Females with PCOS
- Acne localized to the torso
- Individuals with large numbers of comedones

Preventing Relapse and Retrial

• There is a cumulative dose that is too low; 120mg/kg is a minimum target for cumulative dose

• The upper end is less clear, but relapses occur even at high cumulative doses (>220mg/kg)

• Relapse rate is probably around 20-30% when optimal doses are used

• There are still some patient characteristics that make relapse more likely:

  (Young age, Male gender, Severe acne, Females with PCOS, Acne localized to the torso, Individuals with large numbers of comedones)
Isotretinoin
Laboratory Evaluation
Isotretinoin Laboratory Evaluation

- Systematic review and meta-analysis of 116 references evaluating isotretinoin for acne
  - 40mg or more per day
  - At least 4 weeks of treatment
  - Patients aged 9-35
  - 10 or more participants per study
  - Must have reported values for laboratory tests of interest (CBC, HFP, and/or lipid panel)

Isotretinoin Laboratory Evaluation

- Meta-analysis included values from 22 RCT and 4 retrospective studies with a total of 1574 subjects

- 25 additional RCT and 10 retrospective studies lacked data and were not included in meta-analysis. Their results were also summarized

Isotretinoin
Laboratory Evaluation

- **Triglycerides**
  - Mean difference between baseline and 8 weeks was 45.32mg/dL (99%CI 22.73-67.92mg/dL)
  - Mean difference between baseline and 20 weeks was 45.63mg/dL (99%CI 5.15-80.11mg/dL)

- Outside of meta-analysis, TG elevations were reported
  - >200mg/dL (5%-35.9%)
  - >300mg/dL (4.3%-10%)
  - >400mg/dL (1.5%-10%)

- Zane et al reported that 40.4% of patients with normal TG level at baseline had mild elevations during treatment (150-375mg/DL) and 3.6% had transient and reversible moderate to severe elevations (>375mg/dL)

Isotretinoin Laboratory Evaluation

- **Cholesterol**
  - Change from baseline to 16 weeks and 20 weeks did not demonstrate a substantial late effect of isotretinoin

- **Hepatic Function**
  - Analysis for late effects could not be made because of lack of data
  - Zane et al reported moderate elevations (>101U/L) in 1.5% of subjects

- **White Blood Count**
  - Analysis of late effects could not be made because of lack of data

Figure. Cumulative incidence of overall laboratory abnormalities prior to and during isotretinoin therapy. Abnormalities are defined as results above the normal range for triglyceride, total cholesterol (TC), and transaminases (aspartate aminotransferase [AST] values were used if alanine aminotransferase [ALT] values were not available) and as below the normal range for white blood cells (WBCs), hemoglobin, and platelets. Error bars represent upper bound of 95% confidence interval.

Isotretinoin Laboratory Evaluation

- All of the 99% CI calculated in the meta-analysis showed a change from baseline
- None of the intervals crossed the pre-defined thresholds for high-risk or grade 2 abnormalities
- These findings indicate that 0.5% of patients are expected to have a test result above or below the boundaries of the 99% CI
- Authors 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

Isotretinoin
Laboratory Evaluation

Triglycerides

Mean difference between baseline and 8 weeks was 45.32 mg/dL (99% CI 22.73-67.92 mg/dL)

Mean difference between baseline and 20 weeks was 45.63 mg/dL (99% CI 5.15-80.11 mg/dL)

5.8 Lipid Abnormalities
Elevations of serum triglycerides in excess of 800 mg/dL have been reported in patients treated with isotretinoin. Marked elevations of serum triglycerides were reported in approximately 25% of patients receiving isotretinoin in clinical trials. In addition, approximately 15% developed a decrease in high-density lipoproteins and about 7% showed an increase in cholesterol levels. In clinical trials, the effects of triglycerides, HDL and cholesterol were reversible upon cessation of isotretinoin therapy. Some patients have been able to reverse triglyceride elevation by reduction in weight, restriction of dietary fat and alcohol, and reduction in the dose while continuing isotretinoin.

Blood lipid determinations should be performed before ABSORICA is given and then at intervals until the lipid response to ABSORICA is established, which usually occurs within 4 weeks. Especially careful consideration must be given to risk/benefit for patients who may be at high risk of triglyceridemia during isotretinoin therapy (diabetes, hypothyroidism, increased sugar intake, lipid metabolism disorder or familial history of lipid metabolism disorder). If ABSORICA therapy is instituted, more frequent checks of serum values for lipids and/or blood sugar are recommended [see Warnings and Precautions (5.15)].
Figure. Cumulative incidence of overall laboratory abnormalities prior to and during isotretinoin therapy. Abnormalities are defined as results above the normal range for triglyceride, total cholesterol (TC), and transaminases (aspartate aminotransferase [AST] values were used if alanine aminotransferase [ALT] values were not available) and as below the normal range for white blood cells (WBCs), hemoglobin, and platelets. Error bars represent upper bound of 95% confidence interval.

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Hypertriglycerideridemia

Triglycerides

High = 200-499mg/dL (not at risk for pancreatitis)

Very High = >500mg/dL

- Acute pancreatitis associated with elevated TG generally occurs at levels higher than 1000mg/dL
- To reduce the risk of pancreatitis, TG should be reduced to below 500mg/dL

Karalis, D. Adv Ther 2017;34:300-323
Hypertriglyceridemia

- American Heart Association (2011)
  - TG 200-499mg/dL lifestyle intervention
  - TG >500mg/dL lifestyle intervention and TG lowering agent

- Lifestyle interventions:
  - Limit dietary fat
  - Avoid alcohol, added sugar and refined carbohydrates
  - 30-60 minutes of exercise most days

Karalis, D. Adv Ther 2017;34:300-323
Isotretinoin
Inflammatory bowel disease
Possible association between isotretinoin and inflammatory bowel disease

- First case of IBD associated with isotretinoin use was in 1986.
  

Possible association between isotretinoin and inflammatory bowel disease


- Reports filed with the FDA MedWatch system between 1997-2002 were reviewed for strength of causality using the Naranjo adverse drug reaction probability scale.

- Adverse events data from Hoffman LaRoche controlled trials was also reviewed for de novo cases of IBD not reported to the FDA. There were NONE.

- 2 institutions independently requested MedWatch reports.

- 85 cases of IBD or IBD signs/symptoms associated with isotretinoin use were reported to the FDA between 1997 and 2002.
Possible association between isotretinoin and inflammatory bowel disease


- 85 cases of IBD associated with isotretinoin use were reported
  - 4 cases (5%) scored in the “highly probable” range
  - 58 cases (68%) scored “probable”
  - 23 cases (27%) were “possible”
  - 0 cases were “doubtful”

- 3 reported cases documented improvement when isotretinoin was withdrawn and worsening when isotretinoin was reintroduced
Isotretinoin use and the risk of inflammatory bowel disease: a case-control study

- Case-control study using a large insurance claims database
- 8,189 cases (3,664 Crohn’s disease and 4,428 Ulcerative Colitis, 97 IBD unspecified)
- 21,832 controls
- 60 subjects exposed to isotretinoin (24 IBD, 36 controls)
- Ulcerative colitis was associated with previous isotretinoin exposure (Odds ratio 4.36, 95% confidence interval: 1.97, 9.66)
- There was no association between isotretinoin exposure and Crohn’s disease
Potential association between the oral tetracycline class of antimicrobials used to treat acne and inflammatory bowel disease

*Margolis DJ. Am J Gastroenterol 2010 Aug*

- Retrospective cohort study using The Health Improvement Network database of the United Kingdom
- 94,487 individuals with acne who were followed up by a general practitioner for 406,294 person-years
- IBD was noted in
  - 41 individuals exposed to minocycline (24,085)
  - 79 individuals exposed to tetracycline/oxytetracycline (38,603)
  - 32 individuals exposed to doxycycline (15,032)
  - 55 individuals not exposed to any of these antibiotics
Conclusions:

- Tetracycline class antibiotics may be associated with the development of inflammatory bowel disease.
- Prior exposure to tetracycline antibiotics should be considered when assessing the causality of other acne drugs in the development of IBD.
Isotretinoin use and the risk of inflammatory bowel disease: a population-based cohort study

- Retrospective population-based cohort in BC, Canada
- 12 year study period
- The entire population of untreated provincial (British Columbia) residents aged 12-29 years served as the reference group (1,526,946; 11,005 with IBD)
- 46,922 treated with isotretinoin (87 IBD)
- 184,824 treated with topical acne medication (316 IBD)

Isotretinoin use and the risk of inflammatory bowel disease: a population-based cohort study

- **Primary analysis:**

  Compared with untreated participants, no association between IBD and the use of isotretinoin (rate ratio 1.14; 95% CI 0.92-1.41) or topical acne medications (rate ratio 1.11; 95% CI 0.99-1.24) was found.

- **Analysis according to age:**

  Isotretinoin use was associated with a significant risk of IBD in those aged 12-19 (rate ratio 1.39; 95% CI 1.03-1.87) but no association was found in those aged 20-29 (rate ratio 0.93; 95% CI 0.67-1.29)

Alhusayen RO et al. JID doi:10.1038/jid.2012.387
Isotretinoin use and the risk of inflammatory bowel disease: a population-based cohort study

Analysis according to disease type:

- No significant association between isotretinoin therapy and IBD among patients with UC (rate ratio 1.31; 95% CI 0.96-1.80) or Crohn’s disease (rate ratio 1.17; 95% CI 0.90-1.52).

- A modest but statistically significant association between topical acne medications and UC was found (rate ratio 1.19; 95% CI 1.00-1.42). There was no such association with Crohn’s (rate ratio 1.07; 95% CI 0.93-1.23).

Alhusayen RO et al. JID doi:10.1038/jid.2012.387
Isotretinoin and Risk of Inflammatory Bowel Disease

- Nested case-control study and meta-analysis
- Cohort of women aged 18-46 years who had received at least one prescription for an oral contraceptive between May 1, 2001-December 31, 2009 in a large US health claims database
  - 2,159 cases of IBD
  - 43,180 controls

Isotretinoin and Risk of Inflammatory Bowel Disease

- 10 cases were exposed to isotretinoin (5 UC and 5 Crohn)
- 191 controls were exposed to isotretinoin
- The adjusted risk ratio for IBD was 0.99 (95% CI 0.52-1.90)
- RR for UC = 1.10 (95% CI 0.44-2.70)
- RR for Crohn = 0.91 (95% CI 0.37-2.25)

- Pooled RR from 5 studies = 0.94 (95% CI 0.65-1.36)

Isotretinoin and Risk of Inflammatory Bowel Disease: A French Nationwide Study

- Data from National Health Insurance system for all French people covered by the general scheme (76% of the whole French population)
- 50 million individuals
- 7,593 cases of inflammatory bowel disease (26 exposed to isotretinoin)
- 30,372 controls (140 exposed to isotretinoin)

Isotretinoin and Risk of Inflammatory Bowel Disease: A French Nationwide Study

- Isotretinoin was not associated with increased UC risk but was associated with a decreased CD risk.

Disproportionate reporting by attorneys to the FDA Adverse Event Reporting System

- 2214 cases of IBD resulting from isotretinoin were reported to FDA AERS
  - 1944 (87.8%) were reported by attorneys
  - 132 (6.0%) were reported by physicians
  - 112 (5.1%) were reported by consumers

- Only 3.6% of the total reports for all drugs during the same time period were reported by attorneys

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An amicus brief is a document that is filed in a court by someone who is not directly related to the case under consideration. The most classic example is a document filed by an advocacy group, such as the American Civil Liberties Union. The additional information found in such a document can be useful for the judge evaluating the case, and it becomes part of the official case record.
Amicus Brief

- Amicus Brief submitted to the Supreme Court of New Jersey by:
  - American Medical Association
  - American Academy of Dermatology
  - American Acne and Rosacea Society
  - Dermatological Society of New Jersey
  - Medical Society of New Jersey

“Peer Reviewed Medical Literature Shows No Statistically Significant Association Between Isotretinoin and IBD”
Wound healing
### Table 2. Summary of Panel Recommendations

<table>
<thead>
<tr>
<th>Procedural Intervention</th>
<th>Consistency of Evidence</th>
<th>Recommendation</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical dermabrasion</td>
<td>Inconsistent</td>
<td>Not recommended</td>
<td>D</td>
</tr>
<tr>
<td>Manual dermabrasion and microdermabrasion</td>
<td>Consistent</td>
<td>There is insufficient evidence to delay manual or microdermabrasion</td>
<td>B</td>
</tr>
<tr>
<td>Chemical peel</td>
<td>Consistent</td>
<td>There is insufficient evidence to delay superficial chemical peels</td>
<td>B</td>
</tr>
<tr>
<td>Cutaneous surgery</td>
<td>Inconsistent</td>
<td>There is insufficient evidence to delay cutaneous surgery</td>
<td>D</td>
</tr>
<tr>
<td>Laser hair removal</td>
<td>Consistent</td>
<td>There is insufficient evidence to delay laser hair removal</td>
<td>B</td>
</tr>
<tr>
<td>Fractional ablative/nonablative laser</td>
<td>Consistent</td>
<td>There is insufficient evidence to delay fractional ablative or nonablative laser procedures. Fully ablative laser procedures are not recommended at this time</td>
<td>B</td>
</tr>
</tbody>
</table>