Use of isotretinoin for the treatment of acne

Megha M. Tollefson, MD
Associate Professor of Dermatology and Pediatrics
Mayo Clinic
March 4, 2017
DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

Megha M Tollefson, MD

F048 - Translating Evidence into Practice: Acne Guidelines

DISCLOSURES

I do not have any relevant relationships with industry.
Background

• Isomer of retinoic acid
• Used in the treatment of acne for over 30 years
• Decreased sebum production, decreased acne, decreased acne scarring
• FDA-approved for severe, recalcitrant, or nodulocystic acne vulgaris
Controversies

• Dosing and indications
• Depression/mood
• Inflammatory bowel disease
• Laboratory monitoring
• iPLEDGE
Dosing

- Conventional dosing
  - Severe acne vulgaris
  - Initiate at 0.5 mg/kg/day, continue at 1 mg/kg/day
- Early studies showed less relapse with
  - 1 mg/kg/day vs 0.5 mg/kg/day
  - Cumulative >120 mg/kg vs <120 mg/kg with dose-dependent plateau at 150 mg/kg total
Dosing

• Is there a role for isotretinoin in more moderate acne?

• What is the optimal dosing?
  • Daily
  • Cumulative
Alternate dosing schedules

- Randomized, controlled comparative study
- 60 patients with moderate acne
  - Conventional, low-dose, or pulsed dosing
- Had 1 year FU
- Low-dose just as efficacious as conventional (pulsed inferior) and with less side effects
- Patient satisfaction highest in low-dose group

Lee JW et al. BJD 2011; 164:1369-1375.
Alternate dosing schedules

- RT, not blinded or placebo-controlled
- 120 pts of all severities, 4 diff dosing regimens
  - Conventional (A)
  - Alternate day (B)
  - Intermittent (C)
  - Low-dose QOD (D)
- Group A better for severe acne
- A,B and D similar for moderate
- All similar for mild

More on low-dose

- Open label, non-comparative, prospective; 70 patients
  - Low dose + pulsed azithromycin
    - 94% clearance (62/66)
    - 11% relapse at 1yr FU

- Prospective, 150 patients with mild to moderate acne
  - Treated to complete resolution
  - Cumulative mean 81 mg/kg
  - 9% relapse

Cumulative Dosing

- 120-150 mg/kg based off old studies
- Many not of optimal quality
  - Vague and inconsistent definitions of clearance, remission, and relapse
- Optimal cumulative dose likely varies with severity
Cumulative dosing

- Prospective observational
- 180 patients, treated until no new lesions x 1 month
- Higher relapse rates at 1 yr FU in those treated with <220 mg/kg
  - 47.4% vs 26.9%
  - But p=0.22 after adjusting for age, gender, race, treating physician, and duration of treatment
- Separate study indicated no impact of cumulative dose on rate of relapse if treated until 2 months clear
- Needs to be studied further

Fed vs. unfed state

Dosing summary

• Conventional vs. low vs. intermittent dosing

<table>
<thead>
<tr>
<th>Acne Severity</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>• Conventional dosing</td>
</tr>
<tr>
<td></td>
<td>• Cumulative dosing of 120-150 mg/kg as a target but tailored to each patient</td>
</tr>
<tr>
<td>Mild to moderate</td>
<td>• Low-dose has similar efficacy to conventional with similar relapse rates; less side effects</td>
</tr>
<tr>
<td></td>
<td>• Lower cumulative dosing may be effective</td>
</tr>
<tr>
<td></td>
<td>• Intermittent dosing not as effective</td>
</tr>
</tbody>
</table>

• With food

Oral isotretinoin is recommended for the treatment of severe nodular acne
Oral isotretinoin is appropriate for the treatment of moderate acne that is treatment-resistant or for the management of acne that is producing physical scarring or psychosocial distress
Low-dose isotretinoin can be used to effectively treat acne and reduce the frequency and severity of medication-related side effects. Intermittent dosing of isotretinoin is not recommended
Will my child get depressed?

- Teenager with severe nodulocystic scarring acne
- Refractory to other treatments
- Parents have read that isotretinoin may cause depression and are hesitant to start it
Depression/mood

• Prior sporadic reports and FDA Adverse Events Drug Reporting System cases describing depression, suicidal ideation, suicide

• Multiple population-based and prospective studies since then
Association of suicide attempts with acne and treatment with isotretinoin

• Population-based retrospective cohort study

• Increased risk of attempted suicide up to 6 months after treatment *but*
  • risk was already rising before treatment

Sundstrom et al. BMJ 2010;341:c5812
Suicidal Ideation, Mental Health Problems, and Social Impairment Are Increased in Adolescents with Acne: A Population-Based Study

- Cross-sectional, questionnaire-based study of almost 4K teenagers
- 14% with substantial acne
  - Increased suicidal ideation
  - More mental health problems
  - Social impairment

<table>
<thead>
<tr>
<th>Table 2. Number (n) and frequency (%) of suicidal ideation and mental health problems (SDQ) in the sample (N) and across acne severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acne severity, n/N (%)</td>
</tr>
<tr>
<td>-----------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Suicidal ideation</td>
</tr>
<tr>
<td>All</td>
</tr>
<tr>
<td>Boys</td>
</tr>
<tr>
<td>Girls</td>
</tr>
<tr>
<td>Mental health problems (SDQ)</td>
</tr>
<tr>
<td>All</td>
</tr>
<tr>
<td>Boys</td>
</tr>
<tr>
<td>Girls</td>
</tr>
</tbody>
</table>

Abbreviation: SDQ, Strengths and Difficulties Questionnaire.
## Prospective cohort studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Control</th>
<th>Measures</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohen et al.</td>
<td>Patients treated with isotretinoin</td>
<td>Oral or topical acne therapy</td>
<td>Depression scale (CES), Depression inventory @ baseline and 2 months</td>
<td>No correlation between isotretinoin use and depression (p=0.497, 0.2)</td>
</tr>
<tr>
<td>Kaymak et al.</td>
<td>Isotretinoin treatment</td>
<td>Topical treatment; not randomized</td>
<td>DLQI, Beck Depression inventory (BDI), Hospital anxiety and depression scale @ baseline, 2 mo, 4 mo</td>
<td>No difference at baseline, All scales improved more in isotretinoin group (p&lt;0.05)</td>
</tr>
<tr>
<td>Bozag et al.</td>
<td>Moderate to severe acne pts given isotretinoin</td>
<td>Healthy volunteers</td>
<td>BDI, State and Trait Anxiety Inventory @ baseline, 1 mo, 4 mo</td>
<td>Higher scores at baseline in acne group, significant improvement at 4 mo. (p&lt;0.05)</td>
</tr>
</tbody>
</table>
# Prospective cohort studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Control</th>
<th>Measures</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chia et al.</td>
<td>Teenagers with mod to severe acne on isotretinoin</td>
<td>Mod to severe acne- topical and oral abx; not randomized</td>
<td>CES-D depression scale @ baseline and 3-4 mo</td>
<td>Scores equal in 2 groups at baseline; both improved with treatment</td>
</tr>
<tr>
<td>Nevoralov a &amp; Dvorakova</td>
<td>Mod to severe acne, rx isotretinoin</td>
<td>None</td>
<td>BDI @ baseline, 1 mo, then q3 mon</td>
<td>BDI scores improved with treatment (p &lt;0.0001)</td>
</tr>
</tbody>
</table>

## Prospective cohort studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Control</th>
<th>Measures</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rehn et al.</td>
<td>Finnish military, prescribed isotretinoin</td>
<td>None</td>
<td>DLQI, BDI @ baseline, weeks 4-6, weeks 10-12</td>
<td>BDI and DLQI improvement (p &lt;0.001)</td>
</tr>
<tr>
<td>Gnanaraj et al.</td>
<td>150 Mod to severe acne patients</td>
<td>None</td>
<td>Hamilton Depression scale</td>
<td>Improvement in depression scores @ 3 months (p&lt;0.001)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Weeks 4–6</th>
<th>Weeks 10–12</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI [mean ± SD]</td>
<td>3.0 ± 3.948</td>
<td>2.0 ± 3.589</td>
<td>1.8 ± 3.783</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BDI ≥ 10 [n (%)]</td>
<td>9 (7.1%)</td>
<td>7 (5.6%)</td>
<td>4 (3.2%)</td>
<td>0.205</td>
</tr>
<tr>
<td>Suicidal ideation [n (%)]</td>
<td>17 (13.5%)</td>
<td>9 (7.1%)</td>
<td>9 (7.1%)</td>
<td>0.010</td>
</tr>
<tr>
<td>Leeds [mean ± SD]</td>
<td>3.6 ± 1.955</td>
<td>2.5 ± 1.527</td>
<td>1.8 ± 1.272</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>DLQI [mean ± SD]</td>
<td>3.8 ± 3.283</td>
<td>2.3 ± 2.655</td>
<td>3.9 ± 2.986</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Summary - Depression/mood and IBD

- Sporadic reports of mood changes, depression, suicide in the past
- No evidence-based link of isotretinoin and increased depression, suicide, or suicidal ideation on a prospective and population basis.
- Treatment with isotretinoin likely improves mood and depression symptoms
“But, doctor, what is this I hear about inflammatory bowel disease?”
Inflammatory bowel disease

- First report in 1985
- Review of FDA adverse event reports
  - 85 reported cases between 1997 and 2002
    - Authors classified 68% as probably linked to isotretinoin
  - 2214 cases between 2003-2013
    - 88% reported by attorneys
    - 3.6% for all other drug reactions

Isotretinoin and IBD

- Case-control study; insurance claims database
  - Incident IBD cases identified and matched 3:1 controls
  - UC but not CD associated with prior isotretinoin exposure

- Nested Case-control study
  - Better study design
  - IBD cases matched to 20 controls
  - No increased risk for IBD with isotretinoin

Population-based studies

- University of Manitoba
  - 1.2% of IBD cases used isotretinoin prior to diagnosis
  - 1.1% of controls

- British Columbia
  - Isotretinoin (46K) vs topical treatment (185K) vs no treatment (1.5 million)
  - No significant association between isotretinoin and IBD
  - Some association between topicals and UC

Population-based studies

• French National Health Insurance system
  • ~7600 IBD cases identified
  • 1:4 cases:controls
  • 26 IBD cases (0.3%), 140 controls (0.4%) exposed to isotretinoin
    • No increased risk for UC
    • Decreased risk for CD (OR 0.45)

• Olmsted County
  • 1078 patients with acne
  • IBD less frequent in those exposed to isotretinoin than those not (0.9% vs 2.6%, p =0.03)

Summary- IBD and isotretinoin

- Early case report and anecdotal suggestion
- No evidence from population-based studies
  - Suggestion of acne link to IBD

“But, I really hate getting my blood drawn”
Laboratory Monitoring

• Meta-analysis, 26 studies
• Isotretinoin associated with elevated
  • WBCs
  • Liver function tests
  • Lipid/triglyceride levels
• Most changes present by 8 weeks
• Monthly laboratory testing unnecessary
  • i.e. baseline and with dose increases

Lee et al. JAMA Derm 2016.
Laboratory Monitoring

- Retrospective review of 515 patients
  - Insignificant changes in WBCs and platelets
  - LFT elevations infrequent and not significant
  - TGs and cholesterol elevation in ~20% but max grade 2
  - Detected approximately 2 months into treatment

Laboratory Monitoring

• Systematic review of isotretinoin and pancreatitis
  • 4 cases of hypertriglyceride-induced pancreatitis
  • 16 cases of pancreatitis a/w isotretinoin (normal triglyceride levels)

Opel et al. BJD In-press.
Pregnancy prevention

- Hundreds of reports of isotretinoin-exposed pregnancies
- iPLEDGE now the 3rd risk management program to prevent pregnancy
  - Mandatory
  - No difference in preventing fetal exposures between SMART and iPLEDGE

Shin et al. JAAD 2011; (65): 1117-25.
Pregnancy

• 150 isotretinoin-exposed pregnancies per year

• Anonymous survey of 75 iPLEDGE participants, women of childbearing potential
  • 19% of those who chose abstinence were not
  • 34% of those sexually active did not comply with 2 forms of BC

• Patient-independent forms of birth control should be considered
Surgical procedures

• Evidence is limited
  • Case reports of abnormal/keloid scarring
  • Cohort studies- No abnormal scarring in 17 patients undergoing chemical peels or dermabrasion (on isotretinoin or 1-3 months post-isotretinoin)
  • Cohort studies- No abnormal scarring in ~300 patients undergoing laser
  • Cohort study- 3/25 with dry sockets after wisdom tooth extraction
• Retrospective cohort study of isotretinoin-exposed vs non-exposed patients
  • No difference in rates of atypical/abnormal wound healing

Wootton et al. BJD 2014;170:239-244.
Summary

• Conventional dosing best for severe acne
• Low-dose isotretinoin can be used in moderate acne, with decreased side effects
• No evidence-based causal relationship between isotretinoin and anxiety/depression
  • Treatment with isotretinoin may improve symptoms
• No evidence-based causal relationship between isotretinoin and IBD
  • Risk may actually be decreased
• Less laboratory monitoring
• All patients must adhere to iPLEDGE
  • Patient-independent BC should be considered
The Dermatology Foundation has supported & advanced my career.