Use of isotretinoin for the treatment of acne

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DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

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F025 - 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
• Surgical procedures
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 questions

• 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

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

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</td>
</tr>
<tr>
<td></td>
<td>tailored to each patient</td>
</tr>
<tr>
<td>Mild to moderate</td>
<td>• Low-dose has similar efficacy to conventional with similar</td>
</tr>
<tr>
<td></td>
<td>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 2. Number (n) and frequency (%) of suicidal ideation and mental health problems (SDQ) in the sample (N) and across acne severity

<table>
<thead>
<tr>
<th>Acne severity, n/N (%)</th>
<th>Whole sample, n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No/little</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>394/3,620 (16.9)</td>
</tr>
<tr>
<td>Boys</td>
<td>117/1,596 (7.3)</td>
</tr>
<tr>
<td>Girls</td>
<td>277/2,024 (13.7)</td>
</tr>
</tbody>
</table>

| Mental health problems (SDQ) |            |       |           |
| All                          | 421/3,647 (11.5) | 318/3,155 (10.1) | 76/384 (19.8) | 27/108 (25.0) | <0.01 |
| Boys                         | 108/1,609 (6.7) | 81/1,377 (5.9) | 16/179 (8.9) | 11/53 (20.8) | <0.01 |
| Girls                        | 313/2,038 (15.4) | 237/1,778 (13.3) | 60/205 (29.3) | 18/55 (29.1) | <0.01 |

Abbreviation: SDQ, Strengths and Difficulties Questionnaire.
Systematic review and meta-analysis: isotretinoin and depression

Huang and Cheng JAAD 2017.
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
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)

Routine monitoring of liver function tests, serum cholesterol, and triglycerides at baseline and again until response to treatment is established is recommended. Routine monitoring of complete blood count is not recommended.

Opel et al. BJD 2016.
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

<table>
<thead>
<tr>
<th>Risk management program</th>
<th>No. of fetal exposures</th>
<th>No. of treatment courses</th>
<th>Fetal exposure rate/1000 treatment courses</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMART</td>
<td>18</td>
<td>5788</td>
<td>3.11</td>
<td>.69</td>
</tr>
<tr>
<td>iPLEDGE</td>
<td>11</td>
<td>4124</td>
<td>2.67</td>
<td></td>
</tr>
</tbody>
</table>

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

All patients treated with isotretinoin must adhere to the iPLEDGE risk management program. Females of child-bearing potential taking isotretinoin should be counseled regarding various contraceptive methods, including user-independent forms.
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. Tolkachjov et al JAAD 2017..
## Timing of surgical procedures - systematic review

<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 manuals 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>

Spring et al. JAMA Derm 2017.
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
• Recommendations for timing of surgical procedures should be reconsidered
The Dermatology Foundation has supported & advanced my career.