Interventions for rosacea

*Cochrane review*

10 May 2012

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Rosacea

- Chronic skin condition in mainly fair-skinned people
- Starts 2nd-3rd decade in life
- 4 subtypes
  - Subtype 1: erythematotelangiectatic rosacea
  - Subtype 2: papulopustular rosacea
  - Subtype 3: phymatous rosacea
  - Subtype 4: ocular rosacea
- 1 variant: granulomatous rosacea
- Pathogenesis?: multiple hypotheses
- Therapies?: numerous options....
The process..

- Course Evidence Based Medicine in Amsterdam
- Contact Skin Group van Cochrane Collaboration
- Title registration
- Finding coauthors
- Writing protocol
- Conducting the review
- First review published in 2004
- First update 2005
- Second update 2011
Methods

• RCTs
• Adults with rosacea
• Any type of intervention, either alone or in combination, versus placebo or active treatment
• Primary outcomes: QoL and participant-assessed changes in rosacea severity

• Secondary outcomes: Physician-assessed changes in rosacea severity (e.g. global evaluation, lesion count), drop-out rates and adverse events
Searches

2 authors independently, no language restrictions!

- MEDLINE
- EMBASE
- BIOSIS
- Science Citation Index
- Cochrane Skin Group Specialised Register
- Cochrane Central Register of Controlled Trials
- Ongoing trials
- Checking references of found studies
- Contact authors and pharmaceutical companies for unpublished studies
Selection of studies en data extraction

2 authors independently
- Checked all references for eligibility
- Risk of bias assessment
- Data extraction
- Data analyses

- Conclusions
- After peer reviewing etc, publication in Cochrane Library
- Keeping it up-to-date
Results

Number of identified records
• 2441 records identified for first review (2004)
• 640 additional records for first update (2005)
• 2198 additional records for last update (2011)

Total number of included studies : 58

Most studies were conducted in participants with papulopustular rosacea with a study duration of 2-3 months
Several studies showed effect on erythema of:

- Topical metronidazole, azelaic acid and sulphacetamide/sulphur, however, limited data

- Doxycycline 40 and 100 mg, and zinc sulphate, however, more research is required

We could only include 2 RCTs with laser and/or light based therapies, those might be effective, but limited data were provided
PDL laser
Intense pulsed light

Before

6 months after last treatment (4 cycles)

Papageorgiou Br J Derm 2008
Results for subtype 2

10 studies metronidazole vs placebo. Pooling was only possible for a few of those

Physician’s global evaluation of improvement

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Topical metronidazole</th>
<th>Placebo</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Bjerke 1989b</td>
<td>44</td>
<td>50</td>
<td>26</td>
</tr>
<tr>
<td>Breneman 1998</td>
<td>26</td>
<td>104</td>
<td>6</td>
</tr>
<tr>
<td>Nielsen 1983a</td>
<td>24</td>
<td>41</td>
<td>8</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>195</td>
<td>139</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>94</td>
<td>40</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 3.55, df = 2 (P = 0.17); I² = 44%
Test for overall effect: Z = 4.79 (P < 0.00001)

Metronidazole is effective for treatment of papulopustular rosacea
Results for subtype 2 (II)

4 studies with azelaic acid, 3 could be pooled

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Azelaic cream Events</th>
<th>Total</th>
<th>Placebo Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bjerke 1999</td>
<td>62</td>
<td>76</td>
<td>22</td>
<td>38</td>
<td>18.7%</td>
<td>1.41 [1.05, 1.89]</td>
<td></td>
</tr>
<tr>
<td>Thiboutot 2003a</td>
<td>100</td>
<td>164</td>
<td>71</td>
<td>165</td>
<td>45.2%</td>
<td>1.42 [1.14, 1.76]</td>
<td></td>
</tr>
<tr>
<td>Thiboutot 2003b</td>
<td>98</td>
<td>169</td>
<td>56</td>
<td>166</td>
<td>36.1%</td>
<td>1.72 [1.34, 2.20]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>409</strong></td>
<td><strong>369</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>1.52 [1.32, 1.76]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 260
Estimated events: 149
Heterogeneity: Chi² = 1.82, df = 2 (P = 0.44); I² = 0%
Test for overall effect: Z = 5.77 (P < 0.00001)

Azelaic acid is effective for treatment of papulopustular rosacea
Results for subtype 2 (III)

Adverse events metronidazole vs placebo

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Topical metronidazole</th>
<th>Placebo</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bitar 1990</td>
<td>10</td>
<td>50</td>
<td>37.3%</td>
<td>1.67 [0.66, 4.24]</td>
</tr>
<tr>
<td>Bjerke 1989b</td>
<td>1</td>
<td>50</td>
<td>6.4%</td>
<td>0.94 [0.06, 14.60]</td>
</tr>
<tr>
<td>Breneman 1998</td>
<td>4</td>
<td>104</td>
<td>24.9%</td>
<td>0.67 [0.15, 2.87]</td>
</tr>
<tr>
<td>Koçak 2002</td>
<td>0</td>
<td>20</td>
<td>31.5%</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Nielsen 1983a</td>
<td>4</td>
<td>41</td>
<td>100.0%</td>
<td>0.78 [0.23, 2.70]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>265</td>
<td>209</td>
<td>100.0%</td>
<td>1.09 [0.58, 2.06]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>19</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity</strong></td>
<td>Chi² = 1.52, df = 3 (P = 0.68); I² = 0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect</strong></td>
<td>Z = 0.28 (P = 0.78)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adverse events azelaic acid vs placebo

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Azelaic cream</th>
<th>Placebo</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bjerke 1999</td>
<td>30</td>
<td>76</td>
<td>76.8%</td>
<td>1.00 [0.62, 1.62]</td>
</tr>
<tr>
<td>Thiboutot 2003a</td>
<td>9</td>
<td>164</td>
<td>7.7%</td>
<td>4.53 [0.99, 20.64]</td>
</tr>
<tr>
<td>Thiboutot 2003b</td>
<td>8</td>
<td>169</td>
<td>15.5%</td>
<td>1.96 [0.60, 6.40]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>409</td>
<td>369</td>
<td>100.0%</td>
<td>1.42 [0.92, 2.19]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>47</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity</strong></td>
<td>Chi² = 4.57, df = 2 (P = 0.10); I² = 56%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect</strong></td>
<td>Z = 1.59 (P = 0.11)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Results for subtype 2 (IV)

3 studies topical metronidazole versus azelaic acid

Rosacea improvement patient-assessed:
- in *Elewski 2003* and *Wolf 2006*: no statistical significant difference
- in *Maddin 1999* azelaic acid was more effective

Rosacea improvement physicians-assessed:
- in *Elewski* and *Maddin* azelaic acid more effective
  (in *Wolf*: no statistical difference)

More adverse events with azelaic acid in *Elewski*, but not in *Wolf* and *Maddin*
Results and conclusions topicals

• Topical metronidazole and azelaic acid are both effective and safe
• Azelaic acid might be more effective than metronidazole but more research is needed

Data not presented today, but
• Topical metronidazole has shown to be effective in maintaining remission
• Azelaic acid once a day is as effective as twice a day (one study)
No evidence that these treatments are effective:

- Benzoylperoxide (or combined with clindamycin)
- Sulphacetamide 10% + sulphur 5%
- Permethrin
- Pimecrolimus
- 4-ethoxybenzaldehyde (flavonoid cream)

No studies could be included regarding topical retinoids or special cosmetics
Results of oral treatments for subtype 2

2 studies with tetracyclines: old (1966, 1971), short (4-6 weeks) and of poor quality. Clinicians have no doubt about effectiveness, but evidence is lacking

- Physician-assessed: tetracycline was more effective than placebo
- Patient-assessed (1 study): no difference between the groups

Studies of *del Rosso 2007, Fowler 2007, Sanchez 2005* showed effectiveness of doxycycline 40 mg over placebo
Results of oral treatments for subtype 2

No statistical significant difference in number of adverse events between both groups

There is evidence that 40 mg is at least as effective as 100 mg but with less adverse effects (Del Rosso 2008)

No studies could be included with azithromycin, minocycline or isotretinoin
Subtype 3 (phymas):

- Evidence is lacking (no RCTs). Both surgical as well as laser therapy show good cosmetic results

Before

After Co2 laser
(Madan et al, Br J Dermatol 2009)
• Some evidence that topical cyclosporine 0.05% ophthalmic emulsion is more effective than artificial tears

• Up to 60% have ocular rosacea

• RCTs investigating effect of different treatment modalities on ocular rosacea are warranted
Further conclusions

No studies could be included that addressed the effectiveness of:

- Dietary measures (avoiding triggers in food)
- Avoiding triggers in general
- Use of sunscreens
- Use of certain cosmetics (non-irritating, camouflaging redness etc)
Take Home messages

• Insufficient evidence for interventions subtype 1
• For subtype 2, topical metronidazole, azelaic acid, and doxycycline (40 mg) are effective and safe for short-term use
• 40 mg is at least as effective as 100 mg with evidence of less adverse effects
• Some evidence that tetracycline is effective
• No studies could be included for subtype 3
• For ocular rosacea (subtype 4) cyclosporine 0.05% ophthalmic emulsion more effective than artificial tears
Future research...

- High-quality studies of the more widely-used treatments for rosacea, i.e. tetracycline, minocycline, azithromycin, isotretinoin, topical retinoids, and light-based therapies

- RCTs addressing
  - interventions for ocular rosacea
  - interventions for phymas
  - dietary measures, sunscreens, special cosmetics etc. for reducing symptoms of rosacea
I am very grateful to my coauthors:

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- Zbys Fedorowicz (UKCC Bahrain Branch)