SYSTEMIC REVIEW ON THE TREATMENT OF ACNE SCARRING

Dr. Alison M Layton
Disclosures

- **Sponsorship or research funding**
  - Unrestricted research grants Galderma and GSK for basic science research one relating to acne scarring

- **Honorarium**
  - Unrestricted educational talks at international meetings Galderma, MEDA and GSK
  - As member of a drug-monitoring committee Galderma and independent monitor for a clinical study L’Oreal

- **Shareholder**
  - None

- **Involvement in the review**
  - Clinical expertise and intellectual input to the review and responses to referee comments
What will be covered

• Background
  • Why this systematic review is important
• Methods used
• Interventions assessed
• Results from studies
• Key messages
  • Relevance to future research
Scarring Is Frequent: Even With Mild/Moderate Acne

- **87%** prevalence of acne scars in a population of 973 subjects with primarily mild-moderate acne (843/973 pts)

- **50%** of acne scars are clinically relevant

- Also confirmed that acne scarring on **chest and back** is quite common
  - **38%** and **51%** of pts in this group

Acne of any severity can lead to scarring

<table>
<thead>
<tr>
<th>Country</th>
<th>Frequency of scars in active acne patients</th>
<th>Scar frequency according to acne severity on face</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Almost clear/mild</td>
</tr>
<tr>
<td>France</td>
<td>37%</td>
<td>22%</td>
</tr>
<tr>
<td>Brazil</td>
<td>44%</td>
<td>30%</td>
</tr>
<tr>
<td>USA</td>
<td>43%</td>
<td>28%</td>
</tr>
</tbody>
</table>

Risk factors

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Probability of scarring (odds ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Brazil</td>
</tr>
<tr>
<td>Acne severity</td>
<td></td>
</tr>
<tr>
<td>Severe or very severe acne vs. other severities</td>
<td>3.4 [2.7–4.2]</td>
</tr>
<tr>
<td></td>
<td>France</td>
</tr>
<tr>
<td>Time elapsed between acne onset and first effective treatment</td>
<td>6.8 [5.1–9.0]</td>
</tr>
<tr>
<td>3 years or more vs. 0–&lt;3 years</td>
<td></td>
</tr>
<tr>
<td>Relapse after treatment</td>
<td>1.6 [1.4–1.9]</td>
</tr>
<tr>
<td>Yes vs. no</td>
<td>USA</td>
</tr>
<tr>
<td></td>
<td>1.9 [1.6–2.2]</td>
</tr>
</tbody>
</table>

Qualitative survey involving dermatologists in France (n=106), Brazil (n=120) and the USA (n=120) who filled out a pen-and-paper census form for each active acne patient they saw in consultation over 1 week (France = 1,366; Brazil = 1,718; USA = 1,972)

Psychological Impact of Acne Scars Should Not Be Underestimated

- Acne scarring: “a risk factor for suicide”.
- Demonstrated significant psychosocial disability
  - Increased anxiety, depression, lowered self esteem
- Higher psychopathology than acne
  - Related to disease duration
  - Increased problems in females

Presence of acne scars has a negative impact on perceptions

- **No acne scars**
  - 14% describe the person as shy
  - 24% think the person makes others uncomfortable
  - 27% think the person is fairly skilled at sports
  - 31% describe the person as healthy
  - 26% think the person is stressed

- **Acne scars**
  - 23% describe the person as shy
  - 30% think the person makes others uncomfortable
  - 23% think the person is fairly skilled at sports
  - 21% describe the person as healthy
  - 35% think the person is stressed

Online survey in USA, UK, Japan, Germany, France and Brazil among respondents 18 years and over (n=4,618) who reacted to three randomly selected facial pictures of individuals with either clear skin or digitally superimposed acne scars, but no active acne lesions.

ACNE PRIORITY SETTING EXERCISE

Launched in 2013
YOU JOINED THE FIGHT AGAINST ACNE!!

Here are the top ten questions you voted for...

1. What management strategy should be adopted for the treatment of acne in order to optimise short and long-term outcomes?
2. What is the correct way to use antibiotics in acne to achieve the best outcomes with least risk?
3. What is the best treatment for acne scars?
4. What is the best way of preventing acne?
5. What is the correct way to use oral isotretinoin (Roaccutane) in acne in order to achieve the best outcomes with least risk of potentially serious adverse effects?
6. Which lifestyle factors affect acne susceptibility or acne severity the most and could diet be one of them?
7. What is the best way of managing acne in mature women who may/may not have underlying hormonal abnormalities?
8. What is the best topical product for treating acne?
9. Which physical therapies including lasers and other light based treatments are safe and effective in treating acne?
10. How long do acne treatments take to work and which ones are fastest acting?
Questions and concerns about managing acne scars

• Do physical interventions work?
• Is preventative treatment of acne the best policy?
• Concerns about payments made for treatments in the private sector
  • Laser treatments £1,700 - £3,500
  • Dermabrasion £1,000 - £5,000
  • Chemical peels £60 - £100
  • Microneedling £200- £350
Previous reviews

- Cochrane systematic review of lasers in 2000
  - No RCTs where lasers compared to placebo or alternative lasers
  - 27 studies of poor quality case series with small numbers
  - Lack of studies prevented any conclusions to be drawn about effectiveness of lasers
  - Recommended well designed randomised controlled comparisons of laser therapies
Background

- http://www.nets.nihr.ac.uk/identifying-research
- NIHR HTA (Health Technology Assessment Programme) panel prioritised the review for funding
- Commissioned the Cochrane Group

Objectives

- To assess the effects of interventions for treating acne scars
- Recognising the need to better inform caregivers and consumers
Methods

- **Randomised controlled trials**
  - Split face or parallel arms
  - Any active intervention or combination vs active intervention, placebo or no treatment

- **Participants**
  - All ages, gender and ethnic groups diagnosed by dermatologist or clinician appropriately skilled to confirm the diagnosis of acne scars
  - All grades of scar severity
  - Excluded studies predominantly or only looking at keloid scarring

- **Active interventions included**
  - Chemical peels, dermabrasion, midrodermabrasion, laser therapy, radiofrequency, punch techniques, dermal grafting, tissue-augmenting agents, needling, subcision, intralesional steroid injections, silicone gel, cryotherapy, retinoids, imiquimod, 5-fluorouracil, interferon, bleomycin, surgery or combined therapy.
Methods

• **Primary outcomes**
  • Participant reported scar improvement
    • Measured by a scar improvement, grading or severity scale over
      • 24 weeks (short term)
      • > 24 weeks considered long term
  • Adverse effects enough to cause withdrawal from the study
    • Serious if life threatening or impact on ability to function
    • Severe defined by the intensity
Methods

- **Secondary outcomes**
  - Investigator assessed scar improvement
    - measured by a scar improvement, grading or severity scale
  - Participant satisfaction
    - measured by a satisfaction questionnaire
  - Quality of life impact
    - measured by global of disease specific means
  - Participant reported short term adverse effects
    - up to 4 weeks, e.g. pain, erythema, oedema, infection
  - Investigator reported short term adverse effects
    - up to 4 weeks
  - Duration in days of the post-procedure downtime
    - the number of days participant unable / unwilling to go out into the public
Selection of studies and data extraction

• Searches extensive
  • Electronic searches of databases, trial registers, manufacturers websites for trial information, authors for information on missing data and on-going trials

• Two independent review authors
  • Identified studies from abstracts and literature for retrieval
  • Then reviewed full text for eligibility for inclusion
  • Assessed risk of bias
  • Extracted and analysed the data
  • If information not clear contacted authors
  • Third author included if consensus not reached on any point
  • Used GRADE = Grading of Recommendations, Assessment, Development and Evaluation to assess quality of evidence and to inform strength of recommendations
  • Created summary of findings tables
Interventions for acne scars

24 RCTs
7 parallel RCTs
17 within-individual split face studies

Active intervention to placebo or no treatment
2 parallel RCTs
5 split face RCTs

Active interventions compared
17 RCTs

- 23 single centre
- 789 participants in total
- Sample sizes
  - 6 - 147;
  - 15 studies had < 30 participants
Demographics

Studies conducted in:
USA = 7
China = 1
Denmark = 2
Egypt = 3
Iran = 2
South Korea = 6
Thailand = 2
Turkey = 1

Participants:
Adults aged 18 years or older with facial scarring
20 studies Males and females; 706 participants
3 studies females only; 76 participants
1 study males only; 8 participants
No studies examined scars on the back

Funding of the 24 trials:
5 supported by industry
4 by academic institutions
15 did not report source of funding
### Interventions examined in RCTs

#### Resurfacing Procedures
- Chemical peeling
- Laser resurfacing
  - Non fractional non-ablative
  - Fractional
  - Fractional radiofrequency

#### Lifting Procedures
- Subcision
- Injectable fillers

#### Combination Interventions
- Fractional laser plus intradermal platelet-rich plasma (PRP)
- Fractional laser plus punch elevation
- Microdermabrasion plus photodynamic therapy with aminolevulinic acid (ALA-PDT)

#### Other
- Needling
- Needling plus chemical peeling
Risk of bias table showing risk of bias against each item presented as percentages across all included studies.

Risk varied from low to high:
- Blinding of participants and personnel (performance bias)
- Blinding of outcome assessment (detection bias): participant-reported
Risk of bias summary across individual studies

Performance bias
Blinding of participants and personnel

Detection bias
Blinding of outcome assessment
Participant reported
Summary of results

Types of scars included

• 21/24 trials included “atrophic scars”
• 2/24 did not specify the atrophic scars mentioned acne scars
• 1/24 included atrophic and hypertrophic scars
• 0/24 trials included mention of scars on the back
Summary of results

Primary outcome measures
- Participant-reported scar improvement
  - 14/24 trials included this primary efficacy outcome measure
- Participants with serious or severe adverse effects enough to withdraw from the study
  - 20/24 trials included this primary outcome

Secondary outcome measures
- Participant satisfaction
  - 8/24 studies considered this outcome
- Quality of life
  - No trials considered QoL as a measure
- Participant and Investigator reported short-term adverse effects
  - 23/24 studies
Outcomes reported under 14 pair-wise comparisons

• Non-fractional non-ablative laser vs placebo or no treatment
• Fractional laser vs non-fractional non-ablative laser
• Fractional laser vs placebo or no treatment
• Fractional laser vs radiofrequency
• Fractional laser vs combined fractional laser plus any active intervention
• Fractional laser vs chemical peeling
• Fractional laser vs combined chemical peel plus needling
• Chemical peeling vs placebo or no treatment
• Chemical peeling vs combined chemical peeling plus active intervention
• Chemical peeling vs needling
• Needling vs placebo or no treatment
• Injectable filler vs placebo or no treatment
• Injectable filler vs subcision
• Combined microdermabrasion plus ALA-PDT vs combined microdermabrasion plus placebo-PDT
Participant and investigator short term > 50% improvement
32 participants per arm showed that fractional CO2 laser given for 4 sessions at monthly intervals improves acne scars significantly more than non fractional non-ablative Q switched 1064 nm Nd:YAG laser at week 24*

Investigator assessed adverse effects demonstrated PIH lasting 2-3 weeks in
6/32 treated with the fractional CO2 laser
10/32 with the non-fractional non-ablative laser

*Statistical significance
Very low quality evidence
Unclear risk of detection bias
Fractional laser vs radiofrequency

Patient reported scar improvement of > 50% at 8 weeks

A parallel study 20 patients per arm randomly divided received 3 sessions at monthly intervals of 1550 nm Er.Glass non-ablative fractional laser or comparator fractional radiofrequency

Both treatments improved scars

Not significant
Very low quality evidence
High risk of detection bias
Fractional laser vs combined chemical peel plus needling

**Patient reported scar improvement of > 50% at 12 months**  
A parallel group study 13 patients per arm demonstrated both fractional non-ablative laser 1540nm Er:Glass laser vs chemical peeling TCA 20% combined with skin needling given monthly for 6 sessions improved scars.

All participants in both groups reported pain, transient oedema and erythema for < 4 weeks.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Fractional laser n/N</th>
<th>Combined chemical n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leheta 2014b</td>
<td>9/13</td>
<td>9/13</td>
<td>1.00 [0.60, 1.67]</td>
<td></td>
</tr>
</tbody>
</table>

No statistical significance  
Very low quality evidence  
High risk of detection bias
Chemical peeling vs placebo

A study comparing chemical peeling (varying strengths of glycolic acid peels or 15% glycolic acid cream given bi-weekly) to placebo showed chemical peeling given for 24 weeks significantly better than placebo*

48 patients completed the study

No severe adverse events that resulted in withdrawal from the study, 7 withdrew as intolerant of the higher concentration of the peeling agent

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Good response &gt; 60%</th>
<th>Partial 30-60%</th>
<th>Minor &lt;30%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical peel</td>
<td>6/34</td>
<td>22/34*</td>
<td>6/34*</td>
</tr>
<tr>
<td>Placebo</td>
<td>0</td>
<td>4/14*</td>
<td>6/14*</td>
</tr>
</tbody>
</table>

*Significantly better response with chemical peeling p<0.05
Chemical peeling vs chemical peeling and needling

Participant reported scar improvement at 32 weeks

A study showed that 1 session of deep chemical peeling (using non-hydro-alcoholic solution of phenol oil in 60% concentration formula) vs chemical peeling with TCA 20% combined with skin needling for 4 sessions at 6 weekly intervals, improved acne scars in 10 participants in each treatment arm.

All participants in both groups reported transient erythema lasted 4 weeks in the chemical peeling group and 2-4 days in the chemical peeling plus needling group.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Chemical peeling n/N</th>
<th>Combined treatment n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leheta 2014a</td>
<td>10/10</td>
<td>10/10</td>
<td>1.00 [0.83, 1.20]</td>
<td></td>
</tr>
</tbody>
</table>

No statistical difference
Very low quality evidence
High risk of detection bias
Chemical peeling vs needling

Participant reported short term assessment at week 4

A study in 27 participants showed that both chemical peeling (full strength TCA 100% CROSS n=12) and skin needling (dermaroller n=15) given for 4 sessions at monthly intervals improved acne scars by at least 50%

Participant satisfaction was positive for both treatments

Short term adverse effects showed no differences between interventions

No statistical difference

Very low quality evidence

High risk of detection bias
Chemical peeling with TCA
Injectable filler vs placebo

Parallel study of 147 participants showed injectable filler (polymethylmethacrylate suspended in bovine collagen) vs saline injections given for 1 session improves atrophic acne scars by 24 weeks.

Global Aesthetic Improvement Scale reported a significant difference in favour of Injectable fillers with 77% of participants confirming improvement vs 42% of placebo group*

No difference between the adverse effects was noted between groups. Participant satisfaction significantly higher with injectable filler.

Review: Interventions for acne scars
Comparison: 12 Injectable fillers versus placebo or no treatment
Outcome: 3 Participant satisfaction

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Injectable fillers n/N</th>
<th>Placebo n/N</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karnik 2014</td>
<td>82/97</td>
<td>26/50</td>
<td>1.63 [1.23, 2.15]</td>
<td></td>
</tr>
</tbody>
</table>

*Statistical significance
Moderate quality evidence
Low risk of detection bias
Challenges in interpretation

- Scar subtypes and classification
- Genesis of scars
  - Immune mechanisms
  - Natural history
- Standardised tools
Acne Scars

- Subtypes of scars depend on increase or loss of collagen
  - Atrophic, hypertrophic and keloid
- Severity of scarring not necessarily related to severity of acne
Several risk factors are linked with scar development

- **Acne severity**
  - Any severity
  - More frequent in severe/very severe acne

- **Timing of treatment**
  - Delay to first effective treatment

- **Genetic predisposition**
  - Ethnicity, family history

- **Site of lesion**
  - Face vs. back and chest

- **Inflammation and abnormal remodelling**
  - Inflammation extent/duration
  - Prolonged angiogenesis
  - Different immune response
  - Overactive collagenases and/or MMP/TIMP ratios

MMP – matrix metalloproteinase; TIMP – tissue inhibitors of metalloproteinases

Acne scars have previously been classified by scar shape

**Icepick scars**
- Narrow (<2 mm)
- Extend to deep dermis/subcutaneous tissue
- Sharply marginated
- Opening often wider than apex

**Rolling scars**
- Usually >4–5 mm
- Shallow
- Occur from dermal tethering
- Give an undulated appearance to skin

**Boxcar scars**
- Usually 1.5–4 mm
- Shallow or deep
- Round to oval shape
- Sharp vertical edges
- Do not taper

Inconsistencies in classifying acne scars

Classification of acne scars is difficult even for acne experts

Editor
There is relatively little information available concerning validated acne scar description.\(^1\)\(^-\)\(^6\) In the regular meetings of the Global Alliance to Improve Outcomes in Acne, an international group of dermatologists with an interest in acne research and management,\(^7\)\(^-\)\(^9\) we have also noticed that there are often variations in how dermatologists describe and/or classify acne scars. We therefore organized a short survey to identify how much agreement is there on acne scar classification within our membership of dermatologists with a specific interest in acne.

terminology is currently in use, we specifically avoided supplying any terminology or scar definitions within the survey. A total of 23 (43%) completed surveys were received.

Results: general questions
Fourteen (61%) of the respondents indicated that they were not satisfied with existing acne scar classifications, yet 17 (74%) felt that scar classification affects treatment choice. Seventeen (74%) of the respondents indicated that they classify scars using the system published by Jacob (Fig. 1); four individuals classify simply based on ‘atrophic’ or ‘hypertrophic,’ one individual classified scars by severity (mild, moderate, severe), and the last individual said general shape/size. One person also reported using the Jacob system in the general practice setting, but the more detailed system pub-
Immunity and acne scarring

Acne scarring is determined by an inability to mount an effective immune response

Non Scarrers:
- Immune response - more rapid, more potent, greater innate component

Scarrers:
- Immune response – slower, extended and more highly sensitised to antigens

Potential targets involved in scar formation

Strong increase in level of IL-2 +++ in normal skin and acne lesions in patients prone to scarring
- Supports persistent chronic activation and proliferation of CD4+ T lymphocytes

Moderate increase in level of IL-10 ++ in normal skin and acne lesions in patients prone to scarring
- IL-10 inhibits function of antigen-presenting cells
- Inhibits IFN-γ production by T-cells and macrophages

Activation of innate immunity

Suggests different profiles of skin innate immunity in the normal skin of acne patients who develop and do not develop scars.

Patients not prone to scar: IL-10, IL-2 low & MMPs/TIMPs high
Patients prone to scar: IL-10, IL-2 high & MMPs/TIMPs low

Relevant to trial design

MMP – matrix metalloproteinase; TIMP – tissue inhibitors of metalloproteinases
Genesis of atrophic acne scars

• Global assessments and lesion counting (including scars ≥ 2 mm)
• Digital photography tracking of lesions determined by expert on live assessment
  – Visia CR® system (Canfield)

Genesis of atrophic acne scars

- 99% of scars were derived from papules/pustules and post-inflammatory lesions
- Only 1% of scars were derived from comedones
- **52%** of scars that appear during the first 6 months still present at 2 years
Natural History Atrophic Acne Scars

• Atrophic acne scars continually form
  ...some resolve
    – 36% resolved within 6-months
    – 64% did not

• Duration of transient acne scars:
  • mean 41 days; median 28 days

• Derivation: 98% from papules and post-inflammatory lesions

IMPLICATIONS
Importance of early treatment of primary acne lesions in scar prevention
Relevant to trial design – need long term follow up

Associated acne - macules
# Standardised tools

<table>
<thead>
<tr>
<th>Acne Scar System</th>
<th>Severity Scheme</th>
<th>Regional Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leeds 1994</td>
<td>Numeric (Maximum 30 for each region)</td>
<td>Face, chest and back</td>
</tr>
<tr>
<td>Echelle d’Évaluation Clinique des Cicatrices d’Acne 2007</td>
<td>Numeric (maximum 540)</td>
<td>Face</td>
</tr>
<tr>
<td>Qualitative Global Acne Scarring Grading System 2006</td>
<td>Four descriptive grades</td>
<td>Face, chest and back</td>
</tr>
<tr>
<td>Quantitative Global Acne Scarring Grading System 2006</td>
<td>Numeric (maximum 84)</td>
<td>Face</td>
</tr>
<tr>
<td>Patient and Observer Scar Assessment Scale (POSAS) 2004</td>
<td>Numeric (maximum 50 observer/maximum 60 patient)</td>
<td>Face</td>
</tr>
<tr>
<td>Global Aesthetic improvement Scale (GAIS) 2013</td>
<td>Five descriptive grades</td>
<td>Face</td>
</tr>
<tr>
<td>Facial acne scar evaluation tool (FASET) to assess atrophic scars 2015</td>
<td>Global, Dispersion, Numeric</td>
<td>Face</td>
</tr>
</tbody>
</table>
Conclusions on quality of evidence

- Lack of good quality evidence of different interventions due to
  - poor methodology
  - underpowered studies
  - lack of standardised assessments of improvement
  - confounding factors such as acne and scar duration & skin phototype

- Lack of studies that establish efficacy of treatments compared to placebo or sham

- Comparator studies of active treatments suggest no difference
  - In the absence of studies that establish efficacy compared to placebo or sham interventions, this finding of no evidence of difference between two active treatments could mean that neither work
Conclusions on clinical benefits

- No studies included the back

- Nothing to confirm short term benefit will translate to long term effects

- Moderate quality evidence for dermal fillers

- No high quality evidence to advocate any treatment for first-line use in the management of acne scars
Key results

- Based on participant reported scar improvement
  - Fractional ablative laser was more effective in producing scar improvement than non-fractional non-ablative laser.
  - Fractional radiofrequency was similar to fractional non ablative laser.
  - Chemical peeling was more effective than placebo.
  - Chemical peeling showed similar improvement to skin needling.
  - Chemical peeling combined with skin needling showed similar improvement to fractional non ablative laser and deep chemical peeling.
  - Injectable fillers provided better scar improvement vs placebo.

- Based on short term adverse effects participant reported and investigator assessed
  - No significant difference between treatments and all acceptable.
Future studies

- Consider
  - Placebo/sham trials
    - to establish whether any of the active treatments produce meaningful patient benefits
  - Adopting patient-reported outcomes as a primary measure,
  - Utilisation of standardised / validated core outcome measures
  - Evaluation several months after the treatment has been done
  - Given the genesis of scars split face designs
  - Reporting serious adverse events
    - was a research gap found is this review
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Editorial Group Cochrane Skin Group
Thank you!

alison.layton@hdft.nhs.uk