Cochrane systematic review update:

New findings on treatments for vitiligo

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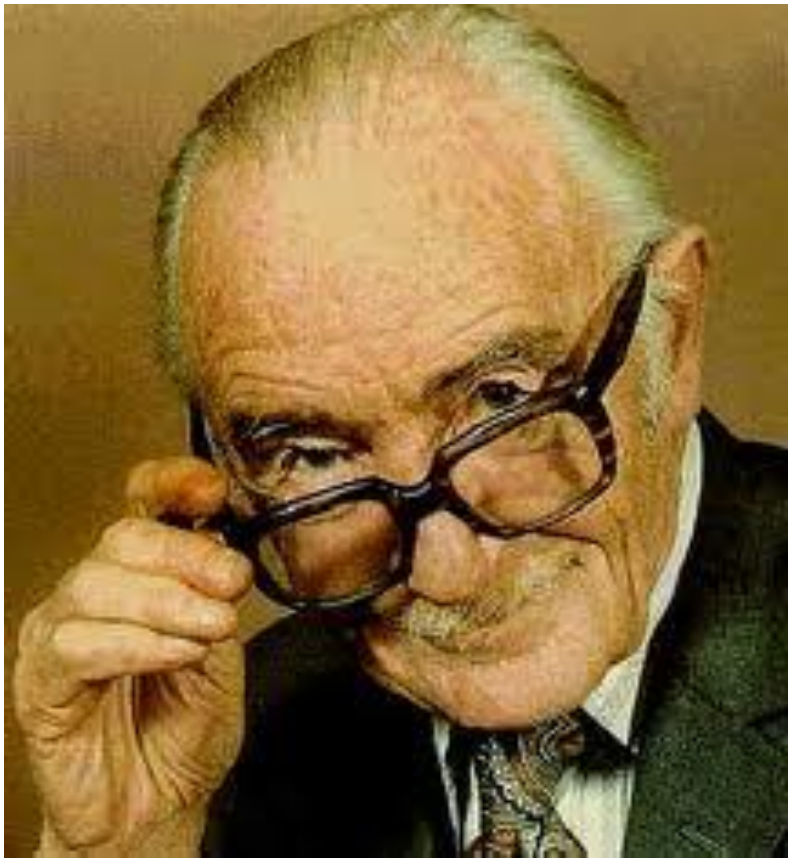
Evidence-Based Update
Loughborough
May 23rd 2013

Outline

- About Cochrane Systematic Reviews
- 2010 Update of ‘Interventions for vitiligo’
  - Recommendations from 2010 update
- 2013 update- progress so far

Cochrane Collaboration



Archie Cochrane
1909-1988

"It is surely a great criticism of our profession that we have not organised a critical summary,
by specialty or subspecialty, adapted periodically, of all relevant randomised controlled trials"

Image: Cardiff University Library, Cochrane Archive, University Hospital Llandough

Cochrane Collaboration

- Worldwide network of review groups
- Clinicians, consumers, statisticians / methodologists, researchers
- Aim: Preparing, maintaining and promoting the accessibility of systematic reviews of the effects of health care interventions

Systematic Reviews

Cochrane systematic reviews-strengths

- Predefined, rigorous and explicit methodology
- Usually include only RCTs
- Critical appraisal of studies
  - Assess methodological quality / risk of bias

Why a systematic review of interventions for vitiligo?

Why a systematic review of vitiligo?

- Increase in number of published RCTs since 2006 review
- Update already in progress in 2008
- Review needed as part of vitiligo workstream of NIHR Programme Grant awarded to Centre of Evidence-Based Dermatology
- Lay the foundation for future RCTs

Review group members

• Maxine Whitton	Consumer
• Urba Gonzalez	Clinician
• Mariona Pinart	Research Fellow
• Jo Leonardi-Bee	Methodologist
• Clare Lushey	Research Fellow
• Jonathan Batchelor	Clinician

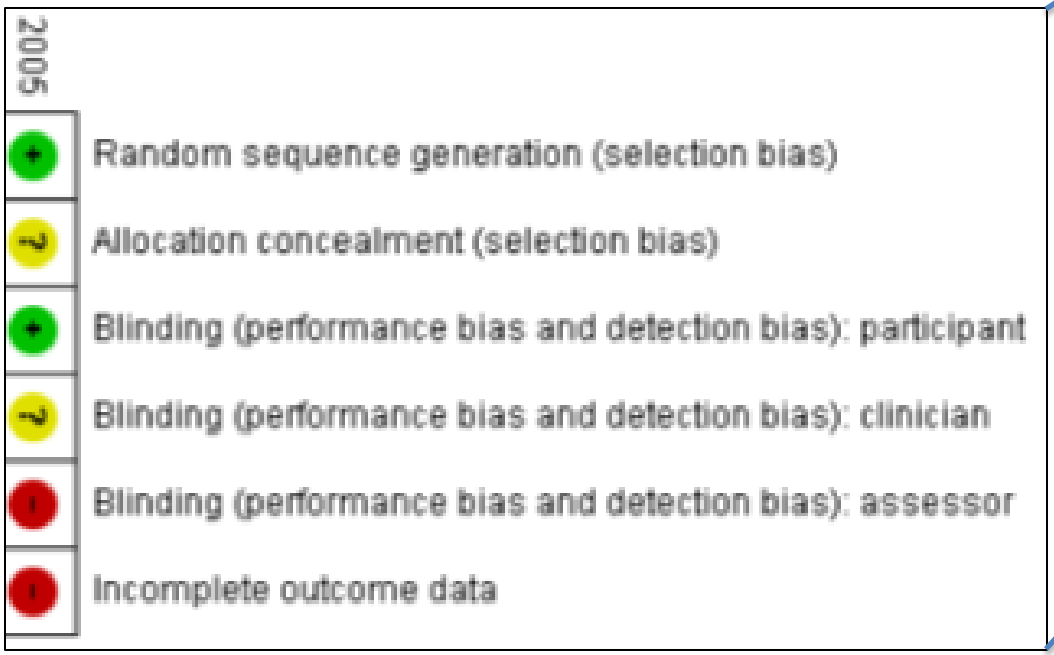
Outcomes

- Primary
  - Quality of life improvement
  - Proportion of participants achieving > 75% repigmentation (= treatment success)
- Secondary
  - Cessation of spread
  - Long-term repigmentation (at 2 years)
  - Adverse effects

‘Interventions for Vitiligo’

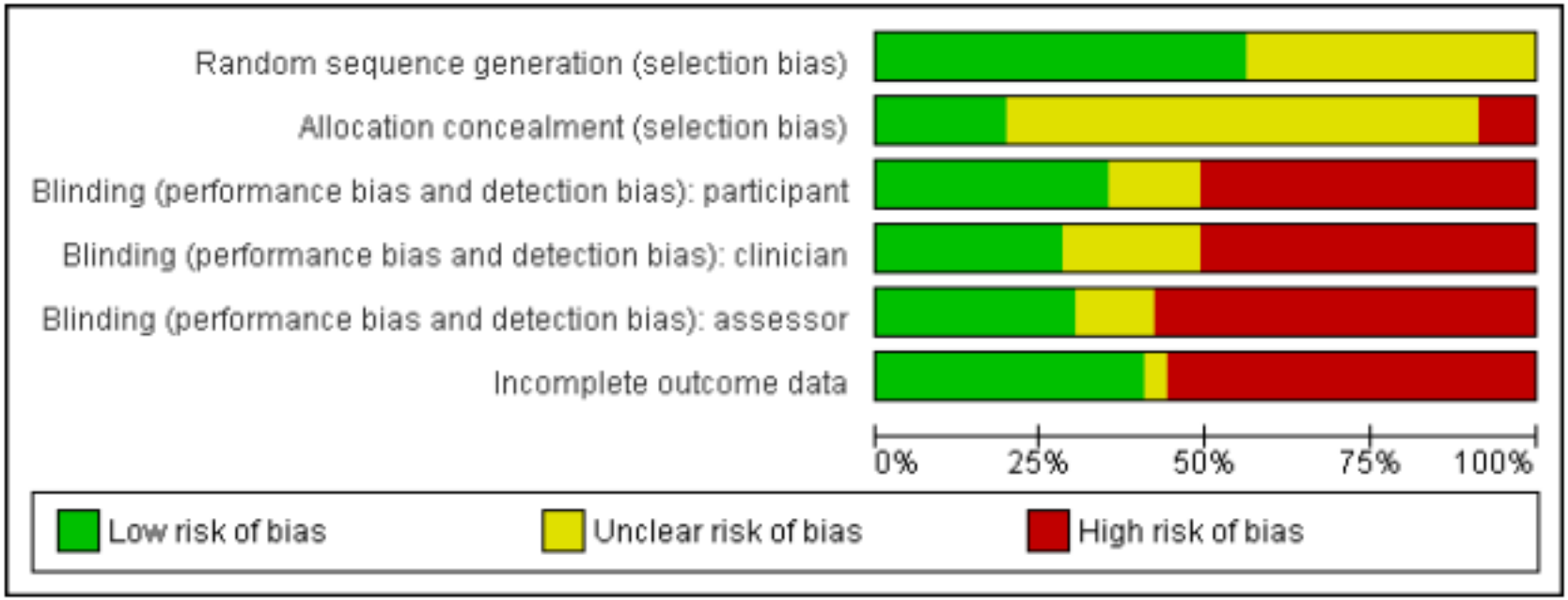
- Search for new RCTs
  - Total of 57 RCTs including old studies
- Data Extraction
- Risk of Bias assessment
- Inputting of data into RevMan
- Write-up (Published in Cochrane Library 2010)

Risk of bias assessment



Risk of bias assessment

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Summary of main results

- 38 new RCTs since original review (2006)

- Many new interventions
  - Topical: pimecrolimus, tacalcitol, 5-fluorouracil, topical lactic acid, catalase / dismutase
  - Oral: Zengse pill, *Polypodium leucotomos*, levamisole, antioxidant pool, minipulses of prednisolone, azathioprine
  - Light: monochromatic excimer light, BB-UVB, Er:YAG laser
  - Surgical: minipunch and split skin grafts, transplantation of autologous melanocytes
  - Psychological interventions (one study)

Summary of main results

- Many interventions used in combination
- Commonest kind of intervention in new RCTs: Light source +/- other intervention (29 studies)
- Many new studies assessing NB-UVB +/- other intervention

Some evidence for use of:

- Clobetasol propionate
- Laser + tacrolimus or hydrocortisone butyrate
- MEL + tacalcitol
- Fluticasone propionate + UVA
- Ginkgo biloba

- Meta-analysis only possible for 2/57 studies

Overall completeness and applicability of the evidence

- Only 4 studies assessed quality of life
- Many different scales used to measure repigmentation
- Only 6 studies assessed cessation of spread
- None of the studies assessed long-term repigmentation

Quality of the evidence

- Improved quality of reporting
  - ?Awareness of CONSORT statement*
- Randomisation described adequately 56%
  - Allocation concealment 25%
- Double blinding 33%
- Intention-to-treat 39% (mostly due to trials with no dropouts)

*Begg C et al. Improving the quality of reporting of randomized controlled trials: the CONSORT statement *JAMA* 1996;276:637-639

Conclusions

- Need for
  - Standardised measures of vitiligo
  - Long-term studies (up to 2 years if possible)
  - Cessation of spread to be used as outcome
  - Patient-centred outcomes
  - More long-term studies of NB-UVB
  - More studies of calcineurin inhibitors
  - Larger studies of combination interventions
  - More studies of complementary interventions
  - More studies of psychological interventions
  - Studies of cosmetic camouflage

Stating the obvious?

ONLINE FIRST

Guidelines for Designing and Reporting Clinical Trials in Vitiligo

Urbà González, MD, PhD; Maxine Whitton, BA (Hons), Hon MSc; Viktoria Eleftheriadou, MD; Mariona Pinart, PhD; Jonathan Batchelor, BMedSci, BM, BS, MRCP; Jo Leonardi-Bee, BSc(H), MSc, PGCHE, PhD

Objective: To create guidelines for randomized controlled trials (RCTs) investigating interventions used in the management of vitiligo.

Participants: Guideline developers included authors (clinicians, patient representatives, and a statistician) of the Cochrane systematic review "Interventions for Vitiligo" plus the coordinator of the vitiligo priority-setting partnership at the Centre of Evidence-Based Dermatology at the University of Nottingham.

Evidence: The guidelines are based on the assessment of the quality of design and reporting of RCTs evaluating interventions for vitiligo included in the 2010 update of the Cochrane systematic review "Interventions for Vitiligo."

Consensus Process: We reviewed and commented on the sources of bias in existing RCTs on interventions for vitiligo (selection bias, blinding assessment, attrition bias, characteristics of participants, interventions, and outcomes) based on the findings of the Cochrane review, and we used open discussion on guideline drafts focusing on the study question (participants, interventions, and outcomes), study design (research methods), and reporting.

Conclusions: Much opportunity exists for improving the design and reporting of vitiligo clinical trials. The proposed guidelines will help overcome methodologic challenges faced when conducting RCTs to answer treatment questions.

Arch Dermatol.
Published online August 15, 2011.
doi:10.1001/archdermatol.2011.235

2013 Update

- In progress
- Final search completed April 2013
- Double data extraction almost complete – 4 studies still awaiting checking
- Presentation can only cover what we have done so far
- No analysis or firm conclusions possible

2013 update

- 33 additional published RCTs to be included
- Nearly 40 ongoing RCTs registered in clinical trials registers since last update (5 from China)
- Studies conducted in 18 countries – none in the UK for this update, 1 in the previous update (Yones)
- 15/33 (45%) single intervention comparison studies

Outcomes

PRIMARY OUTCOMES

1) Quality of life using validated tool
   - 5/33 (15%) studies reported on Quality of Life

2)Repigmentation >75%
   - 23/33 (70%) studies reported on our primary outcome >75% repigmentation

5/33 (15%) studies reported on both primary outcomes

Secondary Outcomes

1) Cessation of spread (stabilisation)

Not reported in any of the studies

2) Long-term permanence of repigmentation (at least one year of follow-up)

Not reported in any of the studies

3) Adverse Effects

28/33 studies (85%) reported adverse effects

Methodological Quality of the Studies

- Randomisation (requirement for inclusion in the review)
- Method of randomisation
- Allocation concealment
- Blinding
- Intention-to-Treat (ITT) analysis

Randomisation

- All included studies randomised
  - If method of randomization not stated, we contacted the author
- One study excluded as a result – consecutive enrolment admitted
- Method of randomisation reported in 26/33 studies (78%) (computer generated sequence, block randomisation etc.)

Allocation concealment

- “Allocation concealment ensures there is no selection bias during randomisation” (CONSORT statement)

- Only 5/33 studies concealed allocation (e.g. sealed envelopes, explicit mention that randomisation code was not broken)

Blinding

- Within-participant studies are sometimes difficult to blind
- Where two different types of interventions are compared (e.g. topical vs light) blinding is not possible
- Some studies were open label studies
- 17/33 (52%) studies were assessor blinded

Intention to Treat (ITT)

- 13 /33 (40%) performed ITT analysis
- As with previous update, this was mainly due to trials with no drop-outs

2010 – 2013
What has changed?

- More studies of calcineurin inhibitors (8)
- More single intervention studies (15)
- More studies reporting method of randomisation (75% vs. 56%)
- New interventions (tetrahydrocucurminoid cream, fractional CO2 laser, Helium-Neon laser, oral vitamin E in combination with other interventions)
- CONSORT flow diagram used in one RCT

No Change

- Not many paediatric studies
- No studies of psychological interventions or cosmetic camouflage
- Many different outcome measures
- No long-term follow-up studies

Acknowledgements

- Cochrane review team: Mariona Pinart, Urba Gonzalez, Jo Leonardi-Bee, Khaled Ezzedine, Viktoria Eleftheriadou, Zainab Jiyad

Any questions?