H1- Antihistamines for Chronic Spontaneous Urticaria

Dr Maulina Sharma
Consultant Dermatologist
Derby Hospitals NHS Foundation Trust
Chronic Spontaneous/ Idiopathic Urticaria

- Recurrent itchy weals, up to 24 hr
- More than 6 weeks’ duration
- Associated angio-oedema
- No obvious identifiable cause
Chronic Spontaneous Urticaria

- Unpredictable
- Disabling
- 20% still suffer after 10 years
Impact of CSU
Impact of CSU

To assess the effects of H1-antihistamines for CSU

- Whether one antihistamine superior to another
- Combination better than monotherapy?
- High doses superior to standard?
- Duration of benefit from H1-antihistamines
- Risks and side effects
- Quality of life
Criteria for studies

RCTs only including cross over designs and quasi RCTs
All other designs excluded

• Participants
  Any age with clinical diagnosis of CSU/CIU

• Exclusions
  Urticaria of less than 6 weeks
  Other types of urticaria including immune complex, papular, contact, physical, cholinergic or auto-inflammatory
Interventions

Any H1-antihistamine, first or second generation, any dose, any route of administration

With or without concomitant medications

Duration:
Short (up to 2 weeks)
Intermediate (2 weeks up to 3 months)
Long term (more than 3 months)
Comparators

- No treatment (placebo) or any active pharmacological compound
- Included head-to-head comparisons
  - Excluded terfenadine, astemizole (withdrawn)
    e.g. acupuncture, psychological interventions
Outcomes

Primary
- Proportion with complete suppression of urticaria
- With good or excellent response
- Participants with 50% QoL

Secondary
- Adverse events (serious requiring withdrawal)
- Minor adverse events
- Relapse with one month of stopping H1-antihistamines
Searches (up to June 2014)

- Exhaustive searches of all bibliographic data bases
  - Cochrane skin group specialised register
  - Cochrane central register of Controlled Trials (Cochrane library)
  - MEDLINE (from 1946)
  - EMBASE (from 1974)
  - PsycINFO (from 1806)

- Trials registers
  - The meta Register of Controlled Trials
  - The US National Institutes of Health Ongoing Trials Register
  - The Australian New Zealand Clinical Trials Registry
  - The WHO International Clinical Trials Registry platform
  - The EU Clinical Trials Register

- Reference lists
Results

9759 participants
34 trials reported outcome data for 23 comparisons
### Included studies

#### First generation antihistamines
- Hydroxyzine
- Pheniramine

#### Second generation antihistamines
- Cetirizine
- Desloratadine
- Ebastine
- Emedastine
- Fexofenadine
- Levocetirizine
- Loratadine
- Ketotifen
- Mizolastine
- Rupatadine

#### Other comparators
- Montelukast
- Doxepin
Design and Duration

Some unusual designs:

Garavaglia 1995 (drop-outs replaced by new recruits)

Wang 2012 (dose reduction study)

Weller 2013 (single body part)

Staevska 2014
(cross-over after randomisation and in-hospital stay; levo vs hydroxy; after 5 days crossed without wash-out)

• 17 short term
• 55 intermediate
• None long term
Randomisation: 12 out of 73 described adequately

Allocation: 4 studies used coded sealed envelopes; 5 studies at high risk, 3 were open label

Blinding: 20 studies adequate; 8 not blinded to participants or personnel

Blinding of outcome assessment: 14 adequate; 8 did not attempt it
Risk of Bias

Selective reporting:
24 studies low risk

20 studies risk associated:
- no. of participants not reported
- mean scores and graphs only
- no adverse events reported
- whether concomitant meds allowed
- lab results done but not reported
- duration of follow up not reported
- results in placebo arm not reported
Quality of Evidence

GRADE
Of 73 studies: 31 industry sponsored, 6 through research grants and non-profit organisations

Notable methodological limitations
- Only 12 adequately randomised
- Only 4 adequate concealment
- Only 20 adequately blinded (participants and personnel)
- Only 14 adequately blinded for outcome assessors
- 20 studies incomplete reporting of outcome date (attrition bias)
- 20 studies high risk of selective reporting bias
Key Findings

Limitations:
- Considerable variation in interventions and comparators
- Outcomes reported were not comparable
- Of the 23 comparisons, 10 provided outcome data for meta-analysis
  - H1 antihistamines at standard doses are better than placebo, though no clear winner!
  - Limited evidence to support increased doses
Cetirizine 10 to 20 mg versus placebo:
Proportion of participants with complete suppression of urticaria

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Cetirizine</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td>Go 1989</td>
<td>14</td>
<td>28</td>
<td>5</td>
</tr>
<tr>
<td>Subtotal (95% Cl)</td>
<td>28</td>
<td>28</td>
<td>45.3%</td>
</tr>
<tr>
<td>Total events</td>
<td>14</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.30 (P = 0.02)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Cetirizine</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td>Breneman 1995</td>
<td>18</td>
<td>60</td>
<td>7</td>
</tr>
<tr>
<td>Subtotal (95% Cl)</td>
<td>60</td>
<td>62</td>
<td>54.7%</td>
</tr>
<tr>
<td>Total events</td>
<td>18</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.40 (P = 0.02)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total (95% Cl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
</tr>
<tr>
<td>Cetirizine</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>Total events</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%
Test for overall effect: Z = 3.33 (P = 0.0009)
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.93), I² = 0%
# Desloratadine 5 to 20mg versus placebo: Proportion of participants with complete suppression of urticaria

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Desloratidine</th>
<th>Placebo</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.1.1 Short-term duration of intervention (desloratadine 5 mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hoxha 2011</td>
<td>3</td>
<td>34</td>
<td>2.60 [0.14, 46.97]</td>
</tr>
<tr>
<td>9.1.2 Short-term duration of intervention (desloratadine 10 mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hoxha 2011</td>
<td>11</td>
<td>34</td>
<td>8.54 [0.54, 134.83]</td>
</tr>
<tr>
<td>9.1.3 Short-term duration of intervention (desloratadine 20 mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hoxha 2011</td>
<td>21</td>
<td>34</td>
<td>15.97 [1.04, 245.04]</td>
</tr>
<tr>
<td>9.1.4 Intermediate-term duration of intervention (desloratadine 5 mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Di Lorenzo 2004</td>
<td>18</td>
<td>40</td>
<td>37.00 [2.31, 593.70]</td>
</tr>
</tbody>
</table>
# Levocetirizine 5 to 20 mg versus placebo:
Proportion of participants with complete suppression of urticaria

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Levocetirizine</th>
<th>Placebo</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.1.1 Short-term duration of intervention (levocetirizine 5 mg)</td>
<td>9 37</td>
<td>0 12</td>
<td>6.50 [0.41, 104.06]</td>
</tr>
<tr>
<td>Hoxha 2011</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11.1.2 Short-term duration of intervention (levocetirizine 10 mg)</td>
<td>17 37</td>
<td>0 12</td>
<td>11.97 [0.77, 185.38]</td>
</tr>
<tr>
<td>Hoxha 2011</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11.1.3 Short-term duration of intervention (levocetirizine 20 mg)</td>
<td>30 37</td>
<td>0 12</td>
<td>20.87 [1.37, 317.60]</td>
</tr>
<tr>
<td>Hoxha 2011</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11.1.4 Intermediate-term duration of intervention (levocetirizine 5 mg)</td>
<td>27 51</td>
<td>0 49</td>
<td>52.88 [3.31, 843.81]</td>
</tr>
<tr>
<td>Nettis 2006</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Key findings

- Cetirizine 10 mg OD short-term and intermediate-term duration was effective in completely suppressing urticaria

- Desloratadine 5 mg OD for at least an intermediate term and at 20 mg in the short term in completely suppressing urticaria

- Levocetirizine 5 mg effective for complete suppression in the intermediate term but not in the short term

- Levocetirizine 20 mg effective in the short term for complete supression but 10 mg was not

- Rupatadine showed good/ excellent response at either 10mg or 20mg (RR 1.35, 95% CI 1.03 to 1.77; 1 study; n=245).
Key Findings

- Adverse events e.g. headache, dry mouth and somnolence tolerable with most antihistamines

- Evidence is less clear for improvement QoL (e.g. reduction in sleep disturbance from itching, less distress from appearance of hives) many studies did not address this
Implications for research

- Use of higher doses of H1-antihistamines
- Studies to be conducted over a longer duration period
- Assessment of response after stopping treatment
- Trials with two or more active arms rather than placebo
- Standardised outcome scores (e.g. UAS/ UAS7)
- Clearer outcome scores (e.g. no. of participants with complete suppression of urticaria or 75% reduction in itch severity)
- Wider use of standardised and validated quality of life (QoL) scores
Challenges and experience of doing the review

- Large review
- Consistency within the review
- Consistency within studies
Large review

- Labour intensive
- Steep learning curve >>>>
- 4 authors
- CSG support, searches
- Cochrane copy edit
- Cochrane Editorial Unit
- Translation of foreign papers
- Information from investigators
Challenges and experience of doing the review

- Large review
- Consistency within the review
- Consistency within studies
Consistency within review

- Protocol updated
- Changes to author team
- Cochrane Reviews changed in format plus methodological issues (RoB), quality of evidence, conduct and reporting expectations
- Data extraction of foreign language studies
- Location of studies (ILLs)
- Several studies part of wider multicentre trials - some published some not
- Nomenclature of CIU/CSU changed over time
Challenges and experience of doing the review

- Large review
- Consistency within the review
- Consistency within studies
Consistency within studies

- ‘Chronic urticaria’, refractory to antihistamines
- Interventions H1 large and disparate class
- Comparators were very wide changed original protocol
- Outcomes strictly defined led to studies not being included in analyses e.g. scales of QoL, harmonised between studies
- Clinical heterogeneity
What helps

- Experienced systematic reviewer (CB) and a good team
- Data management systems (spreadsheets and Endnote to keep track of everything), templates
- CSG guidance and patience
- Substantial commitment of time
Updates

- Larger team - to extract further data
- Recruit Chinese co-author
- Time and resources - financial, library access, interlibrary loans, translations
- Defined team roles
- Deadlines
- Centralised data management e.g. data extraction
- Software that simplifies processes
- Widen to include more outcome measures e.g. continuous measures QoL (departure from protocol)
Update - Split?

For
- Split intervention vs. placebo and head to head
- H1 vs. Biologics
- Smaller job for each review

Against
- No good clinical reason to split first and second generation or other interventions
- QoL can be included as not very many
- Biologics-Omalizumab should be separate
Summary of review

- Considerable variation in interventions and comparators
- Outcomes reported were difficult to compare

- H1 antihistamines at standard doses are better than placebo
- Limited evidence to support increased doses

- Cetirizine 10 mg OD effective in short duration
- Desloratadine 5 mg OD effective at intermediate term and at 20 mg in the short
- Levocetirizine 5 mg at intermediate but not short term
- Levocetirizine 20 mg effective in the short term for complete suppression but 10 mg was not

- Side effects of H1 antihistamines tolerable
- QoL measures not well reported
Summary of experience doing the review

• Invaluable experience in acquiring knowledge and skills to perform systematic reviews
• Akin to climbing Mt Everest!
• Huge sense of relief and achievement to see it published!