The Great Chronic Idiopathic Urticaria Raft Debate: After Antihistamines, What’s Best For Next In Line Treatment: Hydroxychloroquine and Dapsone

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- Research Grants
  - NIH, Vanberg Family Fund
- Speaker Honoraria
  - Merck, Astra Zeneca, Genentech
- Organizations:
  - Joint Task Force on Practice Parameters

Objective
- Be able to discuss the role of dapsone and hydroxychloroquine in the management of refractory CIU
**Rationale for Alternative Agents in Chronic Urticaria**

- While most urticaria is antihistamine responsive, not all patients have adequate control with antihistamine therapy at any dose
- **Glucocorticoids** while typically effective, have predictable and nearly universal toxicity for treatment of chronic urticaria
- Alternative Agents
  - Immunomodulatory
  - Immunosuppressant
  - Other

**Alternative Agents for CU**

- Leukotriene Modifiers
- Calcineurin Inhibitors
- Mycophenolate
- Dapsone
- Sulfasalazine
- Colchicine
- Hydroxychloroquine
- COX-2 inhibitors
- Androgens
- Omalizumab
- Methotrexate
- IVIG
- Calcium channel blockers
- Anticoagulants
- Cyclophosphamide
- Gold
- Phototherapy
- Plasmapheresis

**Therapeutic alternatives for chronic urticaria: an evidence-based review, part 1**


**Therapeutic alternatives for chronic urticaria: an evidence-based review, part 2**

Category of Evidence

- Ia: evidence for meta-analysis of randomized controlled trials
- Ib: evidence from at least one randomized controlled trial
- IIa: evidence from at least one controlled study without randomization
- IIb: evidence from at least one other type of quasi-experimental study
- III: evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
- IV: evidence from expert committee reports or opinions or clinical experience of respected authorities, or both


Second-Line Alternative Therapies for Chronic Urticaria

<table>
<thead>
<tr>
<th>Drug</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukotriene Modifiers</td>
<td>Ib</td>
</tr>
<tr>
<td>Dapsone</td>
<td>IIb</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>III</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>Ib</td>
</tr>
<tr>
<td>Colchicine</td>
<td>III</td>
</tr>
<tr>
<td>Calcineurin Inhibitors</td>
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</tr>
<tr>
<td>Omalizumab</td>
<td>III</td>
</tr>
</tbody>
</table>


Alternative Therapies in CIU: Factors in Choosing an Agent

- Safety
- Accessibility
- Ease of use
- Cost
- Efficacy
- Onset of action
- Potential for disease remission
<table>
<thead>
<tr>
<th><strong>Dapsone</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Early reports of efficacy were in patients with urticarial vasculitis</td>
</tr>
<tr>
<td>Mechanisms of action</td>
</tr>
<tr>
<td>- Interference with release or function of lysosomal enzymes and myeloperoxidase generation of toxic halides</td>
</tr>
<tr>
<td>- Disruption of integrin-mediated neutrophil adhesiveness</td>
</tr>
<tr>
<td>- Inhibition of prostaglandin and leukotriene activity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Dapsone</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>5 pts with delayed pressure urticaria treated with response to dapsone 50 mg/d to qod</td>
</tr>
<tr>
<td>- 3/5 complete remission off dapsone</td>
</tr>
<tr>
<td>Few reports in CIU</td>
</tr>
<tr>
<td>Our experience &gt;60% have improvement</td>
</tr>
<tr>
<td>Some with remission</td>
</tr>
</tbody>
</table>

**Delayed pressure urticaria – Dapsone heading for first-line therapy?**

Sonja Alexandra Grundmann, Sabine Kiefer, Thomas Anton Luger, Randolf Brehler
Clinic and Polyclinic for Dermatological Diseases, Muenster University Hospital, Germany

Dapsone in Delayed Pressure Urticaria

- Retrospective study of 31 patients with delayed pressure urticaria
- Confirmed with standardized pressure challenge tests
- All patients failed treatment with high dose antihistamines and montelukast
- Baseline G-6PD and Met-Hb levels


Table 1: Dosage of dapsone therapy.

<table>
<thead>
<tr>
<th>No. weeks</th>
<th>Dapsone</th>
<th>Vitamin C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 week</td>
<td>25 mg</td>
<td>1 g</td>
</tr>
<tr>
<td>2 weeks</td>
<td>50 mg</td>
<td>1 g</td>
</tr>
<tr>
<td>3 weeks</td>
<td>100 mg</td>
<td>1 g</td>
</tr>
<tr>
<td>&gt; 4 weeks</td>
<td>150 mg</td>
<td>1 g</td>
</tr>
</tbody>
</table>


Response to dapsone

![Bar chart showing response to dapsone]
Author's Conclusions

Although the mechanisms of action of sulfone derivatives in pressure urticaria are uncertain, we believe that with adequate monitoring the risk-to-benefit ratio of dapsone therapy in treatment-resistant forms is so impressive that it warrants early treatment initiation.
Low Dose Dapsone in CU

- Small open study in 11 CU patients (3 with DPU)
- Treated with dapsone 25 mg daily
  - Dose increased to 50 mg daily if no response after 4 weeks
- 9/11 had complete response to dapsone 25 mg/d
- 1/11 had complete response to dapsone 50 mg/d


Dapsone + Antihistamine

- 65 CIU pts randomized to 3 months of open label:
  - Dapsone + desloratadine
  - Desloratadine
  - Combination of dapsone plus desloratadine yielded statistically significant improvements in urticaria activity and VAS scores vs. desloratadine alone


Dapsone

- Evidence: IIb
- Advantages
  - Inexpensive
  - Usually well-tolerated
    - Mild anemia expected (Hgb ↓ by 10-20%)
    - Neuropathy uncommon but often irreversible
    - Methemoglobinemia/hepatitis rare
  - May induce remission
  - Requires regular monitoring of CBC
Dapsone

- **Dose**
  - 50-100 mg/d

- **Monitoring**
  - G6PD level prior to starting
  - CBC
    - 1-2 weeks after initiation
    - monthly for 3-6 months then periodically
  - LFT’s periodically

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Hydroxychloroquine

- **Mechanism of action**
  - Suppression of T-cell activation
  - Disruption of antigen processing

- 18 pts with CIU randomized to hydroxychloroquine vs. placebo along with H1, H2 and corticosteroid therapy

- After 12 weeks, QOL and itch was improved with trends of improvement for urticaria score and medication requirement

- Minimal correlation with ASST and autoimmune markers


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GSS: itch severity
US: urticaria score
LAMY & SF-12: general QOL
Hydroxychloroquine

- Evidence: Ib
- Dosing
  - 200 mg qd to bid
- Advantages
  - Safe
    - Risk of retinopathy very rare and related to dose and duration
  - Inexpensive
- Disadvantages
  - Slow onset of effect
    - 12 week trial typically recommended

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American Academy of Ophthalmology Update

Revised Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy

Michael J. Merzen, MD1, Vicki Kallner, MD2, Timothy T. Lap, MD1, Jonathan S. Lyons, MD3, William F. Miller, MD4 for the American Academy of Ophthalmology

Baseline examination within 1st year of use
Annual screening after 5 years of use


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Recommendations for Hydroxychloroquine Retinopathy Screening

<table>
<thead>
<tr>
<th>Risk Factors for Hydroxychloroquine Retinopathy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of use</td>
<td>&gt; 5 yrs</td>
</tr>
<tr>
<td>Cumulative dose</td>
<td>&gt;1000 gms</td>
</tr>
<tr>
<td>Daily dose</td>
<td>&gt; 400 mg/d</td>
</tr>
<tr>
<td>Age</td>
<td>Elderly</td>
</tr>
<tr>
<td>Systemic disease</td>
<td>Kidney or liver dysfunction</td>
</tr>
<tr>
<td>Ocular disease</td>
<td>Retinal disease or maculopathy</td>
</tr>
</tbody>
</table>

Annual screening recommended at initiation of drug if above risk factor(s) present

Factors in Choosing an Alternative Agent: How do Dapsone and Hydroxychloroquine stack up?

<table>
<thead>
<tr>
<th>Factor</th>
<th>Dapsone</th>
<th>Hydroxychloroquine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Accessibility</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Ease of use</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Cost</td>
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<td>+</td>
</tr>
<tr>
<td>Onset of action</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Potential for disease remission</td>
<td>+++</td>
<td>+</td>
</tr>
</tbody>
</table>

+++ : very favorable
++ : favorable
+ : slightly favorable
- : not favorable

After Antihistamines, What’s Best For Next In Line Treatment?

Clearly the answer is dapsone or hydroxychloroquine!