An Update on the Management of Chronic Urticaria

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Disclosures

Advisory Board: ALK and AlImmune
Clinical investigator: TEVA, GSK, Astra-Zeneca, Regeneron

No disclosures relevant to this talk.
Learning objectives

- To learn about the US and European guidelines for treating chronic urticaria
- To review studies of FDA approved therapies for chronic urticaria: antihistamines and omalizumab
- To discuss immunomodulators as alternative therapy for antihistamine-resistant chronic urticaria patients
Definitions

• **Chronic urticaria:**
  – Hives on most days of the weeks for > 6 weeks

• **Chronic idiopathic urticaria (CIU):**
  – Chronic urticaria with no identifiable secondary cause

• **Chronic autoimmune urticaria:**
  – Chronic urticaria with identifiable “autoimmune” testing
Epidemiology & natural history

• Prevalence: approx 1% of the population at some point in their lives
• Adults > children
• Women 2x as often as men
• Typically begins in 3rd-5th decades
• 30-50% have spontaneous remission by 1 year
• Average duration of disease: 2-5 yrs
• Approx 20% of cases last longer than 5 yrs
Diagnostic approach

• A good history and physical exam is most important!
• Optional testing:
  – Labs:
    • Specific labs indicated based on history and physical
    • CBC with differential, ESR or CRP, TSH
    • Urinalysis to rule out urinary tract infection?
    • “autoimmune” testing
  – Skin biopsy (for recalcitrant cases or those with atypical features):
    • Exclude urticarial vasculitis or mastocytosis
    • Define the cellular influx
• 80-90% of cases have no identifiable cause
Systematic review of work-up of CU cases

- Review of 29 clinical studies (6000+ cases)
- Poor association between number of tests ordered and diagnosis reached (38%)
- Secondary cause identified in only 1.6% of cases examined (105 out of 6462)
  - Cutaneous vasculitis: 60
  - Thyroid disease: 17
  - CTD: 16
  - SLE: 7
  - Paraproteinemia: 3
- Similar to a single site study from 2011

“Autoimmune” testing for CIU

- Autologous serum skin test
- CU index, or histamine release assay
- Basophil CD203c expression – marker of activation
- Identification of IgG against IgE or the IgE receptor (FcεR1α)
When to consider a skin biopsy: Features of atypical urticaria

- Individual lesions last longer than 24 hours
- Lesions are painful or burning
- Lesions leave residual bruising
- Urticarial vasculitis should be considered if these features are present
Skin biopsy in urticaria

• Send sample in:
  – Formalin for H&E stain
  – Michel’s media for direct immunofluorescence microscopy

• Biopsy often shows interstitial edema with perivascular mixed infiltrate (lymphs, eo and some PMNs or basophils)

• Other disorders in the differential will show PMN predominance, atypical mast cells, leukocytoclasia and/or vasculitis
Skin Biopsy

Conventional urticaria

Leukocytoclastic vasculitis

Neutrophil-rich urticaria

Urticaria pigmentosa

http://www.skinpathology.org

http://www.actasdermo.org
Management of the CIU patient

- Education
- Urticaria Guidelines: start with antihistamines
- Omalizumab
- Immunomodulators
Educate the CU patient

• Discuss epidemiology and natural history to set realistic expectations.

• Encourage avoidance of non-specific mast cell triggers:
  – Physical factors
  – NSAIDs
  – Stress (physical or psychological)
  – Alcohol
  – Variations in diet??
AAAAAI/AACAAI Urticaria Guidelines

STEP 4
Add an alternative agent
- Omalizumab or cyclosporine
- Other anti-inflammatory agents, immunosuppressants, or biologics

STEP 3
Dose advancement of potent antihistamine (e.g., hydroxyzine or doxepin) as tolerated

STEP 2
One or more of the following:
- Dose advancement of 2nd generation antihistamine used in Step 1
- Add another second generation antihistamine
- Add H1- antagonist
- Add leukotriene receptor antagonist
- Add 1st generation antihistamine to be taken at bedtime

STEP 1
- Monotherapy with second generation antihistamine
- Avoidance of triggers (e.g., NSAIDs) and relevant physical factors if physical urticaria/angioedema syndrome is present.
- Begin treatment at step appropriate for patient’s level of severity and previous treatment history
- At each level of the step-approach, medication(s) should be assessed for patient tolerance and efficacy
- “Step-down” in treatment is appropriate at any step, once consistent control of urticaria/angioedema is achieved

FIG 1. Step-care approach to the treatment for CU.

Chronic urticaria treatment algorithm. This algorithm was voted on after finishing all separate GRADE questions taking into consideration the existing consensus. It was decided that omalizumab should be tried before cyclosporin A since the latter is not licensed for urticaria and has an inferior profile of adverse effects. In addition: A short course of glucocorticosteroids may be considered in case of severe exacerbation. Other treatment options are available, see table 9. > 90% consensus.
Comparing the international US guidelines

**FIGURE 2.** Comparison of treatment algorithms of the international and US guidelines. EAACI, European Academy of Allergology and Clinical Immunology; fgAH, first-generation antihistamine; LTRA, leukotriene receptor antagonist; sgAH, second-generation antihistamine; WAO, World Allergy Organization. *Different spellings as used in the respective guideline. Additional comments: EAACI/WAO: A short course of corticosteroids may be considered in case of severe exacerbation. AAAAI/ACAAI: Begin treatment at step appropriate for patient’s level of severity and treatment history; “step-down” treatment is appropriate at any step, once consistent control of urticaria/angioedema is achieved.

<table>
<thead>
<tr>
<th>STEP 1</th>
<th>The EAACI/WAO Guideline</th>
<th>The AAAAI/ACAAI Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Monotherapy with sgAH</td>
<td>Monotherapy with sgAH</td>
</tr>
<tr>
<td></td>
<td>If inadequate control: After 2-4 weeks or earlier, if symptoms are intolerable</td>
<td>assess for patient’s tolerance and efficacy</td>
</tr>
<tr>
<td></td>
<td>Increase sgAH dose (up to 4x)</td>
<td>One or more of the following:</td>
</tr>
<tr>
<td></td>
<td>If inadequate control: After 2-4 weeks or earlier, if symptoms are intolerable</td>
<td>- Dose advancement of sgAH used in Step 1</td>
</tr>
<tr>
<td></td>
<td>Add on to sgAH: Omalizumab</td>
<td>- Add another sgAH</td>
</tr>
<tr>
<td></td>
<td>If inadequate control: Within 6 months or earlier, if symptoms are intolerable</td>
<td>- Add H1-antagonist</td>
</tr>
<tr>
<td></td>
<td>Add on to sgAH: Ciclosporin*</td>
<td>- Add LTRA</td>
</tr>
<tr>
<td></td>
<td>Add an alternative agent</td>
<td>- Add fgAH to be taken at bedtime</td>
</tr>
<tr>
<td></td>
<td>- Omalizumab or cyclosporine*</td>
<td>- other anti-inflammatory agents, immunosuppressants, or biologics</td>
</tr>
</tbody>
</table>

Antihistamines in CIU (Steps 1-3)

• **STEP 1** – Use a second generation antihistamine (sgAH) daily
  – loratadine, desloratadine, fexofenadine, cetirizine, levocetirizine (most available OTC)

• **STEP 2** - Increase the amount of sgAH or add another form of AH (or LTRA)
  – Increase sgAH up to four-fold (either using a single sgAH or several sgAHs)
  – Add a first generation antihistamine (fgAH) at bedtime -- diphenhydramine, hydroxyzine, chlorpheniramine
  – Add an H2 blocker or LTRA

• **STEP 3** - Increase the amount of “potent” AH (hydroxyzine or doxepin)
The effectiveness of levocetirizine and desloratadine in up to 4 times conventional doses in difficult-to-treat urticaria

Maria Staevska, MD, a Todor A. Popov, MD, PhD,a Tanya Kralimarkova, MD, a Cvetelina Lazarova, MD, a Steliana Kraeva, MD, a Dora Popova, MD, PhD,a Diana S. Church, MD,b Vasil Dimitrov, MD, PhD,a and Martin K. Church, PhD, DScb,c  Sofia, Bulgaria, Southampton, United Kingdom, and Berlin, Germany

**FIG 1.** The study design with the treatment arms and the crossover step. Deslo, Desloratadine; Levo, levocetirizine.
Many pts respond to an increase in sgAH dose and/or addition of a different sgAH

**FIG 2.** The number of patients whose symptoms were relieved by levocetirizine (*Levo*) or desloratadine (*Deslo*) throughout the 4 weeks of the study. The *numbers in parentheses* refer to the number of patients who were symptom free on 5 mg (week 1), 10 mg (week 2), 20 mg (week 3), or after the drug switch (week 4).

Staevska et al. JACI 2010; 125: 676-82.
Omalizumab in CIU

- Two doses approved by FDA: 150mg and 300mg every 4 weeks
- Dosing does NOT depend on IgE level or weight
- No lab monitoring needed; generally well-tolerated (anaphylaxis 0.2%, local rxns 40%)
- Optimal duration of therapy unknown
- No long-term disease modifying effects have been shown
Omalizumab mechanism of action

Randomized control trials of omalizumab in CIU

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Type</th>
<th>Study name</th>
<th>CTG</th>
<th>Doses of omalizumab (mg)</th>
<th>No.</th>
<th>Treatment (in wk)</th>
<th>Follow-up (wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maurer et al</td>
<td>2011</td>
<td>mRCT</td>
<td>XCUISITE</td>
<td>NCT00481676</td>
<td>150, 300, 600/2 or 4 wk</td>
<td>27/22</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Saini et al</td>
<td>2011</td>
<td>mRCT</td>
<td>MYSTIQUE</td>
<td>NCT00130234</td>
<td>75, 300, 600 once</td>
<td>69/21</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Maurer et al</td>
<td>2013</td>
<td>mRCT</td>
<td>ASTERIA I</td>
<td>NCT01292473</td>
<td>75, 150, 300/4 wk</td>
<td>243/79</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>Kaplan et al</td>
<td>2013</td>
<td>mRCT</td>
<td>GLACIAL</td>
<td>NCT01264939</td>
<td>300/4 wk</td>
<td>252/84</td>
<td>24</td>
<td>16</td>
</tr>
<tr>
<td>Saini et al</td>
<td>2015</td>
<td>mRCT</td>
<td>ASTERIA II</td>
<td>NCT01287117</td>
<td>75, 150, 300/4 wk</td>
<td>319/80</td>
<td>24</td>
<td>16</td>
</tr>
<tr>
<td>Staubach et al</td>
<td>2015</td>
<td>mRCT</td>
<td>X-ACT</td>
<td>NCT01723072</td>
<td>300/4 wk</td>
<td>17/8</td>
<td>28</td>
<td>8</td>
</tr>
<tr>
<td>Metz et al</td>
<td>2015</td>
<td>mRCT</td>
<td>MOA</td>
<td>NCT01599637</td>
<td>300/4 wk</td>
<td>44/47</td>
<td>12</td>
<td>8</td>
</tr>
</tbody>
</table>

All studies were CSU/chronic idiopathic urticaria studies.

CTG, clinicaltrials.gov identification number; mRCT, multicenter RCT.

Zhao et al. JACI 2016; 137: 1742-50.
RCTs of omalizumab in CIU show dose-dependent effect on WIS and WWS

WIS = weekly itch score
WWS = weekly wheal score

Zhao et al. JACI 2016; 137: 1742-50.
RCTs of omalizumab show dose-dependent effect on complete responders by UAS7

Zhao et al. JACI 2016; 137: 1742-50.
RCTs of omalizumab in CIU show good safety profile: similar risk of ≥ 1 AE

Zhao et al. JACI 2016; 137: 1742-50.
How long does it take for patients to show a response to omalizumab
Study designs of the 3 pivotal phase 3 studies of omalizumab in CIU

Omalizumab responders by week and by dose in the pivotal phase 3 studies

Kaplan et al. JACI 2016; 137:474-81.
Omalizumab effect on FcERI: basophils affected before mast cells

Beck et al. JACI 2004; 114: 527-530
Could change in dosing help omalizumab non-responders or partial responders?
Updosing of omalizumab may help non-responders

More frequent dosing of omalizumab may help non-responders

<table>
<thead>
<tr>
<th>Table II. Level of improvement (% [n]) in CIU by omalizumab dosing (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>% (N)</td>
</tr>
<tr>
<td>Improvement</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>Mild (&lt;50%)</td>
</tr>
<tr>
<td>Significant</td>
</tr>
<tr>
<td>≥50% Response</td>
</tr>
</tbody>
</table>

CIU, Chronic idiopathic urticaria; Q2W, every 2 weeks; Q4W, every 4 weeks.

Proposed dosing algorithm

FIG E1. Flow chart of the algorithm for omalizumab treatment. *Same time interval was tried 2 to 3 times in case of the UAS being 2 or more before the treatment interval was reduced by 1 week.

Uysal et al. JACI 2014; 133:914.
Are omalizumab effectiveness and safety sustained with long-term use?
TABLE E2. TEAEs causally related to the study drug*  

<table>
<thead>
<tr>
<th>TEAE</th>
<th>Omalizumab (n = 81)</th>
<th>Placebo (n = 53)</th>
<th>Not randomized (n = 71)</th>
<th>All patients (N = 205)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with a TEAE</td>
<td>5 (6.2)</td>
<td>1 (1.9)</td>
<td>6 (8.5)</td>
<td>12 (5.9)</td>
</tr>
<tr>
<td>TEAE, n</td>
<td>8</td>
<td>1</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>Discomfort at administration site</td>
<td>0</td>
<td>0</td>
<td>1 (1.4)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Anaphylactic reaction</td>
<td>0</td>
<td>0</td>
<td>1 (1.4)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>1 (1.2)</td>
<td>0</td>
<td>0</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>1 (1.2)</td>
<td>0</td>
<td>0</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (2.5)</td>
<td>0</td>
<td>3 (4.2)</td>
<td>5 (2.4)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (2.5)</td>
<td>0</td>
<td>0</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>2 (2.5)</td>
<td>0</td>
<td>0</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Presyncope</td>
<td>0</td>
<td>1 (1.9)</td>
<td>0</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>0</td>
<td>0</td>
<td>1 (1.4)</td>
<td>1 (0.5)</td>
</tr>
</tbody>
</table>

Values given as n (%) unless otherwise noted.  
TEAE, Treatment-emergent adverse event.  
*Through 60 weeks on study.
XTEND-CIU study: Long-term use of omalizumab – sustained efficacy at 48 wks

**FIG E2.** Time to CIU/CSU clinical worsening.* *UAS7 of ≥12 for 2 consecutive weeks. Time 0 represents 4 weeks post omalizumab dosing for placebo patients. +Censored indicates an individual patient dropping out of the analysis.

Maurer et al. JACI 2018; 141(3): 1138–1139.e7
XTEND-CIU study: CIU often flares after omalizumab discontinuation

Maurer et al. JACI 2018; 141(3): 1138–1139.e7
Is re-treatment with omalizumab effective?
XTEND-CIU study:
Omalizumab is effective for re-treatment

Maurer et al. JACI 2018; 141(3): 1138–1139.e7
Retreatment with omalizumab results in rapid remission in chronic spontaneous and inducible urticaria

- Retrospective study
- 25 patients
- Immediate response to omalizumab
- Relapse upon discontinuation
- All responded within 4 weeks of first dose when retreated
- No adverse effects reported

What other options exist for the treatment of CIU?
Immunomodulators

- cyclosporine A
- mycofenolate mofetil
- sulfasalazine
- dapsone
- hydroxychloroquine
- prednisone
Alternative agents for CIU are effective

**TABLE V. Efficacy of alternative agents**

<table>
<thead>
<tr>
<th>Alternative agent</th>
<th>Insufficient duration</th>
<th>Failed</th>
<th>Partial</th>
<th>Partial control</th>
<th>Complete control</th>
<th>Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapsone</td>
<td>2</td>
<td>11</td>
<td>7</td>
<td>3</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>10</td>
<td>19</td>
<td>14</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>7</td>
<td>21</td>
<td>9</td>
<td>2</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>2</td>
<td>11</td>
<td>7</td>
<td>3</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>4</td>
<td>9</td>
<td>5</td>
<td>1</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Omalizumab</td>
<td>0</td>
<td>6</td>
<td>5</td>
<td>2</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

Seth et al. JACI Pract 2017; 5: 165-70.
Alternative agents for CIU are relatively well tolerated.

**FIGURE 1.** Frequency of adverse effects and need for discontinuation of alternative agents for CU.

Seth et al. JACI Pract 2017; 5: 165-70.
Cyclosporine A (CSA)

- Mechanism: suppresses T cell activation, causes cytokine release, inhibits IgE receptor-mediated release of histamine, lipid mediators and cytokines by basophils and MCs
- Evidence:
  - Several case reports, retrospective studies, and open-label prospective studies
  - 2000: RPCT (N=30) – 65% response at 4 weeks, with 26% remaining sx free at 20 weeks off CSA
  - 2006: RDBPCT of 16 wks vs 8 wks (N=99) – 63% response at 8 wks, no better at 16 wks
  - 2010: dosing study of 120 pts – 62% response to CsA
- Side effects relatively common: GI sx, headache, paraesthesias (>10%), infections, ??malignancy
- Monitor: BP and renal function regularly, plasma levels

A 2017 meta-analysis suggests that cyclosporine is effective at low-moderate doses

<table>
<thead>
<tr>
<th>Study name</th>
<th>Event rate</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(from 2 to &lt;4 mg/kg/day)</td>
<td>0.971</td>
<td>0.664</td>
<td>0.998</td>
<td>0.015</td>
</tr>
<tr>
<td>Neveryman, 2014</td>
<td>0.971</td>
<td>0.664</td>
<td>0.998</td>
<td>0.015</td>
</tr>
<tr>
<td>Boubouka, 2011</td>
<td>0.710</td>
<td>0.527</td>
<td>0.843</td>
<td>0.026</td>
</tr>
<tr>
<td>Ohtsuka, 2010</td>
<td>0.600</td>
<td>0.348</td>
<td>0.808</td>
<td>0.442</td>
</tr>
<tr>
<td>Kessel, 2010</td>
<td>0.683</td>
<td>0.595</td>
<td>0.760</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Godse, 2008</td>
<td>0.800</td>
<td>0.309</td>
<td>0.973</td>
<td>0.215</td>
</tr>
<tr>
<td>Toubi, 1997</td>
<td>0.760</td>
<td>0.558</td>
<td>0.888</td>
<td>0.014</td>
</tr>
<tr>
<td>Overall (low dose)</td>
<td>0.699</td>
<td>0.631</td>
<td>0.759</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heterogeneity: Q = 4.94, Τ = 0, p-value = 0.423</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study name</th>
<th>Event rate</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(4-5 mg/kg/day)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asero, 2015</td>
<td>0.860</td>
<td>0.683</td>
<td>0.946</td>
<td>0.001</td>
</tr>
<tr>
<td>Baskan, 2004</td>
<td>0.800</td>
<td>0.459</td>
<td>0.950</td>
<td>0.080</td>
</tr>
<tr>
<td>Overall (moderate dose)</td>
<td>0.843</td>
<td>0.693</td>
<td>0.928</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heterogeneity: Q = 0.02, Τ = 0, p-value = 0.653</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>0.718</td>
<td>0.656</td>
<td>0.772</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heterogeneity: Q = 3.19, p-value = 0.074</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Mycofenolate mofetil

- **Mechanism:** Antimetabolite selectively for lymphocytes; impairs expression of adhesion molecules and secondary leukocyte migration.

- **2 studies:**
  - Prospective open-label uncontrolled\(^1\):
    - 9 resistant CU pts – 1g BID x 12 weeks – 6 pts improved and able to discontinue steroids; effect lasted for 6 months
  - Retrospective chart review\(^2\):
    - 19 resistant CU pts – 500mg-3g BID – 60% had remission after mean of 14 weeks, effect had lasted 2-6 wks at conclusion of study

- **Lab Monitoring:** CBC, LFTs

Sulfasalazine

- Mechanism: Anti-inflammatory 5-aminosalicylic acid (5-ASA) derivative
- Dosing: 500mg 1-2 x/day to start, gradually increase to 1 g 2x/day; 4-6 week trial usually enough
- S.E.: nausea, h/a, leukopenia, transaminitis, rarely granulocytosis
- Retrospective chart review of 31 pts with refractory CU showed:
  - 84% of pts improved within 3 months
  - Pts who were hive-free with sulfasalazine plus antihistamine = 32% by 3 mo, 51% by 6 mo
- Lab monitoring: CBC, liver function testing & U/A monthly for first 3 months, then prn

Orden et al. Ann Allergy Asthma Immunol 2014; 112:64.
Dapsone

- Mechanism: Sulfone antimicrobial; Has effects on PMN fxn and activation, hence its use in neutrophil predominant CU
- Generally well-tolerated, widely available, inexpensive
- SE: peripheral neuropathy, methemoglobinemia, agranulocytosis, & allergic rxns like DRESS
- One small randomized control study (N=22)
- Lab monitoring: R/o G6PD deficiency before starting therapy; monitor Hb and LFTs

Double-Blind Placebo-Controlled Trial of Dapsone in Antihistamine Refractory Chronic Idiopathic Urticaria

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Original Article

Dapsone improved itch in CIU

Hydroxychloroquine (HCQ)

- Generally safe, inexpensive, well-tolerated
- Slow onset of action (4-6 weeks), so often start concurrently with another agent
- Start with 200mg twice daily for at least 3 months
- One randomized control study
  - 18 subjects on standard therapy
  - HCQ added to half
  - improved QOL by global symptom severity score and LAMY-7 at 12 wks
  - Trend toward improved urticaria score and medication requirements
- Monitoring: CBC, LFTs, eye exam, muscle strength

Other options are mostly based on case reports and case series

- Methotrexate
- Tacrolimus
- Sirolimus
- IVIG
- Rituximab
- Vitamin D
- Levothyroxine
Take-home points

• CU is a common condition with significant morbidity

• Published guidelines, which start with the use of antihistamines, can help guide therapy for CIU

• Omalizumab, the only other FDA approved therapy for CIU, is effective and safe, although it is not disease modifying

• Several other immunomodulators exist for those pts resistant to initial therapeutic interventions
Questions?